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HPV Testing for Primary Cervical Cancer Screening

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ABBREVIATIONS

AGC	atypical glandular cell
AHRQ	Agency for Healthcare Research and Quality
AIS	adenocarcinoma in situ
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
ASC-H	atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion
ASCUS	atypical squamous cells of undetermined significance, a common diagnostic threshold for positive cytology results
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
CIN	cervical intraepithelial neoplasia, mostly diagnosed with colposcopy, regarded as precancerous changes, and further classified into CIN1, CIN2 and CIN3
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DARE	Database of Abstracts of Reviews of Effects
DOR	diagnostic odds ratio
DNA	deoxyribonucleic acid
DTA	diagnostic test accuracy
FN	false negative
FP	false positive
HC2	Hybrid Capture 2
HIQA	Health Information and Quality Authority
HPV	human papillomavirus
HSIL	high-grade cervical lesions
IARC	International Agency for Research on Cancer
LBC	liquid-based cytology
LEEP	loop electrosurgical excision procedure

MeSH	Medical Subject Headings
NLR	negative likelihood ratio
NPV	negative predictive value
HPV	human papillomavirus
HTA	health technology assessment
NPV	negative predictive value
Pap	Papanicolaou
PCR	polymerase chain reaction
PLR	positive likelihood ratio
PPV	positive predictive value
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomized controlled trial
RNA	ribonucleic acid
SR	systematic review
TN	true negative
TP	true positive
UK	United Kingdom
US	United States

Table of Contents

Executive Summary

Issue

Currently, all Canadian provinces and territories provide access to opportunistic or organized cervical cancer screening with cytology.[1] While the implementation of cytology testing over the last few decades in Canada has contributed to a significant reduction in cervical cancer incidence and mortality, low sensitivity is a known limitation of this test.[1,2] In view of the anticipated higher sensitivity of HPV testing, some experts and stakeholders have called for HPV testing to be used in Canada as the primary screening tool, replacing the cytology test. As noted, to date, no Canadian jurisdiction has implemented routine primary HPV testing.[1] However, a number of Canadian jurisdictions are currently considering, planning, or piloting primary HPV testing for their cervical cancer screening programs

Objectives

Should HPV testing replace cervical cytology in Canadian jurisdictions as the primary screening tool for cervical cancer? If yes, what criteria, including appropriate screening interval and ages to start and stop screening, should guide HPV-based cervical cancer screening programs in Canada?

The objective of this HTA is to address the policy question by assessing the diagnostic test accuracy, clinical utility, safety, cost-effectiveness, patients' experiences and perspectives, ethical issues, and implementation issues of HPV testing as a primary screening tool for cervical cancer screening. This HTA will be conducted to inform decision-making, policy development, capacity planning, and recommendations around primary HPV-based testing for cervical cancer screening.

Clinical Evidence

Methods

A systematic review and critical appraisal of empirical evidence relevant to the clinical effectiveness of cervical cancer screening was conducted. Published literature was identified by searching MEDLINE, Embase, Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects (DARE), and PubMed. Retrieval was limited to documents published since January 1, 2002. Results were limited to English- and French-language publications. The quality of systematic reviews, diagnostic test accuracy studies, RCTs and non-randomized studies was assessed by two reviewers independently using the AMSTAR 2 tool, QUADAS-2 instrument, the Cochrane Risk of Bias Tool, and the Newcastle-Ottawa scale respectively. Data were extracted by one reviewer and verified by another. The results were summarized and categorized based on the outcomes. The heterogeneity of the results was assessed and potential sources were discussed.

Results

Four SRs, 8 RCTs (9 publications), 10 prospective cohort studies, and one retrospective cohort study were identified to be included into this review. For the comparison of the diagnostic test accuracy between HPV tests and cytology, Hybrid Capture 2 (HC2) was the most extensively studied HPV test and was found to be more sensitive and less specific than cytology, including conventional or liquid-based cytology in most included studies. There is evidence to show that other HPV tests were also more sensitive and less specific than cytology, including PCR-based, Multiplexed genotyping, Aptima, Cobas, and Confidence. One advantage of HPV tests was that it became feasible for screening participants to take samples by themselves at home or elsewhere. Self-sampling HPV tests that were sent to individual residences were generally more acceptable than cytology for individuals that did not attend screening programs regularly. Higher colposcopy referral rates were observed among those screened by HPV tests, compared

to cytology. There was limited evidence available to address harms and clinical utility. After two to three years of follow-up, there were no cases of invasive cervical cancer or serious adverse events observed that were related to the screening tests. When screening strategies were compared to each other, among the four HPV triage strategies, primary HPV testing with HPV test and cytology co-testing triage seemed to have the highest sensitivity.

Economics

Methods

A decision-analytic hybrid model was developed to determine, from a health systems perspective, the lifetime cost-effectiveness associated with the following approaches to programmatic cervical cancer screening: 1) primary cytology; 2) primary cytology with HPV triage for equivocal cytology results and 3) primary HPV with cytology triage for HPV positive results. In total, nine different screening strategies were assessed that varied with respect to the screening interval (i.e., starting age of screening) and/or the frequency between screens. The model was based on a previously published decision-analytic model that was adapted to more accurately capture existing Canadian guidelines on the clinical management of cervical cancer screening. The original Markov cohort-level model was converted into a patient-level microsimulation to reflect the natural history and epidemiology of HPV infection, cervical lesions and cervical cancer; at the appropriate time periods, a decision tree was embedded into the microsimulation to capture the impact of screening. The clinical pathway and decision-analytic model were further updated by reviewing existing clinical and economic literature, and the conceptualization of the model and its structure was subsequently validated by gynaecologists. The primary outcome was cost per quality-adjusted-life-years (QALYs) gained, measured in 2017 Canadian dollars.

Results

The current screening strategy of cytology every three years from the ages of 21 to 69 was found to reduce the lifetime risk of cervical cancer by 69% compared to no screening program. Based on the economic evaluation, switching the primary test from cytology to HPV testing and increasing the screening frequency had limited impact onexpected lifetime QALYs but decreased the total expected lifetime cost in Canada with limited harms in terms of higher lifetime risk of developing cervical cancer. Regardless of the population age or vaccination status, primary HPV with cytology triage, every five years, from the ages of 25 to 69 was associated with the lowest costs and lowest QALYs. This strategy would be most likely cost-effective if willingness to pay was under $100,000 per QALY. The reference case findings were consistent in both a prevalent cohort (baseline age of 30, unvaccinated) and a future incident cohort (baseline age of 9, partially vaccinated). However, sensitivity analyses highlighted that parameters in which the model was sensitivie to depended on the population analysed. For the prevalent cohort… for the future incidence cohort.

Qualitative Evidence Synthesis

Methods

A systematic review and qualitative meta-synthesis of empirical qualitative literature relevant to patients' experiences and perspectives with cervical cancer screening was conducted. Published literature was identified by searching MEDLINE, Embase, PsycINFO, CINAHL, PubMed, and the Social Sciences and Humanities segments in Scopus. Eligible reports were those published in English or French of any qualitative design that explored perspectives of women eligible for cervical cancer screening. The quality of each included study was assessed using the CASP Qualitative Checklist. A descriptive analysis of study characteristics was conducted, with the goal to characterize the set of included studies in terms of important study and patient characteristics. Results of published qualitative research were analyzed using techniques of integrative qualitative meta-synthesis. The goals were to first aggregate the results to reflect the range of findings across studies, while retaining the original meaning; and second, to compare and contrast findings across studies, to produce a new integrative interpretation.

Results

A total of 117 primary empirical qualitative research studies were included in the meta-synthesis. Of these, 102 studies recruited participants based on particular aspects of their social or demographic identity including women who belonged to a minority ethnicity or culture, women of low socioeconomic status, Indigenous women, women who lived in rural areas, women who are lesbian, bi-sexual or transgender, older women, as well as other aspects of identity (e.g. obese, incarcerated women, homeless women, HIV positive). A number of factors were identified that act alternately as incentives or disincentives to women's decision-making about participation in cervical cancer screening: Emotions, Cultural and Community Attitudes and Beliefs, Understanding Personal Risk, Logistics, Multiple Roles of Women, Relationships with Health Care Providers, Comfort and Inclusion in the Health Care System, and Knowledge. Many of the factors are closely related. A woman's social location was highly influential on the way she experienced the incentivizing and disincentivizing factors. Few women understood the link between HPV and cervical cancer, which resulted in misunderstandings about the nature and importance of HPV testing. As a result of this misunderstanding, many women may underestimate their personal risk and decline to participate in screening. If Pap cytology is replaced by HPV testing as the primary cervical cancer screening test in Canada, patient education that focuses on the etiology and risk factors of cervical cancer may improve participation rates. Some of the strongest patient preferences will not be affected by a change in screening modality from cytology testing to HPV. For example, both require a cervical cell sample, and therefore the potential for embarrassment, pain, and logistical inconvenience of that procedure is unchanged. The importance of the relationship between patient and health care provider will also continue to be important.

Ethical Issues

Methods

A systematic review to determine the ethical and legal issues that have been identified as raised by HPV as a primary cervical cancer screening test was performed. Given the paucity of results from a search for research addressing this question directly, we performed to a second search to determine the ethical and legal issues that have been identified in cervical cancer screening. This ethical review and analysis focused on equity, non-maleficence, and autonomy issues in relation to a proposed change in screening for cervical cancer precursors, from cytological testing as the primary screening tool to HPV testing for persistent infection with high-risk oncogenic HPV strains as the primary screening tool with cytology used to triage results. It also discussed liability concerns for pathologists and cytologists that have arisen from cytology. Its analysis is consistent with Parker et al.'s recent argument that "avoiding harm and supporting autonomy are under-prioritized in cancer screening policies and practices".

Results

Screening involves balancing the benefits of disease detection (beneficence) with ensuring that theharms and burdens of screening attendance, false positives, and overdiagnosis do not increase (non-maleficence). The implications of a false positive test result are substantially different for a large proportion of the population under the scenario of HPV as a primary screening test: a third of those screened would at some point in their lives receive a diagnosis of a high-risk oncogenic HPV infection. There is no common agreement on the line between an acceptable and an unacceptable balance of harms and benefits in screening. In addition to test characteristics (sensitivity and specificity; positive and negative predictive value), the change to HPV testing as a primary screen changes the nature of the test and introduces new burdens for a substantial portion of the population. The balance of harms and benefits depends on patients and providers following guidelines intended to de-intensify screening (start later and extend intervals) and manage the intensity of treatment. Patient information needs—both for informed choice and for mitigating the burden of knowledge of high-risk oncogenic HPV status—and the time and resources for primary care to manage these needs would change. The perceived greater objectivity of genetic testing over cytological inspection may create a perception of greater medico-legal comfort with the test. However, the same exposure to risk shared between fewer cytologists may be the result, while communication among a larger number of technicians may create new medico-legal risks. There appears to be mixed, and largely speculative, views about the effects on equity of HPV as a primary screen. Some underscreened groups may be especially concerned about the HPV-based screening as

an STI test, and this may lower uptake; some groups may benefit from self-sampling as an outreach strategy targeted to those who experience barriers to clinical sampling.

Implementation Issues

Methods

To understand the issues associated with implementing HPV testing for primary cervical cancer screening, a literature search was conducted and stakeholders were consulted by phone and email. The methods were sequentially designed such that the results of the literature search were used to inform the need and scope of the stakeholder consultations. Information related to implementation issues was identified by searching the following databases: MEDLINE via Ovid; Embase via Ovid; CINAHL via EBSCO; and PubMed. Retrieval was limited to documents published since January 1, 2002. Results were limited to English- and French-language publications. Grey literature was identified by searching the Grey Matters checklist (www.cadth.ca/grey-matters),[3] which includes the websites of HTA agencies, clinical guideline repositories, and professional associations.

To augment the data collected from the literature review, consultations were conducted with targeted experts and stakeholders. Individuals were approached via email and invited to participate in a phone interview or to provide written responses to questions by email, at their convenience. Consultations took place with stakeholders and experts from the Canadian laboratory, pathology, and cancer specialty sectors. Consultations also took place with representatives from countries that are in the process of implementing HPV primary screening, namely England and the Netherlands. After qualitative coding, the final summary of content was organized by topic-specific categories chosen due to their relevance to health service delivery, with the intent to provide information to policy-makers regarding the operational requirements and supports that could help facilitate effective implementation of the recommendations of the expert committee. The categories were: program administration and change management; effects on laboratory structure and workflow; effects on screening participation rates; health care provider barriers and facilitators; and geographical, socioeconomic, and sociocultural issues.

Results

A number of key issues and themes emerged from the review of implementation issues associated with the potential implementation of HPV testing for primary cervical cancer screening. These key issues can be summarized as follows:

- A switch to HPV testing would be a large operational and culture shift for clinicians, patients, and laboratories. Good planning, funding, and coordination would be needed to make sure implementation runs smoothly.
- Acceptance of the new screening strategy by patients and clinicians has the potential to be a challenge — preventing a drop in screening participation rates could be important.
- A major change to laboratory configuration, workflow, and human resourcing would be required; this change could present a challenge.
- There are several facilitators that may help with overcoming these barriers; for example: education, step-wise rollout, organized screening programs, good IT systems, self-sampling.

Conclusions

Cervical cancer screening aims reduce the risk of disease and associated mortality by detecting and treating cancer precursors prior to progression to cervical cancer. Currently, the majority of those who undergo cervical cancer screening in Canada undergo screening through cytology testing, however the type of cytology and the approach to screening age and interval varies.

HPV testing is associated with higher sensitivity and lower specificity than cytology testing and is associated with higher colposcopy rates. Switching the primary test from cytology to HPV testing and increasing the screening frequency could improve the effectiveness and decrease the cost of cervical cancer screening in Canada (depending on willingness to pay) with limited harm in terms of higher risk of cervical cancer. Some of the strongest patient preferences will not be affected by a change in screening modality from cytology testing to HPV. For example, both

require a cervical cell sample, and therefore the potential for embarrassment, pain, and logistical inconvenience of that procedure is unchanged. The importance of the relationship between patient and health care provider will also continue to be important.

A change to an HPV-based screening approach would represent a change for all jurisdictions and stakeholders throughout the screening process.

Revision History

Section	Date	Description/Changes Made	Reason for Change
Clinical Review		Changed assessment tool from ROBINS-I to the Newcastle-Ottawa Scale for non-randomized studies	For time and resource efficiencies, the Newcastle-Ottawa Scale was used to guide the quality appraisal.
Research Questions (all sections)	June 2018	Wording changes	Wording changes made throughout to use gender inclusive language.
Economic Evaluation		Scope of the cervical cancer considered in the economic model is specific to squamous cell carcinoma.	Limited clinical data was identified from the clinical review on how diagnostic test accuracy of HPV and cytology test may differ in terms of detecting precursor lesions of adenocarcinomas.
Patient Perspectives and Experiences	February 2017	Research question refined to: What barriers, facilitators, and preferences about cervical cancer screening are reported by women living in Canada and countries with comparable healthcare contexts? a. How do these differ across social identity groups?	Reflect changes in search strategy and literature available, as described in protocol
Patient Perspectives and Experiences	February 2017	Expanded search criteria to include any modality of primary, population-based cervical cancer screening, not just HPV testing	Literature returned from HPV testing search protocol was deemed insufficient for a meaningful review (< 15 papers).
Patient Perspectives and Experiences	February 2017	Eligibility criteria revised to require mention of HPV or pap smear or cervical cancer in the title of the article	Many articles relevant to cancer screening in general, but not specifically addressing cervical cancer screening. Findings from these articles were not helpful when considering HPV testing.

Context Rationale and Policy Issues

Worldwide, cervical cancer is one of the most frequently diagnosed cancers.[4] In 2017, it is estimated there were 1,550 cervical cancer cases diagnosed and 380 deaths in Canada.[1,5] The incidence of cervical cancer has been decreasing in the past three decades, largely due to routine screening with cytology.[5] A high grade squamous intraepithelial lesion is a collection of cancerous cells confined to the surface of the cervix.[6] When the cancerous cells spread beyond the surface, it is classified as invasive.[6] Squamous cell carcinoma (SCC) and adenocarcinoma account for the majority of cervical cancer, with 70% or more being SCC.[7]

HPV and cervical cancer

Human papillomavirus (HPV) is transmitted through sexual as well as skin to skin contact.[4] It is one of the most common sexually transmitted infections in the world and about three out of every four sexually active Canadians will have at least one HPV infection at some point in their lives.[4] Infection with HPV can lead to the development of a variety of cancers including cervical, vulvar, vaginal, and penile, as well as cancer of the anus, mouth, and throat.[4]

HPV is a major risk factor for the development of cervical cancer and can be directly detected with diagnostic tests that detect the presence of the virus.[6] Approximately 40 HPV genotypes are known to be involved in genital HPV infections, 13 of which have been designated as high-risk HPV types due to their strong oncogenic potential.[2,8] HPV types 16, 18, 31, 33, 45, 52, and 58 are estimated to account for more than 90% of invasive cervical cancer[6] and 99% of cervical cancer is associated with HPV.[4] It is estimated that more than 80% of the population will acquire an HPV infection in their lifetime, with the majority (about 90%) of these infections being transient, resolving on their own within one to two years without causing any issues.[2,9,10]

HPV infection can now be prevented with vaccination.[6] There are several brands of HPV vaccines available in the market and can at least target HPV 16 and 18 that are considered highly oncogenic.[6] The immunization strategies vary in Canadian provinces.[11] School-based programs have been implemented in all Canadian provinces and territories with different eligible ages and dosing schemes.[11] Ontario, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador were the first to implement in 2007, and Nunavut was the last to do so in 2010.[11] The province of Quebec has the youngest eligible age targeting grade 4 and Ontario has the oldest targeting grade 8.[11] The first Canadians immunized for HPV infection due to school-based programs are currently younger than 25 years and many of them remain ineligible for routine cervical cancer screening.

Current Approaches for Screening and Detection of Cervical Cancer in Canada

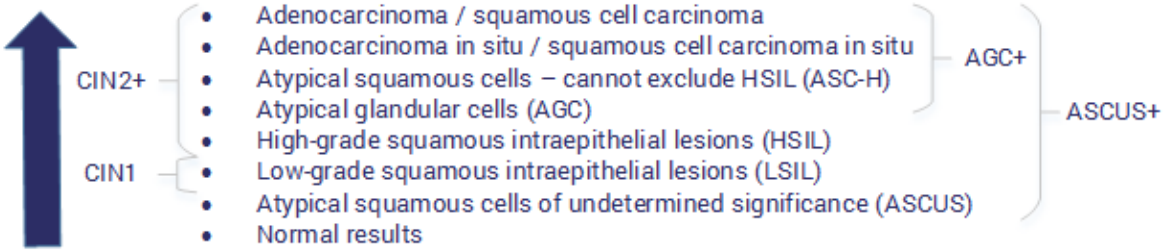
Screening tests are used to identify those people who are at risk of developing cancer.[6] Screening tests allow clinicians to identify changes in the body that are a signal that cancer may develop. A positive screening test does not mean a person currently has or will necessarily develop cancer in the future. Cervical cancer screening aims to reduce the risk of disease and associated mortality by detecting and treating precursor lesions before they progress to cervical cancer.[1,12] The results of a meta-analysis of 21 studies indicated that screening with conventional cytology or human papillomavirus (HPV) tests is beneficial and contributes to a lower risk of developing or dying from invasive cervical cancer.[13] In Canada, data shows that routine screening with cytology improves survival from cervical cancer; the lifetime risk of dying from cervical cancer is currently one in 100 for those who do not undergo screening with cytology and one in 500 for those who do.[14]

Cytology is the microscopic study of cells and their structure. Cytology testing is used to identify the presence of pre-cancerous cell changes in the cervix.[13] There are two types of cytology: conventional (also known as the Pap test) and liquid- based. Conventional cytology involves the collection of cells from the surface of the cervix which are then spread on a slide and visually examined for abnormalities in a laboratory.[6] If more than one test is required for a repeat or a triage test, a separate sample is required for each test to be performed. For liquid-based cytology (LBC), cells are collected in liquid vials and are prepared semi-automatically in the laboratory and then examined. In contrast to conventional cytology samples, a single sample obtained for LBC can be used to perform multiple different tests.

Abnormal cytology results vary in severity. The 2001 Bethesda System is the most commonly used cytology classification system in Canada.[1] It outlines the classification of results from least severe (normal results) to most

severe (adenocarcinoma or squamous cell carcinoma). Cytology test results classified as atypical squamous cells of undetermined significance or greater (ASCUS+) and results of atypical glandular cells or greater (AGC+) may require further diagnostic investigation with colposcopy and potentially biopsy and histology.[1] The Bethesda Classifications correspond with the severity of cervical intraepithelial neoplasia (CIN). The clinical significance of CIN can also be denoted by the following grades: CIN1 (mild dysplasia), CIN2 (moderate to marked dysplasia), and CIN3 (severe dysplasia to carcinoma in situ).[15] Approximately 1% of CIN1 and 12% to 30% of CIN2 or CIN3 cases progress to invasive cervical cancer.[8]

Figure 1: 2001 Bethesda System for the Classification of Cytology Results and Histology Classification [1]



AGC = atypical glandular cells; ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia.

Currently different screening programs and approaches have been adopted in Canada, which vary by province. There are minor differences in the approaches but all are based on regular cytology screening. Existing guidelines recommend that cervical cancer screening with cytology be done every two to three years starting at age 21 through to ages 65 to 70, depending on the jurisdiction.[1] The 2013 Canadian Task Force on Preventive Health Care guideline recommends routine screening with cytology every three years for participants between the ages of 25 and 69 years of age.[16] In a report updated in 2016, the Pan-Canadian Cervical Screening Network reported the following target for cervical cancer screening participation: no less than 80% of eligible participants 21 years to 69 years should be screened in the preceding 42 months,[1] which would correspond to approximately 9.5 million people screened.[17] From 2010 to 2013, the hysterectomy-adjusted participation rates ranged from 64.9% in Ontario to 73.8% in British Columbia.[11] Current screening strategies do not meet the Pan-Canadian Cervical Screening Network target.

From January 1, 2010 to June 30, 2013, the percentage of abnormal cytological results ranged from 3.9% in British Columbia and Prince Edward Island to 14.7% in New Brunswick.[1] These results are reported for a 12-month period. When a participant had multiple cytology results available in the same 12 month period, they were classified only by the most advanced cytology result available.[1] The percentage of negative cytology results ranged from 85.3% in New Brunswick to 96.1% in British Columbia and the Northwest Territories.[1] The least severe results (ASCUS) ranged from 1.6% in British Columbia and Alberta to 8.1% in New Brunswick and the most severe results (HSIL+) ranged from 0.2% in Northwest Territories to 1.0% in Manitoba.[1]

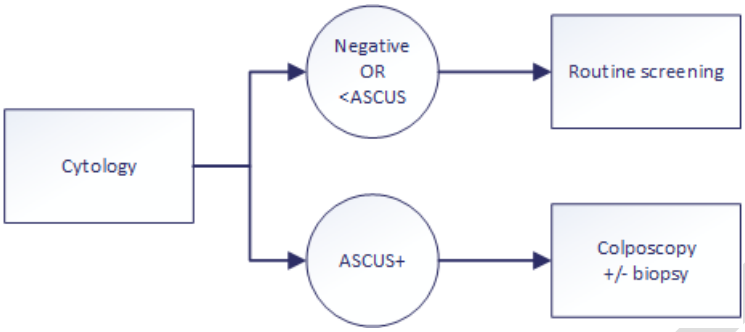
Assessment of the utility of screening tests

Diagnostic test accuracy outcomes, such as sensitivity and specificity, are measures of a screening test's clinical validity that are commonly reported in studies evaluating the performance of tests for cervical cancer screening.[18,19] Sensitivity is the ability of a test to accurately identify people with the disease.[6] Specificity is the ability of a test to accurately identify those who do not have the disease.[6] In the context of using cytology as a screening tool for cervical cancer, a true-positive would be an abnormal cytology results for a person with high-grade squamous intraepithelial lesions (HSIL), and a false-positive would be an abnormal cytology result in a person without confirmed HSIL.

Different testing pathways are used to conduct cytology testing in Canada. The cytology test can be used on its own to determine whether a person requires further investigation or treatment. This pathway is outlined in Figure 2. In this screening scenario, a positive result on cytology is a signal that further investigation is required. Colposcopy is a method used to take a closer look at the surface of the cervix under magnification.[20] This allows the clinician to visualize the cervix and identify any areas of abnormality, or cervical lesions.[20] Colposcopy may be conducted with, or

without, a biopsy to remove some of the abnormal cells for further examination under magnification (histology). If a HSIL or cervical cancer is identified through histology, the patient is referred to treatment. Treatment may involve removal of the cervical lesion for localized lesions.

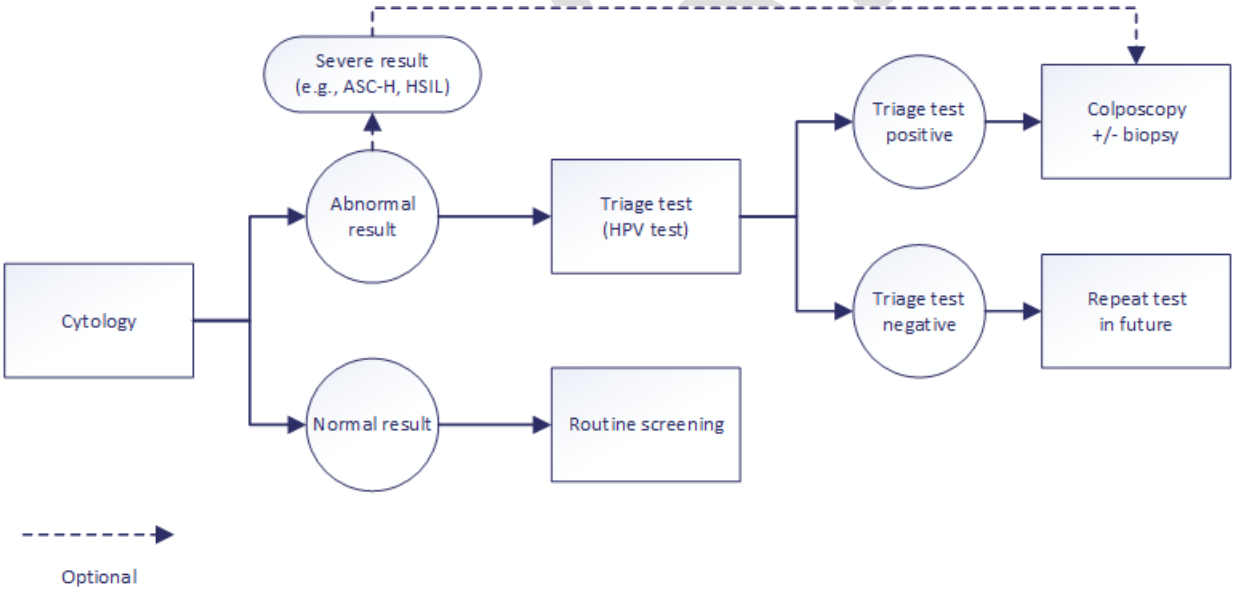
Figure 2: Cytology Screening Pathway



ASCUS = atypical squamous cells of undetermined significance.

Cytology testing can also be used in combination with other studies as a triage test, particularly HPV testing.[6] A triage strategy adopts two or more tests to increase the diagnostic efficacy.[21] This pathway is outlined in Figure 3. When an abnormal result is detected with the cytology test, an HPV test may be used to identify the presence of carcinogenic strains of HPV before deciding whether colposcopy is required. In Canada, this HPV triage test is not currently available in all provinces and may incur a cost to the patient.[4]

Figure 3: Cytology Screening with Triage Pathway



AGC = atypical glandular cells; ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesions.

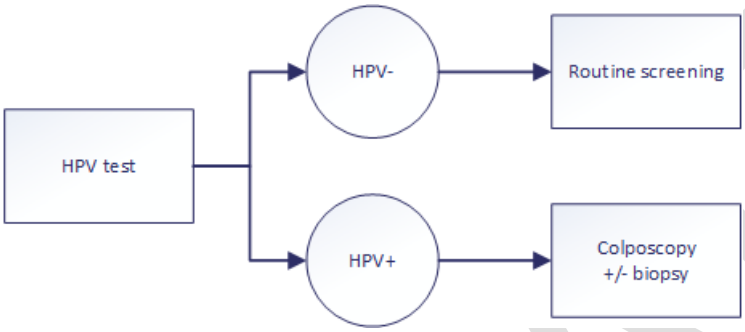
Proposed changes to routine cervical cancer screening: primary HPV testing

The strong causal link between HPV infection and cervical cancer provided the impetus for evaluating the use of HPV testing in screening for SIL and invasive cancer.[6] Generic HPV tests detect the presence of HPV DNA or RNA in a sample of cervical cells, with a positive result indicating an HPV infection.[2,9] Partial genotyping tests indicate both

whether HPV is present and, if so, whether high-risk variants of the virus (16 or 18 or others) are present in the sample.[6] Full genotyping tests identify all of the HPV strains present in the sample.[6] Clinicians usually collect the samples required for HPV testing; however, studies have been conducted to examine the impact of self-sampling (i.e., the screening participant collects their own cervical sample for testing) on participation rates and DTA.[22]

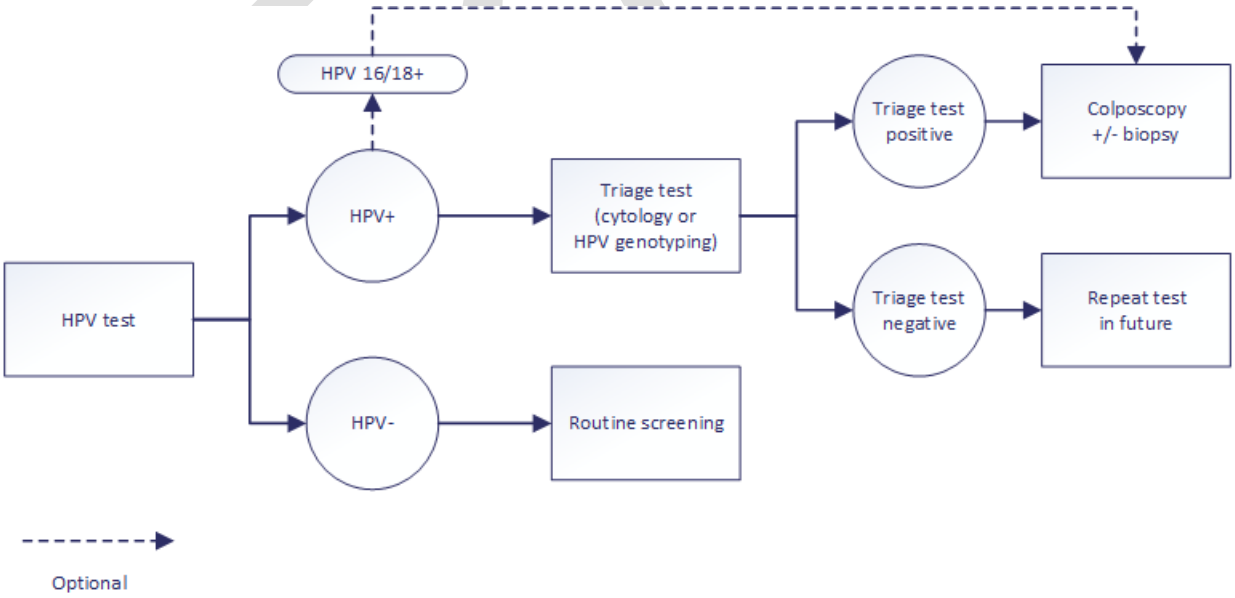
HPV tests can be used alone, administered at the same time as cytology testing (co-testing), or in combination with one or more triage tests.[21] Primary HPV testing alone is outlined in Figure 4**.** In countries that use HPV testing for primary cervical cancer screening, HPV testing is not used alone as a screening test.[6] Due to the high numbers of screening participants who will test positive for HPV due to transient infections, using it as the only test in the pathway will lead to a large number of participants being sent for further invasive testing that may prove to be unnecessary and also potentially costly to the health care system.[6] Due to the concern about the excessive false-positive results associated with HPV testing alone, several triage strategies have been considered in the HPV testing pathway.[6] Triage testing can be done using cytology, HPV tests, or genotyping for high-risk HPV strains (Figure 5).[6]

Figure 4: HPV Testing Pathway



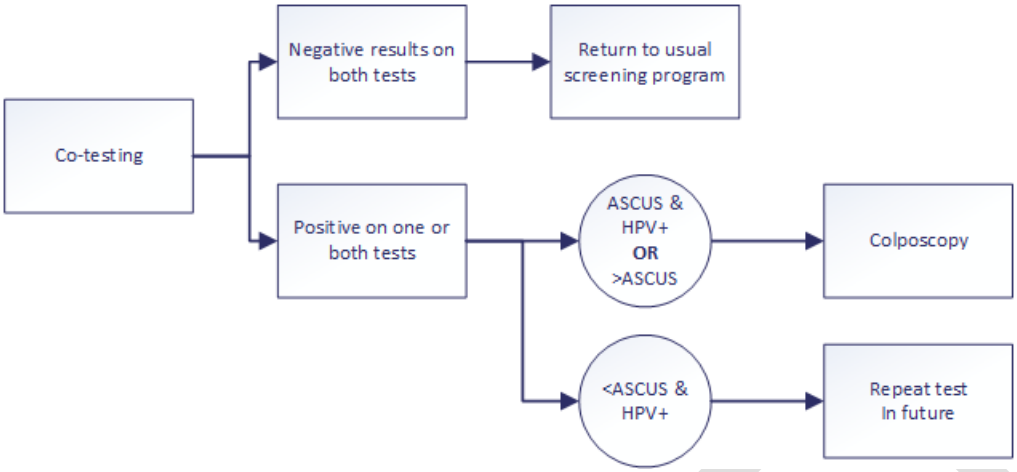
HPV = human papillomavirus.

Figure 5: HPV Testing with Triage Pathway



HPV = human papillomavirus.

Figure 6: Co-Testing Pathway



ASCUS = atypical squamous cells of undetermined significance; HPV = human papillomavirus.

Primary HPV screening has not been implemented in Canada, although it is under consideration in a number of provinces. Notably, the evidence-based guidelines developed to inform the Ontario Cervical Screening Program recommend HPV testing for primary cervical screening, with cytology triage of HPV-positive results,[12] though this practice has not yet been funded but is sometimes available to patients willing to pay for the test out of pocket.[23] Internationally, a transition from cytology to primary HPV testing for cervical cancer screening is proceeding or planned in several countries, including Mexico, Italy, the Netherlands, Australia, Sweden, and Scotland.[8,24] European guidelines recommend primary HPV testing for organized, population-based screening.[25] In the US, co-testing (outlined in

Figure 6) is recommended at five-year intervals between the ages of 30 and 65.[10,26] It has been suggested that, with HPV testing, the screening interval can be extended to at least five years for those with a negative HPV test result, given findings that suggest significantly lower risk of CIN and cervical cancer after a negative HPV test compared with a negative cytology test.[8,10,12,18,25]

Potential advantages and disadvantages of primary HPV testing

HPV-based screening is expected to offer some benefits over cytology, such as higher sensitivity, the potential for increasing the time interval between screening visits, the potential to initiate screening at an older age (thus reducing the number of times screening occurs), and the opportunity to implement self-sampling to encourage screening participation in under- and never-screened populations.[8,27] Based on the evidence, it has been suggested that HPV testing as standalone primary screening strategy or in co-testing should not be used for participants under 30 years of age.[8,10,12,18,25] The higher rate of transient HPV infections among those younger than 30 years combined with the high sensitivity of HPV testing could lead to false-positives in the context of cervical cancer screening (i.e., HPV-positive test results in those without precancerous cervical lesions). This could lead to unnecessary worry for the patient as well as unnecessary interventions, such as referral to colposcopy for those without precancerous changes.[8,10,12,18,25]

There are also potential limitations or disadvantages to adopting HPV testing for routine cervical cancer screening. Of note, due to the sensitivity of HPV testing, there is concern that it may lead to the overdetection of HSIL and thus unnecessary interventions for both transient HPV infections and less serious cervical lesions that would have otherwise resolved on their own, subjecting those affected to unnecessary physical and mental burdens.[8,12] The

guidelines developed for the Ontario Cervical Screening Program highlight that educating patients and practitioners will be an important component of implementing HPV primary testing.[12]

Challenges to primary HPV testing

In addition to issues regarding the potential for detecting more HPV infections and thus having a higher rate of positive results using HPV-based testing, the implementation of a screening program raises a number of issues regarding equity of access to health care services (both the screening services and follow-up diagnostic testing and treatment) and, by extension, health outcomes within different groups – particularly those who may already be at an increased risk for health inequities. The potential extension of the screening interval associated with HPV-based screening may be perceived as an attempt to take care away from those who need it.[22] There are also a number of potential challenges to be considered around the changes to the workflow of clinicians and laboratory specialists. A change in testing strategy may change the number or make up of the laboratory services required in a region and the associated workforce that is required.

Policy Issues

Currently, all Canadian provinces and territories provide access to opportunistic or organized cervical cancer screening with cytology.[1] While the implementation of cytology testing over the last few decades in Canada has contributed to a significant reduction in cervical cancer incidence and mortality, low sensitivity is a known limitation of this test.[1,2] In view of the anticipated higher sensitivity of HPV testing, some experts and stakeholders have called for HPV testing to be used in Canada as the primary screening tool, replacing the cytology test.[8,12] As noted, to date, no Canadian jurisdiction has implemented routine primary HPV testing.[1] However, a number of Canadian jurisdictions are currently considering, planning, or piloting primary HPV testing for their cervical cancer screening programs.[1,12,28]

Policy Question

Should HPV testing replace cervical cytology in Canadian jurisdictions as the primary screening tool for cervical cancer? If yes, what criteria, including appropriate screening interval and ages to start and stop screening, should guide HPV-based cervical cancer screening programs in Canada?

Objectives

The objective of this HTA is to address the policy question by assessing the diagnostic test accuracy, clinical utility, safety, cost-effectiveness, patients' experiences and perspectives, ethical issues, and implementation issues of HPV testing as a primary screening tool for cervical cancer screening. This HTA will be conducted to inform decision-making, policy development, capacity planning, and recommendations around primary HPV-based testing for cervical cancer screening.

Research Questions

The HTA addressed the following research questions. For the purposes of this HTA, the diagnostic efficacy of primary HPV testing as a primary screening tool for cervical cancer includes evidence regarding the diagnostic test accuracy and clinical utility (including safety and other clinical outcomes) of that screening strategy. Details on the specific interventions and outcomes are included in Table 1.

1. What is the diagnostic efficacy of primary high-risk HPV testing, with or without cytology triage, compared with primary cytology-based testing for asymptomatic cervical cancer screening?

2. What are the diagnostic efficacies of primary high-risk HPV testing strategies compared with each other for asymptomatic cervical cancer screening?

3. What is the comparative cost-effectiveness of primary high-risk HPV testing, with or without cytology triage, compared with primary cytology-based testing for asymptomatic cervical cancer screening Canada?

4. What are the perspectives of adults eligible for cervical cancer screening, their family members, and their caregivers regarding the value and impact of HPV testing for cervical cancer screening on their health, health care, and lives?

5. What ethical issues are raised by HPV testing for cervical cancer screening and how might they be addressed?

6. What are the main challenges, considerations, and enablers to implementing HPV testing for primary cervical cancer screening in Canada?

Separate reviews and analyses have been conducted to address each research question. Each is presented in a separate chapter that outlines the specific research methods used and results.

Clinical Review

Methods

Study Design

A systematic review was conducted to address both clinical research questions:

1. What is the diagnostic efficacy of primary high-risk HPV testing, with or without cytology triage, compared with primary cytology-based testing for asymptomatic cervical cancer screening?

2. What are the diagnostic efficacies of primary high-risk HPV testing strategies compared with each other for asymptomatic cervical cancer screening?

A protocol was written a priori and registered on PROSPERO (CRD42017058463). All changes to the protocol were identified, and reasons for the changes are provided in a Revision History table and in a published Protocol Amendment.

Literature Search Strategy

The literature search was performed by an information specialist using a search strategy peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist.[29] The complete search strategy is presented in Appendix 1.

For the clinical search, published literature was identified by searching the following databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, the Cochrane Database of Systematic Reviews via Ovid, the Cochrane Central Register of Controlled Trials via Ovid, the Database of Abstracts of Reviews of Effects (DARE) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were HPV testing, cervical cancer, diagnostic test accuracy, and screening.

No filters were applied to limit retrieval by study type. This search updates a previous literature search initially conducted in 2002 for a CADTH Technology Report on Liquid-Based Cytology and Human Papillomavirus Testing in Cervical Cancer Screening.[30] Retrieval for the current search was limited to documents published since January 1,

2002, supplemented with relevant studies from the previous CADTH report. The search was also limited to English-language and French-language publications. Conference abstracts were excluded from the search results.

The initial searches were completed by March 2017. Regular alerts were established to update the searches until the final report was published. Regular search updates were performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review were incorporated into the analysis if identified prior to the completion of the stakeholder feedback period of the final report. Any studies that were identified after the stakeholder feedback period are described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching the CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters), which includes the websites of HTA agencies, clinical trial registries, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials, and a Google alert was created for the topic of HPV screening.

Selection criteria

The selection criteria for clinical research questions 1 and 2 can be found in Table 1.

Table 1: Selection Criteria for Research Questions 1 and 2 – Clinical Review

Population	
• Asymptomatic adults eligible for cervical cancer screening (≥ 21 years of age, or age at which screening starts in the jurisdiction) • Subgroups: ○ Age (e.g., ≥ 21 years, ≥ 25 years, ≥ 30 years) ○ Vaccination status (i.e., HPV-vaccinated, stratified by vaccine type [i.e., bivalent, quadrivalent, or nine-valent]; not HPV-vaccinated) ○ Relevant patient characteristics that stratify health opportunities and outcomes as described by the PROGRESS-Plus list[31a] • Exclusions: ○ Those with known cervical cancer or previous treatment for HSIL ○ Adults without a cervix ○ High-risk adults who would otherwise be eligible for cervical cancer screening (e.g., immunocompromised, HIV-positive)	
Index Test	
Diagnostic Test Accuracy • Primary high-risk HPV testing[b] with HPV nucleic acid tests[c] alone • Primary[b] high-risk HPV testing with HPV nucleic acid tests[c] followed by LBC or conventional cytology-based testing for HPV-positive samples *Clinical Utility* • Primary high-risk HPV testing[b] with HPV nucleic acid tests[c] and subsequent management of patients with confirmed disease[d] • Primary[b] high-risk HPV testing with HPV nucleic acid tests[c] followed by LBC or conventional cytology-based testing for HPV-positive samples and subsequent management of patients with confirmed disease[d] • Subgroups: • Method of sample collection for high-risk HPV testing (i.e., self-collected, clinician-collected) • Type of assay (i.e., generic, partial genotyping, or full genotyping) • HPV test threshold for a positive result (e.g., 1 pg/mL, 2 pg/mL) • Screening interval (e.g., every year, every 2 years, every 3 years, every 5 years)	
Comparators	
Q1 *Diagnostic Test Accuracy*	***Q2*** *Diagnostic Test Accuracy*

Table 1: Selection Criteria for Research Questions 1 and 2 – Clinical Review

• Primary conventional cytology-based testing (Pap smear) alone[e] • Primary conventional cytology-based testing (Pap smear)[e] followed by high-risk HPV testing of cytology-positive samples • Primary LBC testing alone[e] • Primary LBC testing[e] followed by high-risk HPV testing of cytology-positive samples *Clinical Utility* • Primary conventional cytology-based testing (Pap smear)[e] and subsequent treatment of patients with confirmed disease • Primary LBC testing[e] and subsequent treatment of patients with confirmed disease[d]	• Primary high-risk HPV testing strategies[b] compared with each other • High-risk HPV and cytology co-testing *Clinical Utility* • Primary high-risk HPV testing strategies[b] and subsequent treatment of patients with confirmed disease[d] compared with each other • HR-HPV and cytology co-testing and subsequent treatment of patients with confirmed disease[d]
Reference Standard	

• Colposcopy with histologic examination of tissue specimens, when indicated.
• Reference standard applied to:
  ○ All patients
  ○ All screening test-positive patients and a subset of screening test-negative patients
  ○ All screening test-positive patients
 	
Exclusions:
  ○ Reference standard applied to a subset of screening test-positive patients	

Outcomes	

• Number or proportion of people who accepted screening
• Diagnostic test accuracy
  ○ Number and proportion of people positive and negative on each test[f] (TP, FP, TN, FN)
  ○ Sensitivity, specificity, PPV, NPV, PLR, NLR, DOR to screen for high-grade cervical lesions (HSIL or CIN2+, AGC, AIS) and/or invasive cervical cancer (squamous cell carcinoma or adenocarcinoma)[g]
• Harms of screening
  ○ Anxiety, as measured by standardized scales
  ○ Adverse pregnancy outcomes
  ○ Impacts of false-positives and false-negatives on people (e.g., unnecessary referral to colposcopy)
  ○ Over-diagnosis, including treatment, and related impacts on people (e.g., cervical incompetence, adverse pregnancy outcomes)
  ○ Any other reported harms
• Clinical utility
  ○ Number or proportion of people referred to colposcopy
  ○ Number or proportion of people treated or referred for treatment
  ○ Quality of life, as measured by standardized scales
  ○ Cervical cancer incidence
  ○ Cervical cancer-related morbidity
  ○ Cervical cancer-related mortality	

Study Design	

• Systematic reviews[a]
• Primary studies published after the latest search date of any included systematic reviews including the following types of studies:
  ○ RCTs
  ○ Cohort studies, prospective and retrospective
  ○ Cross-sectional studies	

[a] Systemtic reviews eligible for inclusion were those that systematically searched the literature databases, selected the literature based on pre-specified population, intervention, comparator, and outcome (PICO) criteria, critically appraised the included studies, and drew conclusions with appropriate data synthesis methods.

Table 1: Selection Criteria for Research Questions 1 and 2 – Clinical Review

○ Diagnostic test accuracy studies Exclusions: ○ Case-control studies ○ Case reports ○ Case series ○ Review articles ○ Editorials, letters, and comments ○ Conference abstracts, thesis documents
Study Setting or Facilities for Laboratory Analysis
• Any setting
Country
• Canada, United States, Australia, New Zealand, United Kingdom, countries from the European Economic Area
Literature Search Time Frame
• 2002 to present[h]

AGC = atypical glandular cells; AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia; DOR = diagnostic odds ratio; FN = false-negative; FP = false-positive; HPV = human papillomavirus; HR = high-risk; HR-HPV = high-risk human papillomavirus; HSIL = high-grade squamous intraepithelial lesions; LBC = liquid-based cytology; LEEP = loop electrosurgical excision procedure; NLR = negative likelihood ratio; NPV = negative predictive value; Pap = Papanicolaou test; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = randomized controlled trial; TN = true-negative; TP = true-positive.

[a] Evidence from the ethics literature and preliminary results from the ethics analysis for this project will be used to identify specific patient characteristics that are relevant for population subgroup analyses. Potentially relevant patient characteristics from the PROGRESS-Plus list include, but are not limited to, place of residence, race/ethnicity/culture/language, gender and sex, religion, education, socioeconomic status.

[b] Primary HR-HPV testing means that the HR-HPV test is the initial test in a screening pathway. This includes pathways in which positive results on the HR-HPV test are followed directly by colposcopy or a cytology-based triage test. Co-testing (HR-HPV and cytology at the same time) were included for DTA outcomes as results can be reported as if HPV testing was performed alone as a primary test.

[c] Commercial HPV tests will be considered for inclusion if they detect at least some of the following identified HR-HPV types: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.[8] This may include generic assays, partial genotyping assays, and full genotyping assays. Examples of eligible HPV tests include: Cobas 4800 HPV Amplification/Detection Kit, Roche Molecular Systems Inc.; Linear Array HPV Genotyping Test, Roche Molecular Systems Inc.; Aptima HPV assay, Hologic, Inc.; Aptima HPV 16 18/45 genotype assay, Hologic, Inc.; Cervista HPV HR assay, Hologic, Inc.; Abbott RealTime High-Risk HPV, Abbott Molecular; Digene DML-2000 HPV Test Hybrid Capture II, Qiagen Sciences LLC; Xpert HPV test, Cepheid.

[d] Treatment of HSIL may include excisional therapy (e.g., LEEP, surgical conization, laser vaporization conization) or ablative therapy (e.g., cryotherapy, laser ablation); treatment for invasive cervical cancer may include surgery, chemotherapy, or radiation.

[e] Primary cytology-based testing means that the cytology test (conventional Pap smear or LBC) is the initial test in a screening pathway. This includes pathways in which positive results on the cytology test are followed directly by colposcopy or HR-HPV testing.

[f] Thresholds for a classification of positive and negative on each index test as defined by the study will be reported.

[g] Totals for HSIL or CIN2+ (with a description of whether that number includes or excludes cases of invasive cervical cancer) will be reported as available.

[h] The time frame was extended to the present to identify literature published since the initial search conducted in 2002 for the CADTH Technology Report on Liquid-Based Cytology and Human Papillomavirus Testing in Cervical Cancer Screening.[30]

Inclusion criteria

The population of interest was asymptomatic adults with a cervix. Studies were considered for inclusion if conducted in countries with a health care context comparable to Canada's, so that populations with comparable levels of cervical cancer risk were evaluated. Eligibility for inclusion was limited to studies conducted in Canada, the US, Australia, New Zealand, the United Kingdom, or a member of the European Economic Area. Studies with mixed settings of countries that did and did not meet the review inclusion criteria were included if the results pertaining to the countries that did meet inclusion criteria were reported separately. If results from the countries of interest were not reported separately, those with mixed study locations were included if at least 80% of the countries met the inclusion criteria. A SR was included if at least 80% of the studies included in the analysis were conducted in the countries outlined in Table 1.

Studies assessing commercial high-risk HPV nucleic acid tests were considered for inclusion if they detect at least some of the following 13 high-risk HPV types: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Eligible classes of HPV tests include generic assays, partial genotyping assays, and full genotyping assays. These include tests that use signal amplification (e.g., QiagenHybrid Capture 2 test); nucleic acid amplification techniques, such as polymerase chain reaction tests (e.g., Cobas 4800 HPV test); and probe amplification or modification assays (e.g.,

Cervista HPV HR assay). Where possible, results were reported by threshold of HPV test positivity (e.g., 1 pg/mL or 2 pg/mL).

Eligible cytology tests included Pap tests with conventional cytology-based methods and liquid-based cytology methods (e.g., ThinPrep, SurePath).

The reference standard was colposcopy, with histologic examination of tissue specimens, when indicated.

There was no restriction regarding length of follow-up.

Exclusion criteria

Studies were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or primary studies published before the included SRs. Studies that selected patient samples for inclusion on the basis of cervical cytology results (e.g., known ASCUS, known LSIL cytology results) were excluded. Studies were also excluded if they focused exclusively on HPV types not listed in Table 1 or exclusively evaluated screening interventions with a focus on in situ hybridization, p16 immunostaining, or HPV viral load. Evaluations of earlier versions of commercial tests that have been replaced (e.g., Hybrid Capture 1) were excluded. Studies comparing high risk HPV testing with visual inspection with acetic acid or visual inspection with Lugol's iodine were excluded, as these screening methods are more common in low-resource settings and are not representative of current cervical cancer screening practices in Canada.

Screening and Selecting Studies for Inclusion

Systematic reviews

In order to identify SRs from the broad literature search results, a string of keywords, including ("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta-analyses" OR "meta analysis" OR "meta analyses" OR "metaanalysis" OR "metaanalyses") was created in order to aid in targeting systematic reviews and/or meta analyses for screening.

These keywords were applied to all citations, including literature search update alerts, retrieved through electronic database searches. Two reviewers independently screened the titles and abstracts of the resulting citations in duplicate. The full-text of potentially eligible citations was retrieved, and then screened in duplicate in accordance to the eligibility criteria in Table 1. Discrepancies between reviewers were resolved through discussion.

To inform the inclusion decisions, important SR characteristics (e.g., objectives, PICOS criteria, and study design elements [types of studies included, literature search timeframes, and quality appraisal tools used]) were extracted from the full text of the publications into standardized tables by one reviewer. A second reviewer verified the extractions. SRs were considered for inclusion if they had inclusion criteria that exactly matched, were broader than, or were included by the PICOS criteria summarized in Table 1. SRs that had a different population, intervention, comparators, outcomes, or country settings were excluded.

Reviewers used the systematic review management software DistillerSR[32] (Evidence Partners, Ottawa, Canada) to facilitate screening and selection of SRs.

Primary studies

As relevant SRs were identified, as per the Agency for Healthcare Research and Quality (AHRQ) guidance,[33] where the search was last updated more than one year ago, citations arising through the full CADTH literature search were screened in order to identify primary studies that have been published since the earliest literature search cut-off date. The identified primary studies were screened independently and in duplicate by two reviewers to assess their relevance according to the PICOS criteria outlined in Table 1. DistillerSR[32] (Evidence Partners, Ottawa, Canada) was also used to facilitate screening and selection of primary studies.

Methodological Quality Assessments

Systematic reviews

A review of the methodologic quality of each potentially eligible SRs was done independently by two reviewers using the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2 checklist as a guide.[34] AMSTAR 2 is a broad critical appraisal instrument designed primarily to guide appraisals of SRs of studies of healthcare interventions.[34] It is not intended for the assessment of SRs of diagnostic test accuracy studies; however, in the absence of a validated appraisal tool for SRs of diagnostic test accuracy studies the criteria in the AMSTAR 2 checklist were used as a guide. The authors of the AMSTAR 2 checklist have defined seven critical and nine non-critical domains, although these classifications were not strictly followed in this review given different implications for SRs of diagnostic test accuracy studies.[34] Appraisals were conducted independently and in duplicate, and discrepancies were resolved through discussion. Quality scores and overall confidence ratings were not derived. A summary table outlining the quality assessment of the included SRs is provided in Table 39, which were used to guide inclusion decisions. Only SRs deemed by the two independent reviewers to be of sufficient quality were included in this review. SRs deemed to be of insufficient quality were excluded. The appraisal results were used to inform subsequent discussion on the possible sources of heterogeneity in SRs.

Primary studies

Primary studies that investigated the diagnostic test accuracy (DTA) of HPV tests or testing strategies were evaluated using the QUADAS-2 instrument.[35] For the other outcomes of interest, including test acceptance and clinical utility, the quality of RCTs was assessed using the Cochrane Risk of Bias Tool,[36] and the quality of non-randomized studies, including cohort and cross-sectional studies,was assessed using the Newcastle-Ottawa scale.[37] All quality appraisals were conducted independently and in duplicate by two reviewers. Disagreements were resolved through discussion.

Data extraction

Relevant data included both descriptive data and results reported in all included studies. Separate standardized forms were used to extract relevant information from both SRs and primary studies. From SRs, descriptive data included information about included primary studies, search strategies, participants, interventions, comparators and outcomes measures used. In addition, information about the conduct and results of risk of bias assessments of the primary studies were extracted. For primary studies, data were extracted on study characteristics, study design, population characteristics, intervention, comparators, outcomes, and conclusions. Two reviewers piloted the extraction forms in duplicate among a number of individual included primary studies and SRs. When complete, the reviewers compared the results and repeated the process until the authors' extraction results were consistent with each other. The forms were updated during the pilot phase to reflect additional details reported by the included studies that were relevant to the outcomes of interest. Once consistency was reached, data from each included study was then extracted by one reviewer and checked for accuracy by a second reviewer. Disagreements were resolved through discussion until consensus was reached.

Data analysis methods

All outcome data from both SRs and primary studies were tabulated, summarized narratively, and presented, by outcome, as they relate to each research question. Results from systematic reviews are presented first followed by the results for primary studies. For each outcome a table was prepared to report results, and is accompanied by a narrative summary that describes results within and across studies. Within the summary, attention is paid to describing the direction and size of observed effects and consistency in effects across studies. When differences were observed, an attempt is made to explain those differences by study and patient characteristics. For each outcome of interest, narrative synthesis was conducted for the overall study population and for the subgroups of interest, where possible.

Systematic reviews

For outcomes where meta-analysis results were available, the range of individual study estimates, pooled estimates, and confidence intervals were reported. For SR results where meta-analysis was not possible, the range of individual study estimates was reported, if provided.

When more than one SR addressed an outcome of interest; a matrix of studies included across multiple SRs was constructed. Information regarding the primary studies included in multiple SRs was tabulated to illustrate any overlap between SRs, both generally and by outcome.

Heterogeneity was explored within and between SRs. Within each SR, where possible, the research team reported and discussed any issues of heterogeneity in the primary studies as reported by the SR authors. Had there been outliers in the analyses of the SRs or heterogeneity that was not adequately addressed by SR authors, the CADTH team would have examined the primary studies in order to investigate sources of heterogeneity. Between SRs, if more than one SR was identified for an outcome, the concordance or discordance of SR results would have been examined. If results had been found to be discordant, SR characteristics, for example eligibility criteria or SR quality, would have been explored in an attempt to explain the discordance.

Primary studies

For any primary studies included after the search date of any included SR, the individual estimates for each outcome were reported alongside SR results with confidence intervals, where available. All results were summarized narratively. Meta -analysis was not undertaken, as the inclusion of primary studies was intended to update and assess concordance or discordance with the results of the SRs.

Once all outcome data were extracted and reported, for each outcome, the results of included primary studies were compared with those of the SRs. Concordance or discordance of the results between the SRs and the primary studies was assessed based on the clinical and methodological characteristics of the studies, for example HPV test or testing strategy used, participant characteristics and study quality.

Results

Quantity of research available

Systematic reviews

A flow diagram illustrating the literature selection process for SRs is provided in Appendix 2.

The authors screened 7,128 citations identified through the literature search strategy outlined for potentially eligible SRs. One hundred and sixty-nine citations from the original set of results were combined with three relevant SRs identified from media screening and the 173 titles and abstracts were further assessed for relevance to this review. After title and abstract screening, 39 citations were deemed to be potentially relevant by consensus. These 39 citations were screened against the PICO criteria a second time resulting in 19 SR publications being ordered for full-text review.

Fifteen SRs were excluded for various reasons described in Table 38 while four SRs[6,22,38,39] were determined to be relevant to the inclusion criteria and were included. The relevant SRs were produced by Melnikow et al. for the AHRQ,[39] the Health Information and Quality Authority (HIQA),[6] Koliopoulos et al. for the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group,[38] and Verdoodt et al.[22] A list of excluded studies, with reasons for exclusion after full-text review, is provided in Table 38.

Final inclusion decisions regarding each SR were made by individual outcome as no single existing SR was able to address all of the outcomes relevant to the research questions. The four included SRs reported outcomes relevant to the diagnostic efficacy of primary HPV testing, with or without cytology triage, compared with primary cytology-based testing for cervical cancer screening of asymptomatic women. The SR produced by HIQA[6] reported outcomes relevant to research question two, which addresses the diagnostic efficacies of primary high-risk HPV testing strategies compared with each other for asymptomatic cervical cancer screening. All were included in this review because collectively they assess different aspects of diagnostic efficacy, and each was deemed to be of high quality, in line with the inclusion criteria in Table 1.

The comparison of characteristics of the relevant SRs is presented in Appendix 5, Table 34 and Table 37.

Primary studies

The authors screened 2,723 citations identified through the literature search for eligible primary studies published after the included SRs. There were 2,655 citations excluded and 68 articles were ordered for full-text review. Forty-eight articles were excluded and 20 publications of 19 primary studies published from 2015 onwards were included for narrative synthesis. All included primary studies were used to address research question one. No relevant primary study was identified to address research question two. The flow diagram is provided in Appendix 3. A list of excluded studies is available in Table 33.

Summary

Four SRs,[6,22,38,39] 9 RCTs,[40-47,48] 10 prospective cohort studies,[49-58] and one retrospective cohort study[21] were identified to be included into this review. Twenty-four publications (four SRs, 9 RCTs, and 10 prospective cohort studies, and one retrospective cohort study) were used to address research question one.[6,21,22,38-56,57,58] One SR[6] was used to address research question two. No primary studies were eligible to address research question two.

Study characteristics

General information about included systematic reviews

The characteristics of the four included SRs are summarized in Table 34. Generally, the aim of the SRs was to assess the use of high-risk HPV testing as part of cervical cancer screening strategies. Each SR approached the topic slightly differently. The Cochrane SR[38] and the HIQA SR[6] assessed the DTA of HPV tests when used for cervical cancer screening. Melnikow et al. reviewed the benefits and harms of using HPV testing for cervical cancer screening.[39] Verdoodt et al.[22] aimed to evaluate the impact of different recruitment strategies on adherence to screening.

The authors of three of included SRs searched for and included RCTs.[6,22,39] Given the focus on DTA outcomes, the Cochrane SR by Koliopoulos et al.[38] limited their literature search to cross-sectional and cohort studies and did not include RCTs in their analyses.

Melnikow et al. searched for articles published between 2011 and 2018 in six electronic databases.[39] There were eight RCTs, five cohort studies and one individual-patient-data metat-analysis included in Melnikow et al.[39] The HIQA SR included a search of MEDLINE and EMBASE for articles published between 2015 and April 2016 to supplement their previously published SR.[6] In the Cochrane SR[38] and Verdoodt et al.[22] two and three databases were searched respectively with a cut-off date of 2015.[22,38] There were 23, 40, and 16 primary studies included respectively by the authors of the HIQA SR, the Cochrane SR, and Verdoodt et al.[6,22,38] Meta-analysis was done in these three SRs;[6,22,38] however, the authors of the HIQA SR[6] chose not to meta-analyze results for their research question comparing various screening strategies to each other and, instead, narratively summarized the results of these studies. Similarly, due to the author's concern regarding heterogeneity between the included studies, Melnikow et al. conducted qualitative synthesis only.[39] Further, studies that were determined to be of low quality were excluded from analysis.[39]

There was overlap in the primary studies included in meta-analyses of Cochrane[38] and HIQA.[6] Due to the limited number of studies identified in both SRs that compared other HPV tests with cytology, the DTA meta-analyses of HPV tests were limited to the comparison of the Hybrid Capture 2 (HC2) test versus cytology. The two SRs included a combined total of 36 primary studies for this comparison.[6,38] The overlap of the primary studies is illustrated in Table 35and Table 36. Eleven primary studies were included in the meta-analyses of both SRs.[6,38] There were 25 studies included in the HIQA analysis[6] that were not included in the SR by Cochrane[38] and 12 studies included by the Cochrane SR[38] that were not included in the HIQA SR.[6] The analysis of screening strategies compared with each other was only done in the HIQA SR;[6] however, three of the studies included in the Cochrane SR[38] were also used in this analysis by HIQA.

General information about included primary studies

The study characteristics of the included primary studies are summarized in Table 40.

Twenty primary studies were identified for inclusion in this review. Nine RCTs (nine publications),[40-47,48] 10 prospective cohort studies[49-58] and one retrospective cohort study[21] were identified.

All 20 studies were used to address research question one. No primary studies were identified to address research question two.

Country of Conduct

Systematic reviews

Based on the location of the corresponding authors, Melnikow et al. were based in the US[39] the HIQA SR was conducted in Ireland,[6] the Cochrane SR was done in Greece,[59] and the SR by Verdoodt et al. was conducted in Belgium.[22]

As outlined in Table 1, the inclusion of publications in this review was limited to those that most closely align with the Canadian health care context. These criteria were applied to the primary studies included in the SRs that are included in this review. Melnikow et al. included studies that were published only in countries rated "very high" on the 2014 Human Development Index, as defined by the United Nations Development Program.[39] A specific list of those countries was not provided in the publication. The authors of the HIQA SR[6] limited inclusion of primary studies to those conducted in industrialized countries including: Canada, the US, the UK, Germany, France, Western and Eastern Europe, Italy, Norway, Switzerland, Taiwan, Chile, Japan, and Russia. Verdoodt et al. did not limit the countries that were considered for their SR; however, their analysis included primary studies conducted only in the Netherlands, Sweden, France, Sweden, the UK, Italy, Argentina, Mexico, and Finland.[22]

The authors of the Cochrane SR[38] did not place any geographical restriction on the studies included. Twenty-one of the 40 included studies were conducted in countries that did not meet the CADTH inclusion criteria: China (7 studies), India (3), Mexico (2), Congo (2), Chile (1), former Soviet Union (1), Latin America (1), Russia (1), Switzerland (1), Vanuatu (1) and Zimbabwe (1).[38] However, the authors of the SR conducted a sensitivity analysis that indicated the observed DTA of HPV tests was similar between high-income and middle-and low-income countries.[38] These analyses were therefore included in this review.

Primary studies

The nine included RCTs were conducted in Canada,[41,43,46] Australia,[44] Italy,[48] Norway,[42] Sweden,[40] the UK,[47] and the US.[45] Eight of the nine included cohort studies were conducted in Germany,[56] Greece,[54] Hungary,[51] Italy,[52,55,57] Spain,[50] and the US,[53] while one prospective cohort study was conducted in both Germany and Greece.[49] Two co-testing studies were conducted in the US.[21,60]

Patient population

Systematic reviews

The CADTH inclusion criteria are outlined in Table 1. For the comparison of primary screening with HC2 versus cytology testing, the authors of the HIQA SR[6] aimed to identify studies examining people aged 18 to 70 years of age participating in a cervical cancer screening program who were not being followed for previous cervical abnormalities. Twenty-one studies included routine screening populations and two studies included populations of potentially higher risk of cervical cancer (those who had a previous abnormal cytology result and those presenting to routine gynecological clinics).[6] Sample size ranged from 231 to 25,577. The age of screening participants in the individual studies was not reported.

For the comparison of HPV-based triage strategies versus each other, the authors of the HIQA SR[6] aimed to identify studies examining participants of a cervical screening program who had a positive primary HPV screening test result and were going to undergo triage testing. Fifteen primary studies were included. Sample sizes ranged from 364 to 40,901.[6] All of the included studies recruited individuals attending routine cervical cancer screening. The median age

of patients of one study (Verhoef et al.) was 42 years and was higher than the other included studies. Participants recruited in one study (Wright et al.) were younger than those in the other studies, with a quarter of participants ranging in age from 25 to 29 years.[6]

The SR by Melnikow et al.included studies involving participants aged 21 years or older who were using HPV testing for cervical cancer screening, with or without cytology triage.[39] Where possible, the authors grouped the results into two age groups: younger than 35 years of age and older than 35 years of age.[39] This grouping reflects the approved age ranges for HPV testing in the US.[39]

The Cochrane SR[38] included studies where all participants were presenting for routine cervical cancer screening and had received both HPV testing and cervical cytology followed by verification of the disease status with colposcopy.[38] Forty primary studies including more than 140,000 participants aged 20 to 70 years were included in the SR.

The SR by Verdoodt et al.,[22] included irregularly or never-screened participants, or those who did not respond to one or more invitations for conventional screening for cervical cancer. Inclusion in the SR was not limited by age; however, the participants in the included studies ranged in age from 25 to 29 years. The number of participants in the self-sampling arms ranged from 800 to 26,886.[22]

Primary studies

All of the included primary studies recruited persons eligible for routine screening programs.[21,40-49,50,51-58] The sample sizes ranged from 120[45] to 16,320[44] in the included RCTs and from 180[53] to 38,348[52] in the included non-randomized studies. Two cotesting studies included 41,955 and 99,549 participants.[21,58] In the included RCTs, participants' age ranged from a minimum of 21 years[45] to 56 years[40] to a maximum age ranging from 60 years[40] to 70 years.[43] In the included non-randomized studies, participants' age ranged from a minimum of 18 years[51] to 30 years[49,53,61] to a maximum age ranging from 55 years[54] to 65 years.[50,51,53] Population characteristics are summarized in Table 2.

Table 2: Sample Sizes and Ages of Participants in Primary Studies

	Sample Size (range)	Minimum Age (range)	Maximum Age (range)
Randomized controlled trials (n = 9)[40-48]	120[45] to 16,320[44]	21 years[45] to 56 years[40]	60 years[40] to 70 years[43]
Non-randomized studies (n = 11)[21,49-58]	180[53] to 99,549[21]	18 years[51] to 30 years[49,53,61]	55 years[54] to 65 years[50,51,53]

Interventions and comparators

Systematic reviews

The index and comparator tests of the included SRs are summarized in Table 34.

The Cochrane SR[38] and one question of the HIQA SR[6] originally aimed to include studies assessing any type of HPV test compared with cytology (LBC or conventional). The HIQA SR[6] eventually limited their analysis to include only the HC2 test after the authors discovered an insufficient number of studies evaluating the other types of HPV tests. Another question of the HIQA SR included a primary HPV test (HC2, Amplicor, Linear Array, Cobas, or GP5+/6+-PCR) combined with a reflex test that could be cytology, another HPV test, HPV genotyping, or infection marker testing. The triage strategies were compared with each other. The results for question two were not meta-analyzed.[6] The Cochrane SR[38] included a variety of HPV tests in their report (HC2, Aptima, Care HPV test, and NASBA+); however, most of their analyses focused on the comparison of HC2 with cytology (LBC or conventional). Melnikow et al. included HPV tests that detect high-risk strains of HPV (HC2 and PCR/GP5+/6+).[39] These were compared with cytology.[39]

The intervention and comparator used in Verdoodt et al.[22] were self-collected HPV sampling versus clinician-collected HPV sampling. The aim of the SR was to determine if there was an increase in screening adherence associated with

different methods of screening recruitment and self-sampling. There were three self-sampling scenarios identified: mail-to-all, opt-in, and door-to-door.[22] If mailed to all, self-samplers were mailed to the participants' homes.[22] The opt-in option waited for participants to request self-samplers after an invitation was sent to their homes.[22] The door-to-door approach involved study staff visiting participants at their home addresses.[22]

The types of HPV strains that could be detected by the HPV tests are compared in Table 3. The HPV types were grouped according to the International Agency for Research on Cancer (IARC) classification.

Table 3: The HPV types detected by the HPV tests

Detection methods	Devices	Partial genotyping capacity	HPV types and classification				
			IARC class I (high risk)			IARC class 2A (probably carcinogenic)	IARC class 2B (possibly carcinogenic)
			16, 18	31, 33, 45, 52, 58	35, 39, 51, 56, 59	68	12 others (26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85, 97)
Signal amplification	Hybrid Capture 2 (HC2) HPV DNA[6,21,38,41,42,52,55,56]	No	+	+	+	+	
Nucleic acid amplification techniques (NATs)	Cobas HPV DNA[6,38,40,51,54,58]	Yes	+	+	+	+	66 only
	Aptima HPV E6/E7 mRNA[6,38,41,50,56]	Yes	+	+	+	+	66 only
	NASBA HPV E6/E7 mRNA (5 types)[38]	Yes	+	31, 33, 45 only			

	NASBA HPV E6/E7 mRNA (9 types)[38]	Yes	+	+	35, 51 only		
	Care HPV DNA[38]	Yes	+	+	+	+	66 only
	PCR 13+[38]	Yes	+	+	+	+	
	Confidence HPV DNA[38,51]	Yes	+	+	+	+	66 only
	Multiplexed genotyping HPV DNA[49]	Yes	+	+	+	+	26, 53, 66, 73 and 82 only

933 + = all of the HPV types in the top row included. HIQA = Health Information and Quality Authority; HPV = human papilloma virus;
934 IARC = International Agency for Research on Cancer.

935

936 **Primary studies**

937 The index and comparator tests used in the included primary studies are summarized in Table 4. All included primary
938 studies compared one type of self- or clinician-sampled HPV test with clinician-sampled tests (that could be cytology
939 or another HPV test).[40-57] Among the nine RCTs, two compared clinician-sample HPV tests to cytology,[40,41] and
940 seven compared self-sampled HPV tests with cytology.[42-48] Among the 11 non-randomized studies, six compared
941 clinician-sample HPV tests to cytology,[49,51,52,54-56] one compared self-sampled HPV tests to cytology,[53] and two
942 compared HPV and cytology cotesting to cytology.[50,57] Kocsis et al. also compared two HPV tests, Confidence versus
943 Cobas.[51] Cook et al. reported the predictive values of Aptima and HC2 HPV tests based on a subset of the
944 Intervention Arm in the HPV FOCAL Trial.[41]

Table 4: Index and Comparator Tests in Primary Studies

First Author, Year Trial Name	Index Test	Comparator Test
Randomized Controlled Trials		
Lamin, 2017[40]	HPV test (Cobas) with cytology triage of HPV positive patients	Cytology with HPV triage (Cobas) of low-grade cytological abnormalities
Cook, 2017[41] **HPV FOCAL Trial, subset of the Intervention Arm**	Clinician-collected HPV test (Aptima)	Clinician-collected HPV test (HC2)
Enerly, 2016[42]	Self-collected HPV test (CLART and HC2) at home	Physician-collected LBC test
Racey, 2016[43]	Self-collected HPV test at home	-Reminder letter for Pap test -Standard of care opportunistic screening
Sultana, 2016[44]	Self-collected HPV test (Cobas)	Clinician-collected Pap test
Williams, 2016[45]	Self-collected HPV test with tampons (Cobas)	Clinic administered Pap test, HPV test, and pelvic exam
Zehbe, 2016[46]	Self-collected HPV test (Not reported)	Clinician-collected Pap test
Cadman, 2015[47]	Self-collected HPV test (HC2)	Physician-collected cytology test
Rossi, 2015[48]	-Self-collected HPV test (HC2) at home -Self-collected HPV test in pharmacy	-Pap test at clinic -Physician-collected HPV test (HC2) at clinic
Non-Randomized Studies		
Chatzistamatiou, 2017[49] **PIPAVIR study**	Clinician-collected HPV test (Multiplexed Genotyping)	LBC
Granados, 2017[50]	HPV co-testing (Aptima and Pap test)	Analysis of Pap results only
Kocsis, 2017[51] **TRACE trial**	HPV test (CONFIDENCE assay)	-HPV test (Cobas and Full Spectrum HPV test) -LBC
Altobelli, 2016[52]	HPV test (HC2)	Conventional cytology
Jin, 2016[21]	Clinician-collected HPV test (HC2)	Cytology from co-testing
Ilangovan, 2016[53]	Self-collected HPV test (Aptima and Cervista Invader)	Pap test
Agorastos, 2015[54]	HPV test (Cobas)	LBC
Chiappetta, 2015[55]	HPV test (HC2) with LBC triage	Cytology test

Table 4: Index and Comparator Tests in Primary Studies

First Author, Year Trial Name	Index Test	Comparator Test
	-women aged 35 to 64	-only women aged 25 to 34
Iftner, 2015[56]	HPV test (Aptima and HC2)	LBC
Pasquale, 2015[57]	Co-testing (HC2 and cytology)	Midwife-collected cytology test
Wright, 2015[58]	Clinician-collected HPV test (Cobas)	LBC

ASCUS = atypical squamous cells of undetermined significance; HC2 = Hybrid Capture 2; HPV = human papillomavirus; LBC = liquid-based cytology

Outcomes

For research question one, comparing HPV testing with cytology, there were four main groups of outcomes of interest that could be addressed using the results of the included SRs and primary studies: DTA, referral to colposcopy, acceptance of screening, and clinical utilities and harms. For question two, comparing HPV testing strategies with each other, there were three main outcomes: baseline DTA, longitudinal DTA, and referral to colposcopy. Baseline DTA was the accuracy to detect CIN2+ or CIN3+ at the time of examination. Longitudinal DTA aimed to predict CIN2+ or CIN3+ in the long run. The coverage of these outcomes is summarized in Table 5.

Table 5: Outcomes Reported by Research Question

Outcome	Number of Systematic Reviews	Number of Primary Studies
Research Question 1		
DTA	2[6,38]	7[21,41,49,51,54,56,58]
Referral to colposcopy	2[6,39]	5[40,41,49,50,55]
Acceptance of screening	1[22]	13[40,42-48,50,52,53,55,57]
Clinical utility and harms	1[39]	0
Research Question 2		
Baseline DTA	1[6]	0
Longitudinal DTA	1[6]	0
Referral to colposcopy	1[6]	0

DTA = diagnostic test accuracy

Critical appraisal

Systematic reviews

Quality of systematic reviews

The Cochrane and HIQA SRs were of moderate quality, with a few limitations identified with the AMSTAR 2 tool. The HIQA SR did not publish the protocol a priori, investigate heterogeneity based on the risk of bias in primary studies, or investigate publication bias.[6] The Cochrane SR did not account for risk of bias in primary studies for review and investigate publication bias.[38]

The primary limitation identified in Melnikow et al. was that they did report sources of funding in primary studies.[39] Melnikow et al.conducted a comprehensive literature search, listed the excluded studies, assessed risk of bias, and considered the risk of bias of individuals studies to draw conclusions[39]

Verdoodt et al. was found to have four limitations: protocol publication a priori, a list of excluded studies, accounting for risk of bias while discussing the results of the primary studies, and investigating publication bias.[22]

Quality of primary studies included in systematic reviews

The authors of the SRs used a variety of tools to critically appraise the included primary studies. In the HIQA SR,[6] the 15 primary studies were appraised with the QUADAS-2 checklist. Three were rated at low risk of bias in four domains.[6] The overall quality of the studies were rated fair to good.[6] The Cochrane SR[38] also used QUADAS to assess the risk of bias of the included studies. They found that, overall, the quality of the evidence for the sensitivity of the tests was moderate and the quality of the tests for specificity was high.[38]

All primary studies in Melnikow et al. were assessed with the U.S. Preventive Services Task Force (USPSTF) criteria, while observational studies were also appraised with the Newcastle-Ottawa Scale.[39] Two Italian and one Dutch trial, New Technologies for Cervical Cancer Screening (NTCC) Phase I and Phase II, and POBASCAM, were rated as good-quality[39] The other trials included in the SR were considered to be fair-quality[39] In the SR by Verdoodt et al.,[22] the methodological quality of the included studies was assessed as moderate to high according to the criteria in the Cochrane risk of bias tool.[22]

Primary studies

DTA studies

Seven primary studies[21,41,49,51,54,56,58] were assessed using the QUADAS 2 checklist for DTA outcomes, as presented in Table 41.[35] The results of quality assessment based on the checklist are provided in Table 41. The first item of the QUADAS 2 checklist explores whether the selection of patients could introduce bias into the study.[35] five studies adequately described how patients were selected and were determined to be at low risk.[41,49,51,54,56] The risk of selection bias was determined to be unclear for Wright et al.[58] and Jin et al.[21] because the publications did not provide enough information on the patient selection to adequately assess how it might lead to bias.[21,58] The second item was whether the conduct or interpretation of the index test introduced bias.[35] The results of the index tests and reference standards were available at the same time for Jin et al. and it was unclear whether the reference standards were known to the authors.[21] This study was considered at unclear risk of selecting patients based on the outcome.[21] The third item was whether the conduct or interpretation of the reference standard introduced bias.[35] Cook et al. blinded the results of index test (Aptima HPV tests) and was considered at low risk.[41] The other six studies were at high risk for the lack of blinding.[21,49,51,54,56,58] The fourth item was whether the patient flow introduced bias.[35] Two studies were considered at high risk for the lack of adjustment for verification bias.[21,41] Cook et al. did not investigate the disease status of test negative patients,[41] while the other study did investigate test negative patients.

For the optional domains of the QUADAS 2 checklist, Jin et al. did not describe the conduct or the interpretation of the supplemental tests (cytology in this case) and the risk of bias was unclear.[21] Other studies described the diagnostic thresholds and were considered at low risk.[41,49,51,54,56,58] Wright et al. and Cook et al. had additional index tests, hybrid HPV tests and HC2 respectively, and described the diagnostic thresholds and the methods to determine the DTA.[41,58] They were considered at low risk of introducing bias due to the conduct or interpretation of them.[41,58]

Non-randomized studies

Six prospective cohort studies[49,50,52,53,55,57] used to address research question one were critically appraised with the Newcastle-Ottawa scale with results presented in Table 42. All of them had somewhat or truly representative samples, non-exposed cohorts drawn from similar communities, exposure ascertained with secure records, comparable cohorts according to the study design, outcome assessment with record linkage, adequate follow-up periods, and adequate cohort follow-up for selected outcomes.[49,50,52,53,55,57] Ilangovan et al.[53] and Chatzistamatiou et al.[49] were rated as high-quality with no limitations identified in eight criteria.[53] Four studies were also rated as high-quality based on one limitation of not demonstrating that outcome of interest was absent at the beginning of study.[50,52,55,57]

RCTs

Nine RCTs were assessed with the Cochrane Risk of Bias tool and are presented in Table 43.[40,41-48] Risk of bias in sequence generation was unclear in three studies.[40,41,45] Risk of bias in allocation concealment or selection bias was high in six studies[40-42,44,45,47,48], low in three.[43,46,47] Risk of bias in blinding of participants and personnel or performance bias was high in seven studies,[40,42,44-48] low in one study,[43] and unclear in the other study.[41] Risk of bias in blinding of outcome assessors or detection bias was high in seven studies,[40,42,44-48]unclear in two studies.[41,43] Risk of bias from missing outcome data or attrition bias was low for all studies.[40,41-48] Risk of bias from selective outcome reporting or reporting bias was low for all studies.[40,41-48] Risk of bias from other biases was low in eight studies.[40,42-48] The risk was unclear in Cook et al. due to insufficient information on the adjustment for verification bias.[41]

Summary of Results

Research Question 1

What is the diagnostic efficacy of primary high-risk HPV testing, with or without cytology triage, compared with primary cytology-based testing for cervical cancer screening of asymptomatic women?

The outcomes and the relevant SRs are listed in Table 44 to Table 53.

Diagnostic Test Accuracy

Systematic reviews

The Cochrane SR directly compared three types of HPV tests (HC2, PCR [13 or more virus strains], and Aptima) to cytology (LBC or conventional).[38] HC2 was the only HPV test that applied more than one diagnostic threshold. The authors adopted 1 and 2 pg/mL or RLU (relative light units) as the thresholds of HPV positivity for HC2 in their direct comparisons. Meta-analysis was done for the 1 pg/mL cut-off value only, as there were not sufficient primary studies to undertake a meta-analysis of HC2 at the threshold of 2 pg/mL or RLU.[38] The Cochrane SR distinguished between the two types of cytology tests, conventional and LBC, and two cytology thresholds, ASCUS and LSIL.

The HIQA SR compared HC2 to cytology (LBC or conventional).[6] The authors considered 1 pg/mL or RLU as the positivity threshold for HC2.[6] The authors analyzed conventional and liquid-based cytology at the threshold of ASCUS.[6]

Overall, both SRs found that HC2 at the threshold of 1pg/mL or 1 RLU was more sensitive and less specific than liquid-based or conventional cytology at the threshold of ASCUS for the detection of CIN2+ or CIN3+.[6,38] The overall trends in the results are summarized in Table 6 and Table 7.

Table 6: Results of the Diagnostic Test Accuracy Comparison Between HPV Tests and Cytology For the Detection of CIN2+

Sensitivity	LBC (ASCUS+)		Conventional (ASCUS+)		LBC (LSIL+)		Conventional (LSIL+)	
	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]
LBC (ASCUS+)	NA	NA	↑[a]	↑	NA	NA	NA	NA
HC2 (1	↑	↑	↑	↑	↑	NA	↑	NA

pg/mL)								
HC2 (2 pg/mL)	≠	NA	≠	NA	NA	NA	≠	NA
PCR (13 or more Hr-HPV strains)	↔	NA	↔	NA	≠	NA	≠	NA
Aptima	NA	NA	NA	NA	NA	NA	NA	NA
Specificity	LBC (ASCUS+)		Conventional (ASCUS+)		LBC (LSIL+)		Conventional (LSIL+)	
	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]
LBC (ASCUS+)	NA	NA	NA	↓	NA	NA	NA	NA
HC2 (1 pg/mL)	↓	↓	↓	↓	↓	NA	↓	NA
HC2 (2 pg/mL)	≠	NA	≠	NA	NA	NA	≠	NA
PCR (13 or more Hr-HPV strains)	↓	NA	↔	NA	≠	NA	≠	NA
Aptima	NA	NA	NA	NA	NA	NA	NA	NA

ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; HPV = human papillomavirus; hr = high risk; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion; NA = not available or not assessed; NR = not reported; PCR = polymerase chain reaction.

[a] Statistical testing methods were unclear

The tests in the first column were tested against the tests in the first rows. ↑ = significantly higher; ↓ = significantly lower; ↔ = insignificant; ≠ = insufficient studies (at least three primary studies required);

The Cochrane SR included comparative test accuracy studies where all participants received both HPV testing and cervical cytology (paired studies) followed by partial or complete verification of the disease status with the reference standard. The HIQA HTA included mostly cohort studies using concomitant cervical cytology and HPV testing and randomized controlled trials where participants were assigned to either cytology testing, HPV testing, or both.

The Cochrane SR compared the DTA among the primary studies that included both the specified intervention and the comparison tests. The statistical significance of the differences was determined by assigning the intervention as a variate in a bivariate random-effects model in the Cochrane SR. The primary studies and the methods used to determine the statistical significance were not clear in the HIQA report. If "higher" or "lower" were mentioned in the HIQA report, it was assumed that the differences in DTA were statistically significant.

Table 7: Results of the Diagnostic Test Accuracy Comparison Between HPV Tests and Cytology for the Detection of CIN3+

Sensitivity	LBC (ASCUS+)		Conventional (ASCUS+)		LBC (LSIL+)		Conventional (LSIL+)	
	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]	Cochrane (2017)[38]	HIQA (2017)[6]
LBC (ASCUS+)	NA	NA	↑[a]	↑	NA	NA	NA	NA
HC2 (1 pg/mL)	↑	↑	↑	↑	↔	NA	≠	NA
HC2 (2 pg/mL)	≠	NA	≠	NA	x	NA	x	NA
PCR (12 or more Hr-HPV strains)	↔	NA	↔	NA	≠	NA	≠	NA
Aptima	↔	NA	NA	NA	NA	NA	x	NA
Specificity	LBC (ASCUS+)		Conventional (ASCUS+)		LBC (LSIL+)		Conventional (LSIL+)	
	Cochrane	HIQA	Cochrane	HIQA	Cochrane	HIQA	Cochrane	HIQA

	(2017)[38]	(2017)[6]	(2017)[38]	(2017)[6]	(2017)[38]	(2017)[6]	(2017)[38]	(2017)[6]
LBC (ASCUS +)	NA	NA	NA	↓	NA	NA	NA	NA
HC2 (1 pg/mL)	↓	↓	↓	↓	↔	NA	≠	NA
HC2 (2 pg/mL)	≠	x	≠	NA	x	NA	x	NA
PCR (13 or more Hr-HPV strains)	↔	NA	↔	NA	≠	NA	≠	NA
Aptima	↔	NA	NA	NA	NA	NA	NA	NA

ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; HPV = human papillomavirus; hr = high risk; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion; PCR = polymerase chain reaction.

[a] Statistical testing methods were unclear

The tests in the first column were tested against the tests in the first rows. ↑ = significantly higher; ↓ = significantly lower; ↔ = insignificant; ≠ = insufficient studies (at least three primary studies required); NA = not assessed

The Cochrane SR included comparative test accuracy studies where all participants received both HPV testing and cervical cytology (paired studies) followed by partial or complete verification of the disease status with the reference standard. The HIQA HTA included observational studies using concomitant cervical cytology and HPV testing and randomized controlled trials where participants were assigned to either cytology testing, HPV testing or both.

The Cochrane SR compared the diagnostic test accuracy (DTA) among the primary studies that included both the specified intervention and the comparison tests. The statistical significance of the differences was determined by assigning the intervention as a variate in a bivariate random-effects model in the Cochrane SR. The primary studies and the methods used to determine the statistical significance were not clear in the HIQA report. If "higher" or "lower" were mentioned in the HIQA report, it was assumed that the differences in DTA were statistically significant.

Both SRs found that the pooled values for HC2, at the threshold of 1pg/mL or 1 RLU, were significantly more sensitive and less specific than liquid-based or conventional cytology at the threshold of ASCUS for the detection of CIN2+ or CIN3+ (Table 8 and Table 9).[6,38]

Table 8: Comparative Sensitivity and Specificity – HPV Tests versus Cytology for the Detection of CIN2+

Test	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Number of Studies
Cochrane[38]			
HC2 (1pg/mL) [all ages]	92.6 (89.6 to 95.3)	89.3 (87 to 91.2)	25
HC2 (1pg/mL) [>30 years]	93.9 (89.3 to 96.6)	91.3 (88.9 to 93.2)	2
Conventional cytology (ASCUS+)	65.9 (54.9 to 75.3)	96.3 (94.7 to 97.4)	16
LBC (ASCUS+)	75.5 (66.6 to 82.7)	91.9 (90.1 to 90.5)	15
Conventional cytology (LSIL+)	62.8 (46.8 to 76.5)	97.7 (96.1 to 98.7)	9
LBC (LSIL+)	70.3 (59.7 to 79.1)	96.2 (94.6 to 97.4)	10
Aptima	92.7 (31.7 to 99.7)	93.3 (47.3 to 99.5)	3
Cobas	NP	NP	2
PCR (13+ hr types)	NP	NP	6

PCR (10-11 hr types)	NP	NP	2
HIQA[6]			
HC2 (1pg/mL)	95.2 (92.5 to 97.1)	88.2 (82.9 to 92.0)	20
Conventional cytology	70.5 (58.2 to 80.7)	95.8 (92.8 to 97.6)	14
LBC	83.7 (62.2 to 94.8)	92.9 (83.5 to 97.2)	8
Combined	75.0 (64.1 to 83.3)	95.0 (92.2 to 96.8)	20

ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN2+= cervical intraepithelial neoplasia grade 2+; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; LSIL = low-grade squamous intraepithelial lesion; mL = milliliter; NP = not pooled; PCR = polymerase chain reaction; pg = picograms

Table 9: Comparative Sensitivity and Specificity – HPV Tests versus Cytology for the Detection of CIN3+

Test	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Number of Studies
Cochrane[38]			
HC2 (1pg/mL)	96.5 (94 to 97.9)	89.2 (86.7 to 91.3)	15
Conventional cytology (ASCUS+)	70.3 (57.9 to 80.3)	96.7 (94.6 to 98.0)	9
LBC (ASCUS+)	76.0 (64.7 to 84.5)	91.2 (90.1 to 90.5)	13
Conventional cytology (LSIL+)	74.4 (67.8 to 80.1)	96.9 (94.9 to 98.1)	5
LBC (LSIL+)	71.9 (61.2 to 76)	96.1 (93.5 to 97.6)	5
Aptima	96 (72.9 to 99.5)	92.8 (86.2 to 96.3)	4
Cobas	NP	NP	2
PCR (13+ hr types)	NP	NP	4
PCR (10-11 hr types)	NP	NP	1
HIQA[6]			
HC2 (1pg/mL)	98.2 (96.7 to 99.1)	87.6 (78.7 to 93.2)	20
Conventional cytology	71.9 (53.6 to 85.7)	96.3 (92.1 to 98.2)	9
LBC	85.0 (53.2 to 96.9)	92.6 (75.5 to 98.2)	6
Combined	78.0 (63.5 to 88.4)	95.1 (91.6 to 97.3)	15

ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia ; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; LSIL = low-grade squamous intraepithelial lesion; mL = milliliter; PCR = polymerase chain reaction; pg = picograms

Other HPV tests or HC2 thresholds (i.e. 2 pg/mL) were not included in the meta-analysis in the HIQA SR in Table 8 and Table 9.[6] There were not sufficient numbers of primary studies in the Cochrane SR for the comparisons between HC2 at the threshold of 2 pg/mL or 2 RLU and cytology for the detection of CIN2+ or CIN3+.[38] In the Cochrane review, for HC2 at the threshold of 1 pg/mL or 1 RLU, the sensitivity was significantly higher and the specificity was significantly lower than LBC or conventional cytology at the threshold of LSIL for the detection of CIN2+.[38] However, there were no significant differences found for the DTA between HC2 (1 pg/mL or 1 RLU) and LBC (LSIL+) for the detection of CIN3+.[38] There was not sufficient data for a meta-analysis of the comparison between HC2 (1pg/mL or 1 RLU) and conventional cytology (LSIL+) for the detection of CIN3+.[38]

As described in Table 6 and Table 7, PCR-based HPV tests that could detect more than 12 high-risk HPV strains were significantly less specific than LBC at the threshold of ASCUS for the detection of CIN2+ in the Cochrane SR.[38] There were no significant differences in the sensitivities between these two types of tests.[38] The other comparisons between PCR-based HPV tests and LBC or conventional cytology at the threshold of ASCUS did not indicate significant differences in DTA.[38]

The Aptima HPV test was also compared to LBC at the threshold of ASCUS for the detection of CIN3+ and there were no significant differences in DTA identified in the Cochrane SR (Table 9).[38]

The ranges and the pooled estimates of the DTA reported in the HIQA SR and the Cochrane SR are provided in Table 44 to Table 49. Corrected estimates were also provided to account for a data extraction error in the Cochrane SR.

In the HIQA SR, the positive and negative predictive values for the prediction of CIN2+ and CIN3+ were compared (Table 50).[6] The pooled values for the negative predictive values of both HC2 and cytology were greater than 99% (99.91% and 99.57% respectively), while the positive predictive values were below 20% (11.8% and 19.9%). These values were calculated assuming a prevalence of 1.6% for CIN2+ and 1.0% for CIN3+ for Irish women aged 25 to 60 years.[6]

The authors of the Cochrane SR[38] considered several factors important to the observed variations in DTA across trials in their SR. These factors included: the difference in sensitivity and specificity of tests in those aged 30 years and over, verification bias, variation in prevalence in different geographic areas (high- versus low-income countries), and the numbers of high-risk HPV types detected.[38]

An analysis was conducted that examined the difference in sensitivity and specificity of HC2 (1pg/mL) at the threshold of CIN2+ when used only for those participants older than 30 years of age. The pooled sensitivity (93.9% [95% CI, 89.3 to 96.6]) and specificity (91.3% [95% CI, 88.9 to 93.2]) among these participants were higher than those observed when analyses included participants of all ages.[38] These results were expected as the specificity of HPV tests are expected to increase in older participants being screened as the prevalence of high grade lesions is higher in the older age group. No data was available for the CIN3+ threshold for those older than 30 years of age.

The DTA values that were adjusted for verification bias (i.e. part or all of the test negative patients underwent colposcopy to verify outcome status) are presented in Table 47. The sensitivity for the detection of CIN3+ was higher in the studies at high risk of verification bias than those at low risk,[38] indicating that sensitivity estimates as reported may be overestimated.

The authors of the Cochrane SR compared the accuracy estimates of the tests based on the geographical region where the primary studies were conducted.[38] Countries were classified as high-income or middle- or low-income. Though the results and methods of this analysis were not presented in the publication, the authors indicated that they did not identify any significant effects on accuracy measures based on geography.[38]

There were not sufficient numbers of primary studies to investigate the variation in DTA due to the types of high-risk HPV detected by the tests.[38] Further, there was no meta-analysis conducted to investigate the DTA of self-sampling HPV tests compared to cytology.[38] In the four primary studies included in the Cochrane SR the sensitivity of self-collected HPV testing ranged from 41% to 97% and the specificity ranged from 77% to 98%.[38] Three of the four studies used HC2, two used Care HPV, and one used both.[38] The impact of self sampling on the DTA of HC2 and Care HPV tests remained to be investigated.

Positive and negative predictive values (PPV and NPV respectively) were determined by the disease prevalence and diagnostic test accuracy.[6] The PPV for the detection of CIN3+ were lower than those for the detection of CIN2+ for HC2 and cytology in Table 50.[6] The PPVs of cytology for the detection of CIN2+ or CIN3+ were higher than those of HC2. However, there was no statistical test to determine the significance of the differences. The NPVs of cytology and HC2 remained above 99% for the detection of CIN2+ or CIN3+.

Primary studies

There were seven primary studies that evaluated the sensitivity and specificity of primary HPV tests included in this review (one RCT,[41] two co-testing studies,[21,58] and four prospective cohort studies[49,51,54,56]). Six of the eight primary studies.[41,49,51,54 ,56,58] supported the conclusion that HPV tests had higher sensitivity and lower specificity than cytology. The detailed results of these studies are presented in Table 44 to Table 48. The HPV tests evaluated in these studies included:

- HC2,[41,56]
- Cobas,[51,54,58]
- Aptima,[41,56]
- CONFIDENCE,[51]
- Multiplex genotyping[49].

The study by Jin et al.[21] observed a sensitivity of 94.1% (95% CI, 90.3 to 96.5) and a specificity of 98.1% (95% CI, 98.1 to 98.2) for HC2 at a threshold of CIN3+ when used in a co-testing scenario for participants 30 years of age or older. In their study, they found that HC2 as the primary HPV test was less sensitive to CIN3+ cases than primary cytology (90.7% [95% CI, 86.4 to 93.8]) and HC2 was found to be slightly more specific than cytology (97.6 [95%CI, 97.5 to 97.7]).[21] The authors acknowledged that the results of their study did not align with other similar studies. They proposed that differences in rates of abnormal cytology could lead to differences in sensitivity and specificity. Sample collection or pathological interpretation may have been factors contributing to these differences but it was not possible to definitively determine this to be the cause. The population included in this study also had lower incidences of LSIL and HSIL as compared to the US national averages. The reason for the superior specificity of HC2 compared to cytology in this study was not clear.[21]

Screening Participation

Systematic reviews

Verdoodt et al.[22] included 16 studies and evaluated screening participation among those who were considered underscreened – those not participating regular cervical cancer screening programs - following an invitation for self-collected HPV testing compared with an invitation for clinician-collected HPV or cytology testing for cervical cancer screening. These results are summarized in Table 10 and full detail is available in Table 51.[22] Control groups in 14 of the studies involved clinician-collected cytology testing; however, two studies used clinician-collected high-risk HPV testing as the control group. Participation in each study arm varied significantly between studies so the authors grouped the analysis according to the invitation scenario.[22] There were three self-sampling strategies identified: mail-to-all, opt-in, and door-to-door.[22] The mail-to-all approach was to directly send the self-sampling devices to the eligible participants.[22] The opt-in approach was to invite the participants and wait for them to opt in self-sampled tests.[22] The door-to-door method was to have staff workers visit eligible participants and deliver self-sampling devices.[22] The participation rates were significantly different when comparing mail-to-all self-collected HPV tests and control. Both the per-protocol and intent-to-treat analyses showed that the mail-to-all option was more acceptable and achieved higher participation rates than the control according to the pooled estimates.[22] In both analyses, the acceptance of the opt-in option was not significantly different from that of the control group.[22] The door-to-door option was not associated with significantly different participation rates compared to clinician-collected cytology, according to both analyses.[22]

Table 10: Participation Rates Reported in Verdoodt et al.[22]

Invitation Approach	Pooled Self-Sampling (95% CI)	Pooled Control (95% CI)	Relative Participation (95% CI)
Per-protocol analysis			
Mail-to-all	20.7% (16.9 to 24.8)	10.3% (6.2 to 15.2)	2.06% (1.44 to 2.96)
Opt-in	9.7% (6.5 to 13.5)	12.2% (10.9 to 13.6)	0.72% (0.53 to 0.99)
Door-to-door	91.3% (65.8 to 100)	54.1% (0.9 to 100)	2.17% (0.33 to 14.13)
Intention-to-treat analysis			

Table 10: Participation Rates Reported in Verdoodt et al.[22]

Invitation Approach	Pooled Self-Sampling (95% CI)	Pooled Control (95% CI)	Relative Participation (95% CI)
Mail-to-all	23.6% (20.2 to 27.3)	10.3% (6.2 to 15.2)	2.40 %(1.73 to 3.33)
Opt-in	14.0% (8.0 to 21.4)	12.2% (10.9 to 13.6)	0.97% (0.65 to 1.46)
Door-to-door	92.4% (71.3 to 100)	54.1% (0.9 to 100)	2.21% (0.32 to 15.48)

CI = confidence interval

Primary studies

Self-sampling HPV tests versus cytology

Six RCTs[42,44-48] compared the absolute participation in populations that were considered underscreened when offered either self-collected HPV testing or cytology for cervical cancer screening. Two studies, one RCT[43] and one observational study,[53] listed the participation rates in different groups and did not test the statistical significance of the differences. These results are summarized in Table 11. With the exception of Zehbe et al., that studied the participation rates in First Nations communities in Ontario,[46] the other seven primary studies recruited or invited those who did not attend regular screening programs for at least one year.[42-45,47,48,53]

Among the six studies that tested the statistical significance in the difference between groups,[42,44-48] five reported higher participation rates in the self-sampling group.[42,44,45,47,48] Zehbe et al. studied the participation rates in First Nations communities and did not find differences.[46] Rossi et al. compared four strategies - a self-sampler delivered to home for self-testing, a self- sample kit obtained in a pharmacy, cytology at clinic, and HPV tests at clinic. Higher participation rates were reported for self-sampling at home compared to the testing at a clinic.[48] They did not find the rates significantly different between those taking self-samplers at pharmacy and those undergoing the test at clinic.[48]

Table 11: Absolute Participation Rates in Self-Sampling vs. Cytology as Reported in Primary Studies

First Author (Year)	Self-Collected HPV % of total offered (n)	Cytology % of total offered (n)
Non-attenders		
Enerly (2016)[42]	33.4% (267), including 98 attending cytology	23.2% (601)[a]
Cadman (2015)[47]	8% (247)	6% (183)[b]
Self-sampling HPV vs cytology in First Nations communities (attenders, non-attenders, and non-pregnant participants)		
Zehbe (2016)[46]	20.0% (54)	14.3% (35)[c]
Not screened in the past year		
Williams (2016)[45]	80% (48)	56.7% (34)[b]
Not screened in the past 30 months		
Racey (2016)[43]	HPV invitation = 31.9% (107) Cytology invitation = 15.4% (51)	Opportunistic screening / standard of care = 8.6% (13)[a]
Not screened within the past three years		
Ilangovan (2016)[53]	67% (121)	33% (59)[a]
Rossi (2015)[48]	Self-sampler at home = 21.6% (974) Self-sampler at pharmacy = 12.0% (540)	Cytology at clinic = 11.8% (235)[c] HPV at clinic = 12.0% (363)[c]

Table 11: Absolute Participation Rates in Self-Sampling vs. Cytology as Reported in Primary Studies

First Author (Year)	Self-Collected HPV % of total offered (n)	Cytology % of total offered (n)
Not screened within the past five years		
Sultana (2016)[44]	Apparently never-screened = 15.8% (1131) Apparently under-screened = 7.3% (518)	6.0% (61)[b] 6.4% (65)[b]

HPV = human papillomavirus
[a] Statistical significance was not tested.
[b] A statistically significant difference was observed between groups.
[c] No statistically significant difference was observed between groups.

Physician-collected HPV tests versus cytology

One RCT[40] and two observational studies[52,57] compared the absolute participation when participants were offered clinician-collected HPV testing or cytology for routine cervical cancer screening.[40,52,57] These results are summarized in Table 12 and details are described in Table 51. In two studies,[40,52] the absolute participation rates were similar between the groups that were offered clinician-collected HPV testing versus those who were offered routine cytology testing, although statistical significance was not tested. Pasquale et al. found that the relative frequencies of participation rates of physician-collected HPV tests were higher than cytology.[57]

Table 12: Absolute Participation Rates in Physician-Collected testing versus Cytology as Reported in Primary Studies

First Author (Year)	**Clinician-Collected HPV % of total offered (n)**	**Cytology % of total offered (n)**
Aged 25 to 64 years attending routine screening		
Altobelli (2016)[52]	40.3% (24,206)	38.7% (14,142)[a]
Pasquale (2015)[57]	67.9% (18,728)	64.7% (18,233)
Aged 56 to 60 years eligible for routine screening		
Lamin (2017)[40]	34.7% (7,325)	34.4% (7,438)[a]

HPV = human papillomavirus
a Statistical significance was not tested.

Referral to Colposcopy

Systematic reviews

In Melnikow et al., four primary RCTs (NTCC Phase II, HPV FOCAL, Compass, and FINNISH) and one cohort study (Zorzi et al.) examining the differences in colposcopy referral rates between primary HPV testing and cytology were narratively summarized.[39] The referral rate was presented as a percentage of the total number of participants who were triaged to colposcopy after their initial screening tests. One round of results were reported for the RCTs and two rounds were available in one RCT, HPV FOCAL trial, and the cohort study.[39] The complete results are presented in Table 52.

When comparing all participants included in the RCTs, colposcopy referral was highest for high-risk HPV testing alone (7.9%). This was followed by:

- high-risk HPV testing with LBC triage (3.8% and 5.7%, Compass and HPV FOCAL trials respectively),
- LBC alone (2.7% and 3.1%, Comapss and HPV FOCAL trials respectively),
- LBC with high-risk HPV testing triage (3.1%, HPV FOCAL trial),
- conventional cytology alone (1.1% and 2.8%, FINNISH and NTCC Phase II trials),

- high-risk HPV testing with conventional cytology triage (1.2%, FINNISH).[39]

In addition, for the second round of screening (occurring approximately four years after the first round) for those who tested negative in the first round of screening, the referral rates were reported in Ogilvie et al. that was reviewed in the SR by Melnikow et al.:

- HPV test (Aptima or HC2) with LBC triage (4.9%)[39]
- LBC at a threshold of ASCUS+ (7.0%)[39]

When the results were subdivided by the age of the participants, the results varied slightly. For participants aged 35 years and older, the results were generally the same, with high-risk HPV testing alone having the highest referral rate (5.8%) and high-risk HPV testing with conventional cytology triage having the lowest referral rate (0.9%).[39,62]For participants younger than than 35 years of age, high-risk HPV testing with LBC triage had referral rates of 19.9% (25 to 29 years of age, HPV FOCAL trial) and 10.8% (30 to 34 years of age, HPV FOCAL trial). The lowest referral rates for this age group were for high-risk HPV testing with conventional cytology triage (2.3%) and conventional cytology alone (1.9% and 3.6%, FINNISH and NTCC Phase II trials resepctively).[39]

The one-arm observational study by Zorzi et al. examined the effectiveness of only primary HPV tests and reported results from two rounds of screening between 2007 and 2009.[39] The colposcopy referral rates were higher at the first round (4.4%) as compared to the second round (2.2%) and the overall combined referral rate was 5.4%.[39]

The screening intervals of the primary studies included in Melnikow et al. ranged from three to five years.[39] The authors indicated that none of these studies were designed or powered to test for differences in colposcopy rates or false negatives with shorter and longer intervals within a trial.[39]

Primary studies

The colposcopy referral rates were examined in two RCTs[40,41] and in three prospective cohort studies.[49,50,55] Colposcopy referral was reported in two different ways: relative to total participants screened or relative to the number of participants who were triaged or randomized. A full summary of results is presented in Table 52.

The colposcopy referral rates reported as a percentage of the total number of participants triaged were available in one RCT.[40] For the Cobas HPV test, the referral rate was 0.3%.[40] Screening with LBC at a threshold of ASCUS+ resulted in a referral rate of 0.2%.[40]

The colposcopy referral rates reported as a percentage of the total number of participants screened were available in two RCTs,[40,41] and three prospective cohort studies.[49,50,55] The referral rates for the RCTs at round one were:

- HC2 (3.1%)[41]
- Cobas HPV test (0.8%)[40]
- LBC at a threshold of ASCUS+ (0.7%)[40]

Although the RCTs recruited individuals eligible for routine screening programs, the populations in the two RCTs were different. The HPV FOCAL trial was conducted in British Columbia, Canada.[41] In Lamin et al., Swedish participants aged 56 to 60 years received Cobas HPV tests for cervical cancer screening.[40] We suspect the differences in population characteristics might contribute to some of the variations in referral rates.

Referral rates reported in the prospective cohort studies were:

- HC2 (1.1%)[55]
- Aptima (3.5%)[50]
- Multiplexed genotyping HPV test (16.3%)[49]
- LBC at a threshold of ASCUS+ (2.7% to 6.4%) [49,50,55]

Because colposcopy referral rates were not usually the primary outcome of interest, the differences between different arms were not tested for statistical significance.

Harms and Clinical Utility

Systematic reviews

Melnikow et al. addressed harms and clinical utility.[39] The findings of Melnikow et al.are summarized in Table 53. There were results from co-testing studies and those using primary HPV tests in Melnikow et al.[39] The co-testing studies were not eligible for the inclusion criteria of this review and are not described below.

Though Melnikow et al.aimed to assess the harms and adverse events associated with cervical cancer screening, no results were identified amongst the included primary studies with regard to cervical cancer mortality, rates of cervical cancer treatment, or harms.[39] The authors commented that the studies included in their SR were not adequately powered to detect the relatively uncommon adverse events that can occur following the biopsy or treatment of cervical lesions. [39] The authors also attempted to address the differences in adverse effects based on different screening intervals. None of the studies identified were designed to specifically compare these outcomes between screening intervals and, due to heterogeneity between the studies, the authors were not able to determine how the screening interval or screening strategies might have related to the potential harms of overdiagnosis and detection or missed cervical cancers.[39]

Melnikow et al. were able to comment on the incidence of invasive cervical cancer detected in participants with negative screening tests in three studies evaluating screening using primary high-risk HPV testing compared to cytology based on the meta-analysis by Ronco et al. in Table 53.[39] The pooled incidence rates were 0.05 and 0.08 in the HPV testing and cytology groups respectively.[39] In the NTCC Phase II study, no cases of invasive cervical cancer or CIN3 were identified among those who were screen negative and were followed up to three and a half years after one round of screening in both the control and intervention groups.[39] After one round of screening and five years of follow-up, the FINNISH trial reported invasive cervical cancer in 0.01% (5 of 57,135) of participants with an initial negative screening result in the high-risk HPV testing group and in 0.003% (3 of 61,241) of participants in the cytology group.[39] The data on invasive cervical cancer was not available in the HPV FOCAL trial.[39]

Primary studies

There were no primary studies identified addressing harms.

Research Question 2

What are the diagnostic efficacies of primary high-risk HPV testing strategies compared with each other for asymptomatic cervical cancer screening?

Evidence was identified related to DTA and colposcopy referral rates, but not for acceptance of screening, harms, or clinical utility.

Diagnostic Test Accuracy – First Round of Screening

Systematic reviews

The authors of the HIQA SR[6] aimed to compare the DTA of different HPV testing and triage strategies. They included 15 studies of participants in cervical cancer screening programs who had a positive result on their preliminary HPV test and then underwent some form of triage testing before proceeding to sample confirmation with colposcopy.[6] Four of the five triage strategies they identified were of relevance to this review. The baseline DTA of the four triage strategies identified in the HIQA SR are listed in Table 13. These strategies included:

1. Primary HPV testing with cytology triage
2. Primary HPV testing followed by triage with partial genotyping for HPV 16/18
3. Primary HPV testing followed by triage with sequential partial genotyping for HPV 16/18 followed by cytology to further triage those positive for HPV 16/18
4. Primary HPV testing followed by co-testing triage (partial genotyping for HPV 16/18 and cytology triage)

These strategies follow the pathway outlined in

Figure 6. No one study compared all of the triage strategies with each other. The baseline DTA results of the four triage strategies were discussed separately in the HIQA SR. [6]

For the first triage strategy, primary HPV testing with cytology triage, the authors of the HIQA SR included six RCTs. Two of the RCTs used colposcopy confirmation only for HPV positive results. Four of the RCTs used colposcopy confirmation for all participants who had the primary HPV and triage test, regardless of the outcome.[6] The results were not pooled. Two of the four RCTs, Castle et al. (2011) and Wright et al. (2016) were publications from the US-based ATHENA trial and reported sensitivities and specificities for both CIN2+ (sensitivity = 52.6% [95% CI; 47.6% to 57.6%) and 46.5% [95% CI; 41.7% to 51.3%]) (specificity = 90.1% [95% CI; 89.4% to 90.7%] and 89.9% [95% CI; 89.1% to 90.6%]) and CIN3+ (sensitivity = 89.9% [95% CI; 89.1% to 90.6%] and 48.3% [42.3% to 54.3%]) (specificity = 89.3% [95% CI; 88.6% to 90.0%] and 89.2% [88.5% to 89.9%]) that were much lower than those reported in the other included studies.

For the second triage strategy, primary HPV testing followed by genotyping for HPV 16 and 18, Two of the studies reported DTA values for the entire screening strategy (HPV test and triage test) while one study reported conditional outcomes that represent the outcomes for the triage test for the population who were screened positive on the primary HPV screening test. Two of the three included studies provided DTA estimates and the results suggested that this strategy was less sensitive, but more specific than primary HPV testing followed by cytology triage.[6]

For the third triage strategy, primary HPV testing followed by sequential HPV genotyping for HPV 16 and 18 and cytology, three studies were included. Two of the studies reported DTA values for the entire screening strategy (HPV test and triage test) while one study reported conditional outcomes that represent the outcomes for the triage test for the population who were screened positive on the primary HPV screening test. The authors of the SR concluded that the results of the two studies examining the strategy as a whole suggest that this strategy was less sensitive, but more specific, than primary HPV testing followed by cytology

For the fourth strategy, primary HPV testing followed by co-testing with genotyping for HPV 16 and 18 and cytology, three studies were identified. Two of the studies reported DTA values for the entire screening strategy (HPV test and triage test) while one study reported conditional outcomes that represent the outcomes for the triage test for the population who were screened positive on the primary HPV screening test. The two included studies examining the strategy as a whole reported DTA estimates that were suggestive that this strategy was similarly sensitive, but less specific than primary HPV testing followed by cytology.[6]

Two studies also compared strategies two, three and four and found the highest sensitivity was reported with primary HPV testing with co-testing triage.[6] The highest specificity was reported for primary HPV testing followed by sequential genotyping for HPV 16 and 18 and cytology.[6]

There appeared to be a trade-off between sensitivities and specificities. The studies reporting higher sensitivities in each triage strategy tended to report lower specificities and vice versa. Due to study heterogeneity and insufficient numbers of primary studies in the triage strategies, there were no meta-analyses conducted for the triage strategies.[6]

Table 13: Baseline Sensitivity and Specificity of Triage Strategies

Systematic Reviews						
Triage strategies	CIN2+			CIN3+		
	Sensitivity Range or values (%)	**Specificity** Range or values (%)	**Number of studies**	**Sensitivity** Range or values (%)	**Specificity** Range or values (%)	**Number of studies**
HIQA (2017)[6]						
1) HPV with cytology	46.5 to 97.6	65.6 to 97.6	6	48.3 to 95.2	62.9 to 97.4	6
2) HPV with genotyping (HPV 16 and 18)	51.8, 56.4, and 89.8	89.7, 96.8, and 31.4*	3	59.5, 67.8, and 92.1	89.2, 96.3, and 30.6*	3

3) HPV with sequential genotyping (HPV 16 and 18) and cytology	26.4, 30.0, and 87.4	96.9, 97.0, and 72.1*	3	31.0, 34.1, and 87.3	96.5, 97.8, and 69.6*	3
4) HPV with co-test genotyping (HPV 16 and 18) and cytology	66.7, 74.5, and 100	82.5, 82.7, and 24.9*,	3	72.8, 78.2, 100	81.7, 81.9, and 23.9*	3

CI = confidence interval; CIN = cervical intraepithelial neoplasia; HIQA = Health Information and Quality Authority; HC2 = Hybrid Capture 2; HPV = human papillomavirus; NR = not reported. *the sequences of specificities was determined by sensitivities in ascending order.

Diagnostic Test Accuracy – Subsequent Rounds of Screening

Systematic reviews

There were five primary studies included in the HIQA SR for longitudinal DTA.[6] The results are presented in Table 14. Longitudinal DTA was discussed based on the four triage strategies identified previously.[6] There was no meta-analysis conducted for any of these four strategies.[6] Not all included studies directly compared cross-sectional and longitudinal DTA.[6] The findings in the HIQA SR were summarized as follows:

- For the strategy with primary HPV testing followed by cytology, five of the six included primary studies reported longitudinal DTA after following the participants for one to four years.[6] High longitudinal sensitivities and specificities were maintained for the detection of CIN2+ and CIN3+.[6]
- One included study, authored by the VUSA-screen researchers, reported longitudinal DTA for primary HPV testing followed by genotyping for HPV 16 and 18.[6] Compared to the baseline DTA reported by the NTCC trial, the longitudinal sensitivity was significantly lower and the specificity was significantly higher.[6]
- For primary HPV testing followed by sequential genotyping for HPV 16 and 18 and cytology, the three-year sensitivities reported in the ATHENA trial were significantly higher than those reported at baseline.[6] In contrast, the three-year sensitivities and specificities were slightly lower in the VUSA-screen trial, as compared to the baseline DTA reported in the Public Health Trial Finland (referred to as FINNISH in the AHRQ SR).[6]
- For primary HPV testing followed by co-testing genotyping for HPV 16 and 18 and cytology, the longitudinal sensitivity was lower and specificity was higher as reported in the POBASCAM trial, as compared to the Public Health Trial Finland (or FINNISH in the AHRQ review).

Primary studies

There were no primary studies identified for the comparison between these four HPV triage strategies.

Table 14: Longitudinal Sensitivity and Specificity of Triage Strategies

Systematic Reviews						
Triage strategies	**Number of studies**	**Length of follow-up**	**CIN2+**		**CIN3+**	
			Sensitivity	Specificity	Sensitivity	Specificity
		Range (years)	Range or values (%)	Range or values (%)	Range or values (%)	Range or values (%)
HIQA (2017)[6]						
1) HPV with	5	1 to 4	62.7 to 80.0	68.0 to 95.3	61.5 to 81.2	67.1 to 94.8

cytology						
2) HPV with genotyping (HPV 16 and 18)	1	3	58.6	74.5	65.4	72.5
3) HPV with sequential genotyping (HPV 16 and 18) and cytology	2	3	69.1 and 81.5	66.6 and 94.0	76.1 and 87.4	63.2 and 93.5
4) HPV with co-test genotyping (HPV 16 and 18) and cytology	1	4	90.3	57.6	96.6	53.6

CIN = cervical intraepithelial neoplasia; DTA = diagnostic test accuracy; HIQA = Health Information and Quality Authority; HPV = human papillomavirus

HIQA = Health Information and Quality Authority; HPV = human papillomavirus; NR = not reported.
[a] The sequences determined by the orders of percentages of total screened.

Referral to Colposcopy

Systematic reviews

The colposcopy referral rates of the previously mentioned triage strategies (

Figure 6) were summarized by the authors of the HIQA SR (n = 6)[6] The results are presented in Table 15. The colposcopy referral rates were not compared to each other or meta-analyzed.[6] Among the four screening strategies that are relevant to the Canadian setting, primary HPV testing followed by co-testing (genotyping for HPV 16 and 18 and cytology) seemed to have higher referral rates than the other three strategies.[6] The differences in the referral rates of total screened between the other three strategies were not clear.[6]

Table 15: Colposcopy referral rates of triage strategies

Triage strategies	% of total screened (range)	% of total triaged (range)	Number of studies
HPV with cytology triage	2.8 to 12.1 (NR in one study)	25.9 to 38.7	6
HPV with genotyping (HPV 16 and 18)	4.5, 12.3 and NR	28.8, 27.6, and 70[a]	3
HPV with sequential genotyping (HPV 16 and 18) and cytology	4.3, 4.4, and NR	9.6, 9.5, and 31.8[a]	3
HPV with co-testing genotyping (HPV 16 and 18) and cytology	20.1, 20.2 and NR	44.8, 43.3, 76.7[a]	3

HIQA = Health Information and Quality Authority; HPV = human papillomavirus; NR = not reported.

[a] The sequences determined by the orders of percentages of total screened.

Primary studies

There were no primary studies identified that reported colposcopy referral rates based on these four triage strategies.

Summary of Results

Summary of Results for Question 1

Four systematic reviews were included for the comparison between HPV tests and cytology.[6,22,38] Twenty-two relevant publications of 21 primary studies were identified that were published after the literature search cut-offs of the included SRs.[21,40-58]

Diagnostic test accuracy outcomes were addressed using the results of the Cochrane review[38] and the review by the HIQA.[6] Authors of the Cochrane review[38] directly compared three types of HPV tests (HC2, Aptima, and PCR [13 or more virus strains]), to cytology. The HIQA review compared HC2 to cytology.[6] Both reviews[6,38] concluded that, at the HPV threshold of 1pg/mL or 1 RLU:

- HC2 was more sensitive than cytology at the threshold of ASCUS for the detection of CIN2+ and CIN3+ (Table 45 [HC2] and Table 44 [cytology])
- HC2 was less specific than cytology at the threshold of ASCUS for the detection of CIN2+ and CIN3+ (Table 45 [HC2] and Table 44 [cytology])

The Cochrane review[38] reported that the sensitivity of HPV testing was higher in the studies at high risk of verification bias and in those at low risk regarding the prediction of CIN3+ in Table 47[38] suggesting that sensitivity is overestimated. For CIN3+, the sensitivities of HPV testing reported in the studies that recruited participants older than 30 years of age were higher than the sensitivities reported in studies where all eligible screening ages were included (93.9% [95% CI; 89.3% to 96.6%] versus 92.6% [95% CI; 89.6% to 95.3%])[38] which is as expected due to a higher prevalence of high grade lesions in this group of participants older than 30 years of age.

The results of seven of the eight primary studies identified since the publication of the SRs supported the conclusion that HPV tests, including HC2, multiplexed genotyping, Aptima, Cobas, and Confidence, demonstrate higher sensitivity and lower specificity than either LBC or conventional cytology.[41,49,51,54,56,58] One retrospective study by Jin et al.[21] found that HC2 was both more sensitive and more specific than cytology. There was no definitive explanation as to why the results of this study were discordant; however, the authors did not specify the diagnostic threshold used for HC2 testing nor did they adjust the results for verification bias.

Acceptance of screening invitations was evaluated in one SR. Based on the summary results of the review by Verdoodt et al.,[22] the pooled estimates in both the per-protocol and intent-to-treat analyses showed that the option of mailing a self-collected HPV test to all eligible participants who were overdue for screening was more accepted than undergoing standard cervical cancer screening. In both analyses, the acceptance of the opt-in self-sampled HPV testing option was not significantly different from that of standard cervical cancer screening.[22] The option of going door-to-door and offering self-collected HPV testing kits to participants overdue for screening was not associated with significantly different acceptance rates when compared to conventional screening.[22]

Based on results of the five primary studies published after Verdoot et al., there was evidence to show higher participation rates for self-collected HPV testing than for conventional cytology testing among women who were considered as non-attenders for cervical cancer screening.[42,44,45,47,48] Among the five studies that tested the statistical significance in the difference between groups,[44-48] three reported higher participation rates in the self-sampling group.[8,44,47] However, Zehbe et al.[46] conducted a cluster randomized study of First Nations communities in Ontario and found similar participation rates between self-sampling and control arms.[46] Rossi et al. compared four strategies, self-sampler delivered to home for self-testing, obtained in pharmacy, cytology at clinic and HPV tests at clinic did not

report significant differences in participation rates.[48] The relative frequencies of participating in cervical cancer screening via clinician-sampled HPV tests was higher than those for cytology in the study by Pasquale et al.[57]

Colposcopy referral rates and the detection of CIN3+ were reported in the SR by Melnikow et al.[39] Among participants who were triaged, higher colposcopy referral rates and detection of CIN3+ were reported in the primary HPV testing arms compared to cytology in round 1.[39] Higher rates of colposcopy referral were observed among participants younger than 35 years versus those aged 35 years and older.[39] There was heterogeneity in screening strategies, settings, and populations observed in the studies included in the SR by Melnikow et al.[39] The one-arm cohort study (Zorzi et al.) reported higher colposcopy referral rates at the first round of screening (4.4%) as compared to the second round (2.2%) two years later.[39]

Four primary studies published after the draft SR by Melnikow et al[39] evaluated colposcopy referral in two different ways: relative to total participants screened or relative to the number of participants who were triaged or randomized.[40,41,49,50,55] Referral rates relative to the total number of participants screened ranged from 0% for LBC to 16.3% for multiplex HPV genotyping.[40,41,49,50,55] In the studies looking at referral relative to the number of participants who were triaged or randomized, the referral rates for Cobas, HC2 or Cobas with LBC triage, and LBC were 0.4% or less.[40]

There was limited evidence available to address harms and clinical utility. Although Melnikow et al.aimed to assess the harms and adverse events associated with cervical cancer screening, limited results were identified amongst the included primary studies dating back to 2011.[39]

Summary of Results for Question 2

Baseline and longitudinal DTA of four different HPV testing and triage strategies were compared in the HIQA SR.[6] There were four primary studies included and, due to heterogeneity, there was no meta-analysis conducted.[6] Based on the results presented in the HIQA SR, there seemed to be a trade-off between the sensitivities and specificities of the four strategies.[6] Primary HPV testing, followed by triage with sequential genotyping and cytology, was less sensitive and more specific than primary HPV testing followed by cytology triage in three included primary studies.[6] Primary HPV testing follow by co-testing with genotyping and cytology was similarly sensitive but less specific than primary HPV testing followed by cytology in two primary studies.[6] Among the four HPV triage strategies, primary HPV testing with HPV test and cytology co-testing seemed to have the highest sensitivity.[6] Primary HPV testing followed by sequential genotyping and cytology seemed to have the highest specificity. There were no additional primary studies identified for these outcomes in the CADTH search.

Longitudinal DTA was summarized based on the same triage strategies.[6] There was no meta-analysis conducted for the three primary studies.[6] The sensitivity and specificity of the primary HPV testing followed by cytology remained high after one to four years of follow-up.[6] The longitudinal DTAs of the other three triage strategies of interest were were compared to baseline DTA.[6] Longitudinal sensitivities were lower than baseline for primary HPV testing followed by either cytology alone, sequential genotyping and cytology, or co-testing.[6] The longitudinal specificities were higher for primary HPV testing followed by cytology alone and co-testing, while they were lower for primary HPV testing followed by sequential genotyping and cytology than baseline.[6] There were no additional primary studies identified for these outcomes in the CADTH search.

The colposcopy referral rates based on the four triage strategies were reported in the same four studies that reported DTA outcomes.[6] The results were not meta-analyzed. Primary HPV testing followed by co-testing genotyping and cytology seemed to have higher referral rates of total screened, compared to primary HPV testing followed by either cytology alone, genotyping alone, or sequential genotyping and cytology.[6]

Companion reports

In order to identify additional information regarding the comparability and agreement of DTA between self- and clinician-sampled HPV tests and between self- and clinician-sampled HPV tests or cytology, we undertook a rapid review of the literature, which has been published separately.[63] The review aimed to address the following questions:

- What is the diagnostic test accuracy of self-sampled HPV tests compared with clinician-sampled HPV tests or cytology for asymptomatic cervical cancer screening?
- What is the clinical evidence regarding the agreement or concordance of self-sampled HPV tests and clinician-sampled HPV tests or cytology for asymptomatic cervical cancer screening?

Based on a review and critical appraisal of one SR, four RCTs, six prospective cohort studies, and two cross-sectional studies it was found that there is evidence to show that self-sampled human papilloma virus (HPV) tests can achieve similar diagnostic test accuracy as clinician-sampled HPV tests with certain combinations of HPV tests and sampling devices for the detection of CIN2 (cervical intra-epithelial neoplasia) or severe diagnosis. For example, GP5+/6+ PCR HPV tests based on cervix specimens sampled with brushes or lavage have similar sensitivities and specificities as clinician-sampled HPV tests. Signal-based HPV tests including Hybrid Capture (HC2), one of the most widely tested HPV tests, are less sensitive and less specific with self-sampled specimens. There are individual studies showing high concordance or fair to high agreement between self- and clinician-sampled HPV tests. However, self-sampled HPV tests are less sensitive and specific than cytology at the threshold of ASCUS (atypical squamous cells of undetermined significance) or more severe dysplasia.

The advantages of self-sampled HPV tests included better acceptance by those eligible for routine screening programs. Self-sampled HPV tests detected more cases with findings of CIN2 or more severe than cytology or co-testing with clinician-sampled HPV tests and cytology.

The limitations of this review include considerable heterogeneity between studies, relatively few studies on the agreement between self- and clinician-sampled HPV tests, and the applicability of the existing evidence to vaccinated populations.

Further detail regarding the methods and results of the rapid review are available on the CADTH website.[63]

Review of Economic Studies

A review of the published and grey literature was conducted to identify relevant economic evaluations that assessed the cost-effectiveness of various HPV screening strategies. Twenty-five unique economic evaluations were identified that addressed the cost-effectiveness of at least two of the three screening strategies of interest (i.e. cytology, cytology with HPV-DNA triage, or primary HPV-DNA with cytology triage) in one of the settings of interest. [24,64-86] Appendix 10 provides details on each economic evaluation.

The applicability of these studies in addressing the research question of interest in this review is mixed. Some of the economic evaluations reviewed all three tests of interest, while other studies often compared cytology on its own with the addition of HPV triage, or compared primary cytology and primary HPV DNA screening with a triage using the opposite approach and excluded cytology alone as a comparator. The age at which screening began and intervals between screenings varied, with age at which screening started ranging from ages 21 to 30 and intervals in between tests ranging from 1 to 10 years. Where most economic evaluations were similar was in the commencement of HPV DNA testing at age 30 when it was included as part of the strategy, with primary cytology used in all screenings prior to that age. Many studies in non-Canadian jurisdictions examined the impacts of incorporating vaccinations to various screening strategies on strategy cost-effectiveness.

Four economic evaluations were conducted in a Canadian setting, two of which were national in scope,[76,80] while the other two were conducted with province specific parameters.[68,85] All studies applied the public health care payer perspective, the perspective of interest, and all but one compared the strategies and comparators of interest, though they followed the broader trend, observed in the entire sample of literature reviewed, of varying starting ages for screening and intervals between screenings. The modelling approach between the studies varied, with two studies employing a cohort-level state-transition model,[76,87] one study using a dynamic-event based microsimulation,[80] and the final study using a patient-level state-transition model.[85] The study by Popadiuk et al. (2016)[80] using a dynamic-event based microsimulation incorporated HPV transmission within the model, but the model only followed a cohort of women for 30 years. None of the models in the Canadian context used a lifetime Markov model to simulate the natural history of cervical cancer amongst Canadian eligible for cervical cancer screening and a decision tree to capture the outcomes of screening. Strategies incorporating HPV DNA testing, either as a primary test or as a triage following equivocal cytology results, appeared on the efficiency frontier in all four studies. The study from which our

proposed model is adapted did not use a lifetime time horizon, nor were any sensitivity analyses conducted.[68]

Primary Economic Evaluation

This section addresses Research Question 3: What is the comparative cost-effectiveness of primary HPV testing, with or without cytology triage, compared with primary cytology-based testing for cervical cancer screening of asymptomatic individuals eligible for screening in Canada?

Economic Review

A review of the published and grey literature was conducted to identify relevant economic evaluations that assessed the cost-effectiveness of various HPV screening strategies. Given the high number of published economic evaluations identified on this topic, the ecoomic review adopted a similar approach to the clinical review by focusing only on studies that were conducted in countries with a health care context comparable to Canada's. With this inclusion criteria, 25 unique economic evaluations were identified that addressed the cost-effectiveness of at least two of the three screening approaches of interest (i.e. primary cytology, primary cytology with HPV triage, or primary HPV with cytology triage).[24,64-86] Appendix 10 provides details on each economic evaluation.

Although most of the economic evaluations reviewed all three screening approaches of interest, , there was considerable variation observed in the sreening strategies that were evaluated between studies. Differences included the targeted age range for programmatic screening, the frequency of screens, the criteria for triage and colposcopy referral, and the management algorithms for abnormal screening findings. The age at which screening started ranged from ages 21 to 30 and screening intervals in between tests ranged from one to ten years. Where most economic evaluations were similar was in the commencement of HPV testing at age 30 when it was included as part of the strategy, and in some cases, the screening strategy incorporated primary cytology prior to that age. Several studies in non-Canadian jurisdictions examined the impacts of incorporating vaccinations to various screening strategies on strategy cost-effectiveness.

Four economic evaluations were conducted in a Canadian setting, two of which adopted a national scope,[76,80] while the other two were province-specific .[68,85] All studies applied the public health care payer perspective and all but one compared the threescreening approaches of interest. However, none fully captured all screening strategies that were of interest to this review due to variations in targetted age range for screening and the screening frequency. The modelling approach between the studies varied, with two studies employing a cohort-level state-transition model,[76,87] one study using a dynamic-event based microsimulation,[80] and the final study using a patient-level state-transition model.[85] The study by Popadiuk et al. (2016)[80] using a dynamic-event based microsimulation incorporated HPV transmission within the model, but the model only followed a cohort of females for 30 years. None of the Canadian models evaluated an HPV vaccinated population. Strategies incorporating HPV testing, either as a primary test or as a triage following equivocal cytology results, appeared on the efficiency frontier in all four studies.

Thus, existing economic evaluations do not fully address the screening strategies of interest to this review and it remains unclear how the economic value of screening may differ between an unvaccinated and vaccinated population. Because of these gaps, a de novo economic analysis on the cost-effectiveness of different programmatic screening strategies for the Canadian population (pre-vaccinated and partly-vaccinated) was conducted as part of the economic review. The economic models identified from the literature provided insights in conceptualizing and developing the model structure and in determining appropriate model assumptions.

Primary Economic Evaluation

Methods

A primary economic evaluation was conducted to assess the lifetime costs, health outcomes and cost-effectiveness of HPV testing compared to cytology as the primary screening tool, with or without triage, as part of an organized

cervical cancer screening program within a Canadian population eligible for screening. A protocol for the economic evaluation was written a priori and followed in the conduct of this review.[88]

Type of analysis

Given the broad implications of implementing a population-level screening program, a cost-utility analysis was conducted. Health outcomes were expressed as quality-adjusted-life-years (QALYs) to capture both the mortality and morbidity impacts related to detecting precancerous cervical lesions and cervical cancer. The primary outcome was the incremental cost per QALY gained, commonly referred to as the incremental cost-utility ratio (ICUR).

Target population and setting

Canadians eligible for cervical cancer screening represented the target population. Of particular interest were the age ranges of nine to 69 years as the lower bound matched the age in which Canadians would be eligible for HPV vaccination while the upper bound reflected the current recommended age for screening cessation.[23] Single birth-year cohorts were defined and analyzed separately to better understand the potential impact of clinical heterogeneity on cost-effectiveness due to an individual's age and potential vaccination history.[89] Separate age cohorts that were tested in the model included a cohort of individuals aged 9 (i.e., "future incidence cohort" in which individuals entering the model are younger than the screening program start age), a cohort of individuals aged 20 (i.e., "incident cohort" in which individuals entering the model are at the start age of the screening program) and, thereafter, at age increments of every 10 years (i.e., aged 30representing a "prevalent cohort" in which individuals entering the model are within the screening age range of the screening program). The proportion of vaccinated individuals eligible for screening within an age cohort was further considered within the analysis. Publicly-funded HPV vaccination programs were introduced in Canada in 2006 with all provinces offering vaccination to pre-adolescent girls at the age of 9.[90]

At the start of the model, all individuals are clear of an infection and have no prior history of cervical cancer. Upon entry into the model, individuals are assigned to a level of sexual activity ranging from low (l=0) to high (l=3) (i.e., $l \equiv [0,1,2,3]$ that corresponds to the number of lifetime sexual partners (i.e., 0-1, 2-10, 11-39 and 40+ lifetime partners). This parameter impacts the age of onset of sexual activity[91] and therefore, the age in which individuals in the model become at risk of acquiring a hrHPV infection. The proportion of females in each sexual activity level was based upon the Psychosocial Impact of cervical Screening and Condylmas: an Epidemiological Study conducted in Canada.[91]

The setting in the model reflected the Canadian health care system. It was assumed that access to all screening tests would be available.

Time horizon

Given that the impact of screening is long-term in terms of reducing the lifetime risks of developing cervical cancer, a lifetime horizon was defined. The model followed a cohort of Canadians eligible for cervical cancer screening up to their life expectancy with screening offered in accordance to the screening strategy being evaluated. The model cycled yearly with costs and benefits discounted at 1.5%, adhering to latest Canadian guidance.[92] Sensitivity analyses were conducted using a 0% and 5% discount rate.[92]

Interventions

The economic review compared the cost-effectiveness of HPV and cytology screening tests in the context of an organized screening program given that these screening tests would be offered as part of the existing Canadian programmatic screening for cervical cancer. By taking a programmatic approach, the economic analysis could further assess the optimal screening frequency and screening age range. The screening program of interest to this review can be broadly categorized into three approaches (i.e., primary cytology, primary cytology with HPV triage, primary HPV with cytology triage), and can be further subcategorized by the frequency and targeted age range for screening. Although some non-Canadian screening programs now offer co-testing, high quality studies that reported harms, safety, and long-term outcomes did not often compare co-testing with primary HPV tests and therefore co-testing was not considered as an intervention in the review. Table 16 outlines the 11 screening programs evaluated as part of this review. In addition, a no screening strategy was also included as a control to validate the economic model.

There are different assays and techniques associated with each screening test. In past economic evaluations, different cytological methods (e.g., conventional Pap smear and LBC) were found to be comparable[93] and, in this economic model, primary cytology refers to both by considering these methods interchangeable. In triage-based strategies (i.e., strategies B and C), the cytological method was assumed to be LBC. As per the implementation section of this review, a separate sample would need to be taken for HPV test under conventional cytology whereas, with liquid-based preparations, the same smear sample can be used for both cytology and HPV test. This assumption has important implications to costs and convenience. In terms of costs, the screening costs would be lower than if the

cytological method was based on Pap smear since only a single physician visit would be required to collect the cervical sample, obviating the need for a repeat physician visit. This would also be more convenient to patients, thereby reducing the risk of non-participation that can arise if a second visit was required for further testing. Of note, alternatives approaches to collect samples (i.e., self-sampling) were not considered in the economic model given the paucity of evidence from the clinical review in terms of diagnostic test performance.

In the case of HPV testing, the clinical review found little evidence on the comparative diagnostic test accuracy between different commercial assays (e.g., Cobas, Hybrid Capture, Aptima) and techniques (e.g, partial genotyping, full genotyping). In fact, the Cochrane review[38] reported a pooled sensitivity and specificity that combined all commercial HPV tests together. Although a subgroup analysis was available within that study that pooled only the diagnostic test accuracy data of Hybrid Capture 2, the results of the subgroup analysis were similar to the original analysis that combined all HPV tests together. In consulting with the clinical experts involved in this review, it was noted that it would be less meaningful to evaluate Hybrid Capture 2 separately in the economic analysis as numerous other HPV tests have since been commercialized. Specific commercial assays were therefore not explored further in the economic review as it was assumed that HPV tests were broadly interchangeable.

Table 16: List of cervical cancer screening programs evaluated

Abbreviation in report	Strategy name for CC routine screening program	Screening frequency	Targeted age range[1]	Expected lifetime number of screening tests[2]
Strategy A: Primary cytology				
A1	A-3yr-21	Every three years	21 to 69	17
A2	A-3yr-25	Every three years	25 to 69	15
A3	A-3yr-30	Every three years	30 to 69	14
Strategy B: Primary cytology with HPV test for equivocal[3] results				
B1	B-3yr-25	Every three years	25 to 69	15
B2	B-3yr-30	Every three years	30 to 69	14
Strategy C: Primary HPV with cytology triage in HPV positive results				
C1	C-3yr-30	Every three years	25 to 69	15
C2	C-3yr-25	Every three years	30 to 69	14
C3	C-5yr-30	Every five years	25 to 69	9
C4	C-5yr-25	Every five years	30 to 69	8

CC= cervical cancer; HPV = human papillomavirus

[1] the initiation age to screening was either the start of the age range in individuals with a history of sexual activities or, the year in which sexual activities began within the targeted age range

[2] Assuming perfect participation in programmatic screening

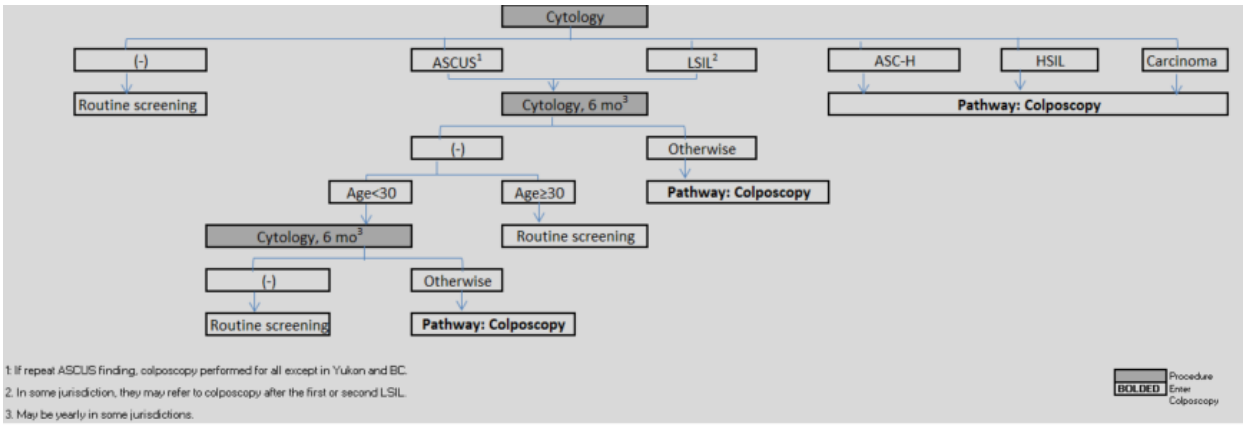
[3] Defined as ASCUS or LSIL

Management of Primary Cytology (Strategy A)

Under this set of strategies, cytology is first conducted on individuals eligible for screening. The management of cytology outcomes in terms of follow-up and treatment was modelled to reflect Canadian clinical practice guidelines for cervical cancer screening.[12,23,94] Figure 7 highlights the screening algorithm captured in the economic model and highlights where variation in clinical practice exists between Canadian provinces.[23]

Cytological results are classified based on the Bethesda system in which squamous cell abnormalities can be classified into ASCUS, ASC-H, LSIL or HSIL. In primary cytology, findings of ASCUS or LSIL during routine screening would result in triage with repeat cytology at six months. If individuals are found to have persistent abnormal cytological findings at six months, they are referred to colposcopy management. If under the age of 30, individuals with a corresponding normal cytology results during repeat testing would have cytology repeated at six months and return to routine screening following two consecutive negative results. If over the age of 30, individuals would return to routine screening upon negative findings in their repeat cytology. At any point of screening, those with ASC-H, HSIL or carcinoma would be immediately referred for colposcopy examination (i.e., colposcopy with or without biopsy) for histological assessment of the cervix.

Figure 7: Management of "Strategy A" Outcomes- Primary cytology

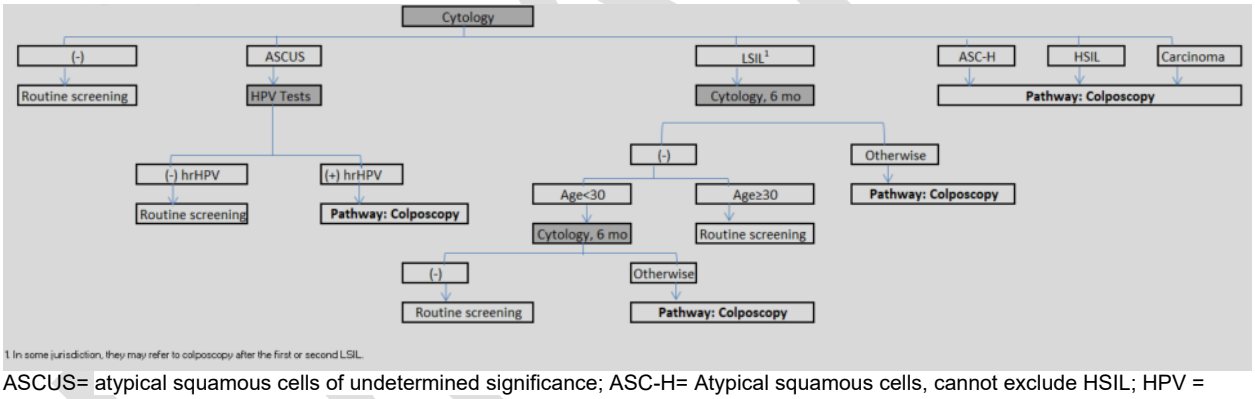


ASCUS= atypical squamous cells of undetermined significance; ASC-H= Atypical squamous cells, cannot exclude HSIL; HSIL= high-grade squamous intraepithelial lesion; LSIL= low-grade squamous intraepithelial lesion;

Management of Primary Cytology with HPV test Triage (Strategy B)

The addition of HPV reflex testing for equivocal cytology results was similar to Strategy A with the exception to how ASCUS findings would be managed (Figure 8). An ASCUS result would result in HPV triage. Patients who test positive for hrHPV following an ASCUS result would be referred immediately for colposcopy examination whereas, patients who test negative for hrHPV would return to routine screening.[94]

Figure 8: Management of "Strategy B" Outcomes- Primary Cytology with HPV tests for equivocal results



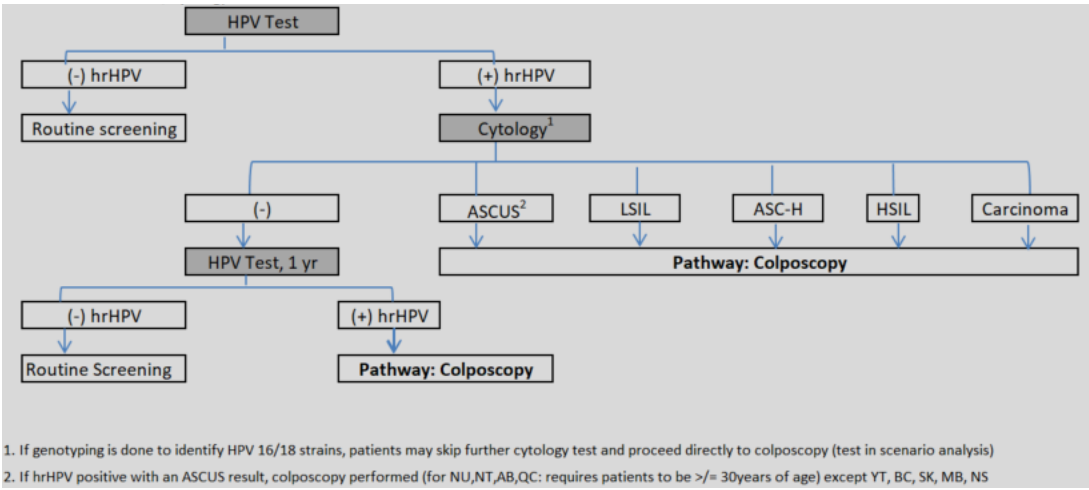
ASCUS= atypical squamous cells of undetermined significance; ASC-H= Atypical squamous cells, cannot exclude HSIL; HPV = human papillomavirus; hrHPV = high-risk human papillomavirus; HSIL= high-grade squamous intraepithelial lesion; LSIL= low-grade squamous intraepithelial lesion;

Management of Primary HPV test with Cytology Triage (Strategy C)

The management of primary HPV testing with cytology triage reflects existing Canadian and international guidelines (Figure 9).[95] HPV testing is first conducted to identify those with an existing hrHPV infection who would be triaged for immediate cytology. In those with abnormal cytological findings, immediate referral for colposcopy would be made, whereas in those with a negative cytological finding, they would undergo repeat screening by HPV test at 12 months. If the repeat test returned as negative, patients would return to routine screening; while, if persistent hrHPV was detected in the repeat test, individuals would be referred for colposcopy to rule out the possibility of a high-grade lesion.[96]

Although the clinical experts consulted in this review noted that the management may differ in screening strategies that also include HPV genotyping, this was not modelled in the current analysis given that the clinical review found limited clinical data on its diagnostic test accuracy.

Figure 9: Management of "Strategy C" Outcomes- Primary HPV with cytology triage in HPV positive results



ASCUS= atypical squamous cells of undetermined significance; ASC-H= Atypical squamous cells, cannot exclude HSIL; HPV = human papillomavirus; hrHPV = high-risk human papillomavirus; HSIL= high-grade squamous intraepithelial lesion; LSIL= low-grade squamous intraepithelial lesion;

Perspective

The perspective of a Canadian Ministry of Health was adopted, consistent with CADTH guidelines for the conduct of economic evaluations.[92] As such, direct and indirect medical costs were captured including the cost of laboratory and diagnostic tests, emergency visits, in-patient visits and medical services. Indirect non-medical costs, such as productivity losses and out-of-pocket costs, were not considered in this analysis.

Decision Analytic Model

Given that the benefits of cervical cancer screening is to detect patients with precancerous cervical lesions who can be treated before it progresses to cervical cancer, the economic model covered the full clinical spectrum from screening to diagnosis to treatment. A hybrid model was developed with two components: i) a state-transition microsimulation that reflects the natural history of disease and ii) a decision tree that captures the impact of screening and modified the disease pathway.

Natural History Submodel (epidemiologic submodel)

The natural history submodel was loosely adapted from an existing Canadian decision-analytic model.[68] Although the modelling approach in the original publication was a Markov cohort model, this was converted to a microsimulation to permit more flexible modelling of how an individual's clinical history and past screening results can impact the natural history and epidemiology of HPV infection, cervical lesions, and cervical cancer and how they are managed within a cervical cancer screening program. Furthermore, deviating from the original model, only high risk HPV infections (i.e., oncogenic strains) were modelled in alignment with the scope of this review. In the original model, low-risk and high risk HPV infections were considered independent and mutually exclusive; this was felt to not align with current evidence in which co-infection by both low-risk and high risk HPV strains is possible.

Although the protocol for this study stated interest in two types of cervical cancer (i.e., squamous cell carcinoma and adenocarcinoma), the clinical review found limited literature supporting the diagnostic test accuracy of HPV and cytology tests in detecting precursor lesions of adenocarcinomas. The original scope of the project was therefore narrowed to focus solely on the impact of screening on squamous cell carcinoma which is estimated to represent from 70%[7] to 90%[97] of all cervical carcinomas. This meant that the potential cytological outcomes of atypical glandular cells, which is a precursor lesion to adenocarcinoma, was largely ignored in terms of how it could potentially influence patient management.

The epidemiological submodel captured the natural history of HPV infection and the potential development of cervical carcinoma. Distinct health states were defined that represented HPV infection, pre-cancerous cervical changes and cervical cancer (

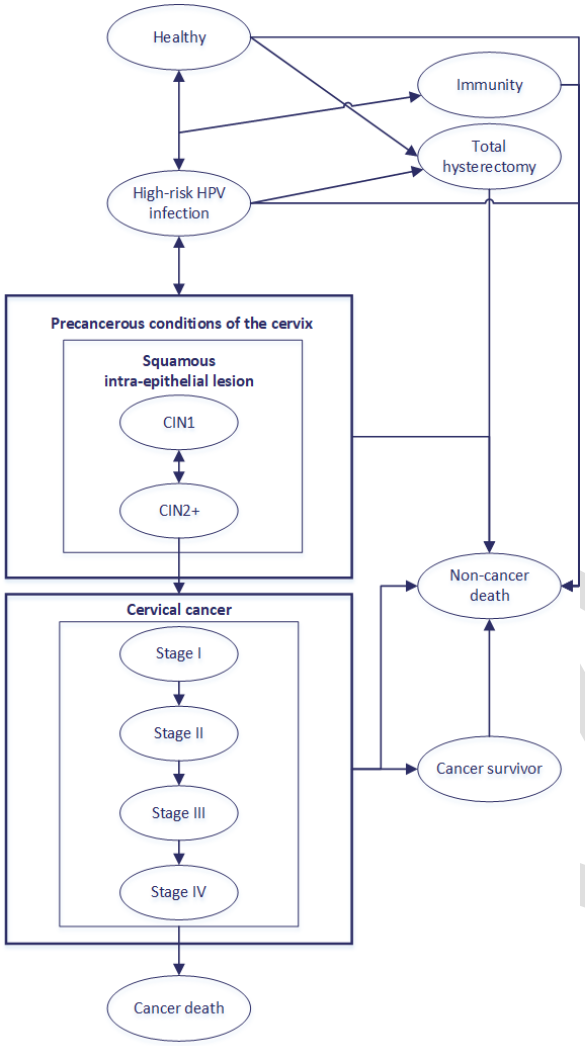
Figure 10). At the start of the model, all individuals were clear of an infection and had no prior history of cervical cancer (defined as healthy). Each year, age-dependent probabilities for death (all cause) and total hysterectomy unrelated to cervical dysplasia were applied. If either of these events occurred, the individual would not be considered at risk of developing cervical cancer. In the case of those who had undergone total hysterectomy, the model would then estimate the expected life expectancy of that individual.

Within the epidemiological submodel, age-dependent risk of acquiring hrHPV infection was applied once an individual was sexually active. Over annual cycles, hrHPV infections could be transient as the infection can clear spontaneously (i.e., returns to the healthy state) or persist and develop into pre-cancerous abnormalities of the cervix. The severity of pre-cancerous lesions reflected histological classification. Although both a two- and three-tiered classification system exists in clinical practice, the two-tier classification (i.e., CIN1, CIN2+) was selected given growing concerns regarding the poor differentiation in the diagnosis of CIN2 and the growing belief that CIN2 is not a distinct clinical entity but rather a heterogeneous mix of CIN1 and CIN3 lesions.[98] Furthermore, this reflected current treatment guidelines in which clinical management of pre-cancerous lesions is based upon the two-tiered system.[96] High Risk HPV infection can progress to either CIN1 or CIN2+. These lesions may spontaneously regress to a lower severity, clear completely or progress to more serious abnormalities. Clearance of a CIN lesion, either spontaneously or through treatment, may lead to the development of HPV-immunity whereby the individual is not at future risk of acquiring HPV infections. Lesions were assumed to be detected only by screening; undetected and untreated CIN2+ lesions can progress towards cervical cancer.

Once cervical cancer developed, regression was not possible. The natural progression from cervical cancer was described by four stages based upon the International Federation of Gynecology and Obstetrics (FIGO) staging system (stage I = local; Stage II-III = regional; IV= distant).[99] Cancer progression was assumed to be sequential and unidirectional with asymptomatic cancer possibly developing into more severe stages. Cancer detection was either made possible from the presence of symptoms or through the outcome of routine screening and, upon diagnosis, patients would receive cancer treatment in alignment to existing clinical practice guidelines depending on their cancer stage.[100,101] Treated cases were tracked during the first five years post-cancer given the increased mortality risk of these patients compared to a general population.[102] Those who remained alive at five years post-cancer entered a cancer survivor health state. In this health state, individuals were assumed to have a life expectancy identical to an age-matched general population (i.e., mortality rates of cancer survivors beyond the first five years of treatment were assumed identical to those of a normal population).

Details on the value of the clinical inputs to the natural history of the condition can be found in section the section on Clinical Parameters.

Figure 10: Disease States and Allowed Transitions for the Natural History Component of the Cervical Cancer model



CIN = cervical intraepithelial neoplasia; HPV =human papillomavirus

Screening Model

The screening model was applied to the epidemiological model when an individual was eligible and participated in screening. Eligibility to participate in programmatic cervical cancer screening was based upon the screening algorithm being evaluated (i.e., age range and screening frequency) and certain criteria in existing Canadian clinical guidelines.[23,94] Specifically, patients who had undergone total hysterectomy unrelated to cervical dysplasia or who had not engaged in sexual activity were assumed ineligible for screening.

The screening algorithm reflected the screening strategy described above under Interventions. Individuals who did not participate in screening (i.e., missed) would continue to be modelled in the epidemiological model but may return at any time to routine screening before their next scheduled screening visit.

Progression through the screening model is dependent on an individual's health state within the epidemiological model at the time of screening (e.g., healthy, pre-cancerous lesion, cervical cancer), the diagnostic performance of the screening tests and the individual's adherence to the clinical management associated with screening (e.g., proportion of positive screens not lost to follow-up). For instance, in an individual with no histologic abnormalities (i.e., <CIN1), a result of ASCUS or worse on cytology would be considered a false positive. However, in subsequent years, they may be infected with HPV and develop CIN2+ lesions. If screened again, a result of ASCUS or worse on cytology would be considered a true positive.

As noted above in both the clinical review and in the description of the screening strategies, results of cytology were based on the Bethesda classification system. Table 17 shows how histological health states used in the epidemiological model were mapped to cytology outcomes.[98]

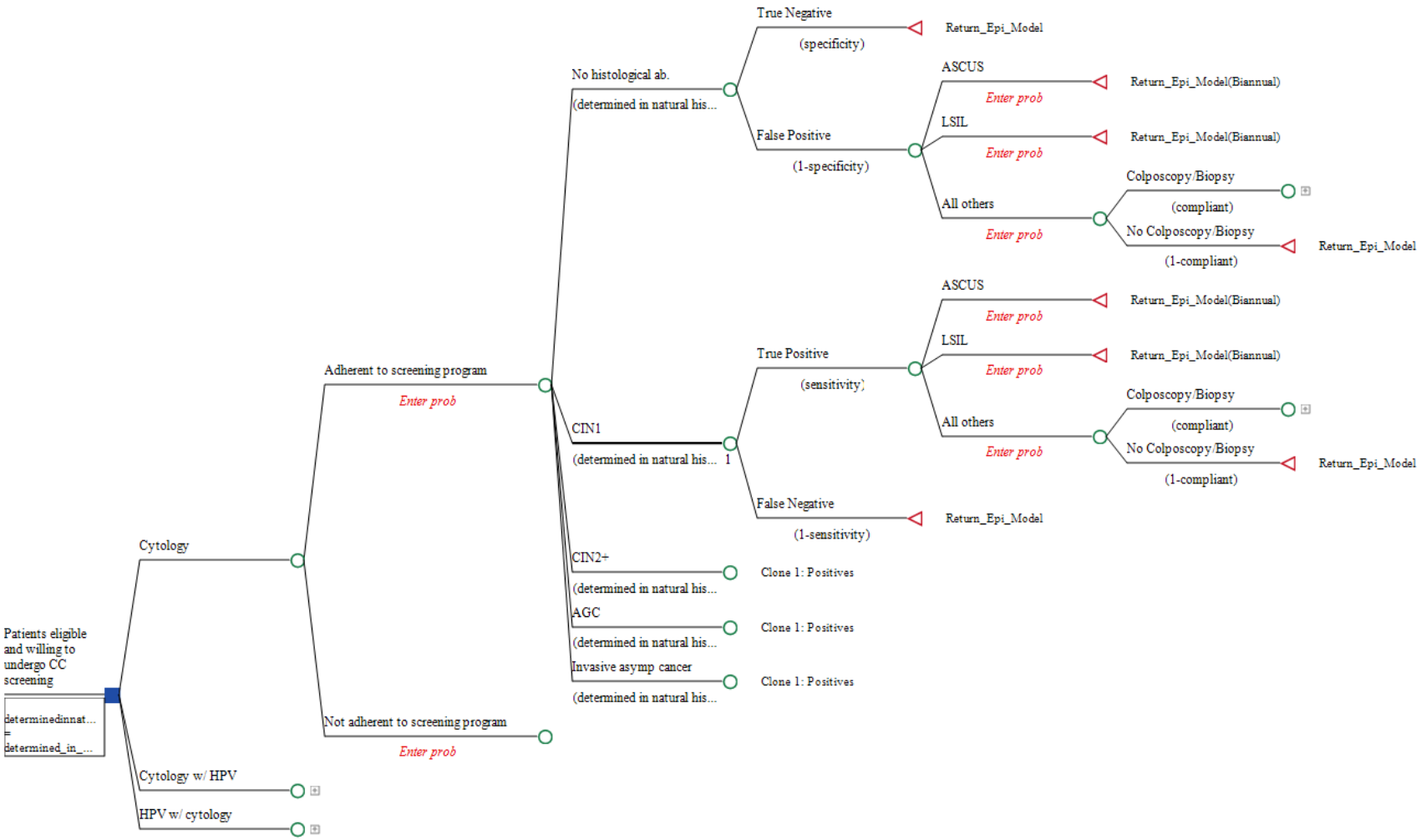
Table 17: Correspondence of cytology and histological diagnostic terms

Cytology			Histology (determined by colposcopy and/or biopsy)
Testing cut-offs		Cell characteristics used as a marker	Actual disease state of cervical tissue
		2001 terminology	
ASCUS+		ASCUS	None
		ASC-H	
		AGC	
	LSIL+	LSIL	CIN1
		HSIL	CIN2+ or invasive cervical cancer

Adapted from CADTH, 1998[93]

In terms of the clinical management of a cervical abnormality identified from screening, this may include repeat screening or histological assessment. Repeat screening was modelled similarly to the above but reflected the increased frequency of screening. In the case of cytology-only (strategies A) and cytology with HPV triage (strategies B), screening occurred every six months and routine screening would resume after two consecutive negative results. In the case of HPV with cytology triage (strategies C), a repeat screen would be given a year after and routine screening would resume if the repeat screen produced negative findings.

Differences in the test characteristics and the order in which the screening tests were applied, alongside the natural epidemiology of an individual therefore permitted the model to generate a different set of costs and health outcomes based on the screening algorithm that formed the basis of the comparative analysis.



1825

1826 **Figure 11: Representation of the Decision Tree Capturing the Screening Algorithms**

Management of abnormal screening outcomes

Based on the screening strategy, individuals with abnormal cervical screening test may be referred for colposcopy to determine individualized management. Most published economic models have assumed that colposcopy and/or biopsy are the diagnostic gold standard for confirming the presence and grade/severity of CIN and cervical cancer and this was similarly assumed in this model. Biopsy-confirmed cervical disease was defined based upon the histological classification of the cervical lesions or cancer (Table 17). Within the model, performing colposcopy on an individual who in fact has no histologic abnormalities as per the epidemiological model (i.e., representing a false positive screening test) would result in negative colposcopy findings and led to appropriate workup. However, in an individual with CIN2+ lesions (i.e., representing a true positive screening test), colposcopy and biopsy would lead to positive colposcopy and biopsy and subsequently determine the individual's appropriate clinical management.

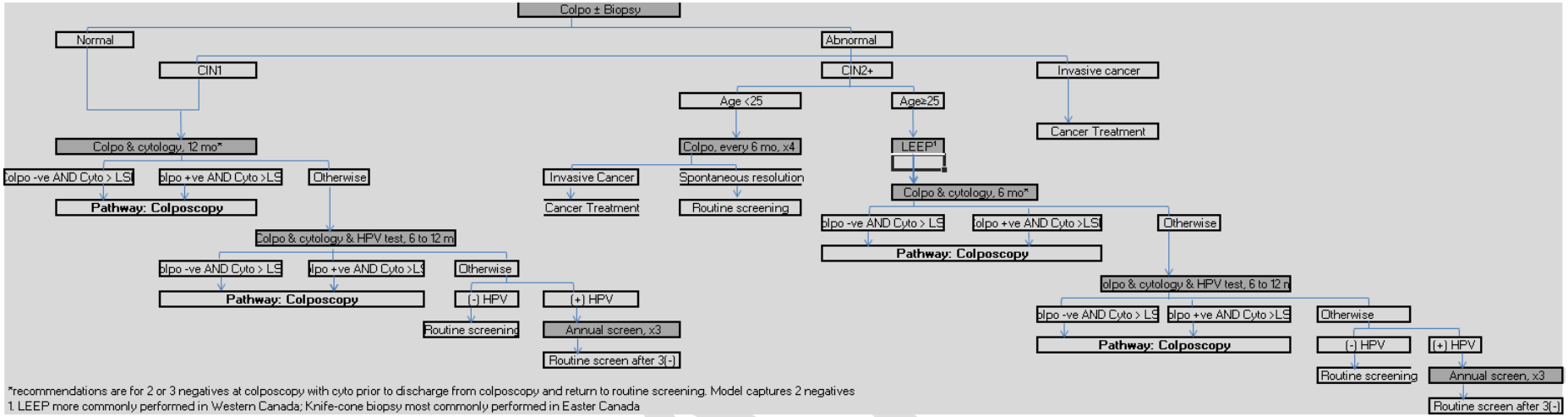
The clinical pathway of colposcopy and/or biopsy were modelled according to current clinical practice guidelines (Figure 12).[94,96] Referral to colposcopy in which the biopsy results were CIN1 or less would be managed conservatively with annual follow-up visits where colposcopy and cytology would be performed over three subsequent years. In individuals with cytology findings greater than LSIL during follow-up care, biopsy would be performed to determine appropriate clinical management. Otherwise, individuals would be eligible for discharge from colposcopy following persistent normal, ASCUS or LSIL cytological findings at the last follow-up visit. Prior to exiting colposcopy, hrHPV testing would be performed during the last follow-up visit to provide an objective risk assignment to inform the screening frquency upon discharge from colposcopy. Individuals with negative HPV test were considered low risk and discharged to routine screening whereas, individuals with positive HPV test were considered elevated risk and discharged for annual surveillance in primary care for another three years.[103]

The clinical pathway to manage abnormal colposcopy with biopsy-confirmed CIN2+ findings was dependent on the individual's age. Those 25 years or older would undergo loop electrosurgical excision procedure (LEEP). In the case of a successful LEEP, this would change the individual natural history within the Markov epidemiological model as they would return to a healthy state given the removal of the cervical dysplasia. Post-treatment SIL management would entail colposcopy and cytology six months after with both tests repeated a year thereafter. Similar to the outcomes of follow-up visits for <CIN1, individuals with cytology findings greater than LSIL during these follow-up visits would have biopsy performed to reassess appropriate clinical management. Otherwise, if cytological findings are equal or less than LSIL throughout the follow-up visits, individuals would be discharged from colposcopy. Prior to exiting colposcopy management, hrHPV testing would be performed at the last follow-up visit to guide the screening interval in primary care in the same manner as above.[103] Conservative management with biannual colposcopy for two years would be offered to individuals with abnormal colposcopy with biopsy-confirmed CIN2+ findings if they were under the age of 25 years. If spontaneous resolution is observed at end of these follow-up visits, individuals would be discharged from colposcopy. If the individual turns 25 years of age during the follow-up period, clinical management would be reassessed based upon the findings of the last colposcopy procedure (i.e., <CIN1 would result in more frequent screening, CIN2+ would receive LEEP). [103]

While an individual is under management by colposcopy, if invasive cancer is detected, the individual would exit colposcopy management and enter clinical management by regional cancer programmes.

Colposcopy may lead to a diagnosis of cervical cancer and result in more timely treatment management at an earlier stage of the disease. Re-referral to colposcopy would be based on routine screening results.

Figure 12: Management of individuals with abnormal cytology smears who proceed with colposcopy/biopsy



CC = cytology and colposcopy; CIN = cervical intraepithelial neoplasia; LEEP= loop electrical excision procedure;

The model was developed in Microsoft Excel 2010.

Clinical Parameters

Natural History

Epidemiology of HPV Infection, Pre-cancer Lesions and Cervical Cancer

Natural history parameters on HPV infection, pre-cancerous lesions and cervical cancer are described in Table 19.

The simulated population was assigned to a level of sexual activity from low (l=0) to high (l=3) corresponding to the expected number of lifetime partners. Proportion of individuals by sexual activity level were based on a calculation of PISCES data performed by Brisson et al[91] with the total proportions (by summing the proportions in the four levels) scaled to 1. The age of onset of sexual activity was determined based on an age- and sexual activity level-specific rate of sexual activity initiation amongst females. The rate of onset was determined by fitting to the data from Canadian Community Health Survey on the percentage of girls who ever had sex (Table 18).[91]

Table 18: Sexual Activity Parameters- Proportion of individuals by sexual activity levels and rate of onset of sexual activity

	Sexual Activity Levels					
	L=0		L=1		L=2	L=3
Number of lifetime partners	0 to 2		2 to 10		11 to 39	40+
Proportion of individuals by sexual activity level	0.16 to 0.36		0.41 to 0.67		0.14 to 0.27	0.01 to 0.02
Rate of onset of sexual activity, by age						
Age	L=0		L=1		L=2 and L= 3	
	Min	Max	Min	Max	Min	Max
9	0	0	0	0	0	0
10	0	0	0.003	0.004	0.011	0.017
11	0	0	0.009	0.013	0.022	0.032
12	0	0	0.009	0.013	0.022	0.032
13	0	0	0.033	0.049	0.129	0.194
14	0.02	0.029	0.033	0.049	0.129	0.194
15	0.057	0.086	0.157	0.235	0.129	0.194
16	0.064	0.096	0.214	0.321	0.202	0.303
17	0.16	0.24	0.214	0.321	0.202	0.303
18	0.16	0.24	0.326	0.489	0.202	0.303
19	0.163	0.244	0.326	0.489	0.257	0.386
20+	0.095	0.143	0.261	0.391	0.271	0.406

Since estimates on the test performance of HPV test are conditioned on underlying histology rather than the HPV's strain, the model made no distinction between different strains of hrHPV. Incidence, progression, and regression estimates therefore represent averages for all viral types.

Estimates on the annual incidence of hrHPV infection were based on an epidemiological modelling study prepared for the U.S. Preventive Services Task Force.[104] In that study, annual age-specific incidence rates were back-calculated in order to produce incidence rates that aligned with several reported HPV-prevalence studies conducted prior to the introduction of HPV vaccination.[104] Although a longitudinal cohort of women aged 15 to 49 years whom were recruited from physician practices in Ontario was identified that could have provided Canadian estimates,[105] this study was not selected for a number of reasons. This study followed-up on 253 of 500 previously HPV-negative women recruited from a prior prevalence survey. Incidence estimates were derived from a small sample size and the incidence of HPV infection beyond the studied age range is not clear. However, as this is one of few Canadian studies identified that reported age-specific annual HPV incidence rates, a sensitivity analysis was conducted with these numbers. The incidence of HPV infection was independent of the individual's sexual activity level. Clearance of

hrHPV infections was based on the above-mentioned US model in which the annual probability was calibrated based on Surveillance, Epidemiology and End Results (SEER) data.[104]

It is difficult to directly estimate the progression and regression between high risk HPV, CIN1 and CIN2+ from published literature given the variation and differences between study designs, follow-up intervals, performance of screening in detecting cervical lesions and protocols to manage abnormal results. As such, the progression and regression of CIN lesions were taken from a recent US model that based these values on both a review of the literature and calibration of data to observed clinical event rates. The estimates reflect an average for all types of hrHPV strains. Although CIN has been historically viewed as a continuum with progression from HPV infection to CIN1, CIN2 and CIN3 assumed to occur slowly over decades, recent understanding of the disease suggest that, amongst younger women, a different disease progression may be more appropriate given higher disease burden. Specifically, younger women can develop a CIN2+ lesion within a short period of time (i.e., <2 years) with most regressing and only a small proportion progressing. Some of the parameters on progression and regression of hrHPV, CIN1 and CIN2+ therefore were age-specific.[104] The only parameter that differed from that model was the progression from CIN2+ to cancer as their estimate was specific to CIN3 health state. The annual rate of progression was instead taken to be 0.18%.[106] The values were confirmed by consultation with the clinical experts involved in this review.[104] The transition from hrHPV infection to CIN1, CIN2+ and cervical cancer stage was obtained from previous economic models and are reported in Table 19.

The effectiveness of LEEP was based on meta-analysis[107] that further incorporated the rates of success reported from a clinical study that was not part of the original meta-analysis.[108]

Canadian age-specific rates of hysterectomy unrelated to cervical cancer (i.e., hysterectomy for reasons other than cervical cancer) were applied.[91] In these individuals, no further screening was assumed necessarily (i.e., not at risk of developing cervical cancer); therefore, these individual do not accumulate further costs related to screening and the model estimated their overall life expectancy.

Once an individual develops cervical cancer, asymptomatic or undetected cancer can progress to more severe stages of the disease. As reported in past economic evaluations, there is limited direct clinical data to inform the rate of progression from localized cervical cancer to distant cancers and the proportion of cervical cancers that presents symptomatically. We therefore adopted an approach taken in past economic evaluations[74,109] whereby the distribution of cervical cancer cases, by disease stage, in an unscreened population was assumed to be a function of both the rate of disease progression and the probability of symptomatic presentation. The progression rates between cancer stages and the probability of symptomatic presentation was varied to calibrate against reported distribution of cervical cases, by stage, in cervical cancer patients who have never been screened.[110-113].

Table 19: Natural History Parameters- Annual values unless otherwise specified

Model Parameters	Value	Probabilistic Distribution	Reference
hrHPV Infection			
Incidence rate of hrHPV infection	Age-specific, ranging from 0.03 to 0.25		Sellors, 2003;[105] Kulasingam [104]
Regression: hrHPV+ to healthy (<35 years)	0.37		Calibrated by Kulasingam [104]
Regression: hrHPV+ to healthy (≥35 years)	0.23		Calibrated by Kulasingam [104]
Progression: hrHPV+ to CIN	0.192		Skinner, 2016[114]
Proportion: CIN1 vs. CIN2+ (<25 years)	0.90		Calibrated by Kulasingam [104]
Proportion: CIN1 vs. CIN2+ (≥25 years)	0.56	Beta (97, 74)	Skinner, 2016[114]
CIN1			
Regression of CIN1 (<24 years)	0.31		Calibrated by Kulasingam [104]
Regression of CIN1 (25≤years<30)	0.12		Calibrated by Kulasingam [104]
Regression of CIN1 (≥30 years)	0.06		Calibrated by Kulasingam [104]

Model Parameters	Value	Probabilistic Distribution	Reference
Proportion: hrHPV+ vs healthy	0.10		Calibrated by Kulasingam [104]
Progression from CIN1 to CIN2+ (20≤years<30)	0.1415	Beta (15,106)	Syrjanen, 1992 [115]
RR, individuals under 20 years of age compared to individuals 20 to 30 years of age	0.39		Kulasingam [104]
RR, individuals under 20 years of age compared to individuals 20 to 30 years of age	2.32		Kulasingam [104]
CIN2+			
Regression of CIN2+ (<30 years)	0.22		Kulasingam [104]
Regression of CIN2+ (30≤years<40)	0.12		Kulasingam [104]
Regression of CIN2+ (≥40 years)	0.01		Kulasingam [104]
Proportion: CIN1 vs healthy	0.04		Calibration
Progression from CIN2+ to cervical cancer (<30 years)	1.8E-3	Lognormal (95% CI: 4E-5 to 0.034)	Cantor, 2005 [106]
RR, individuals between 30 to 40 years of age compared to individuals 30 years of age	0.6	Lognormal (95% CI: 0.2 to 1.5)	McCredie, 2008 [116]
RR, individuals between 40 to 50 years of age compared to individuals 30 years of age	1.2	Lognormal (95% CI: 0.5 to 2.9)	
RR, individuals over 50 years of age compared to individuals 30 years of age	2.5	Lognormal (95% CI: 1.0 to 6.7)	
Probability of successful treatment for LEEP	0.86	Beta (1336,225)	El-Nashar, 2017; [107] Chirenje, 2001 [108]
Cervical Cancer			
Stage I to Stage II	0.148	Uniform (0.212, 0.340)	Chuck, 2004 [68]
Stage II to Stage III	0.293	Uniform (0.226, 0.360)	
Stage III to Stage IV	0.397	Uniform (0.309, 0.484)	
Probability of symptomatic cervical cancer at Stage I	0.15	Uniform (0.109, 0.179)	Myers, 2000; [109] Chuck, 2004 [68]
Probability of symptomatic cervical cancer at Stage II	0.225	Uniform (0.162, 0.261)	
Probability of symptomatic cervical cancer at Stage III	0.60	Uniform (0.399, 0.609)	
Probability of symptomatic cervical cancer at Stage IV	0.90	Uniform (0.561, 0.900)	

CI= confidence interval; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papillomavirus; LEEP= loop electrical excision procedure; RR= relative risk

Mortality

Baseline mortality rates were informed by female age-specific mortality rates from Statistics Canada's lifetables[117] and adjusted to remove age-specific cervical cancer mortality.[118] With respect to cervical cancer patients, stage-specific cervical cancer mortality rates were applied based on the reported five-year observed survival post-diagnosis from the SEER database.[102] As the reported data was based on the TNM staging system, this was mapped to the FIGO classification as follows: localized cervical cancer corresponded to Stage I, regional cervical cancer corresponded to Stages II and III and, lastly, distant cervical cancer corresponded to Stage IV within the model. It was assumed that there would be no cancer-related mortality after five years post-diagnosis and baseline mortality rate would be appropriate in these survivors. As per the original model, it was assumed that individuals with asymptomatic and

untreated cervical cancer had 1.03 times the risk of death compared to individuals who were diagnosed and treated for their cervical cancer. Parameters relating to mortality are summarized in Table 20.

Table 20: Mortality Parameters

Model Parameters	Value	Probabilistic Distribution	Reference
Annual mortality rate, adjusted to exclude mortality due to cervical cancers	Age-specific, ranging from 0.00007 to 0.4721		Statistics Canada, 2015[117,118]
Cervical Cancer-related Mortality			
5- year probability of death for localized cervical cancer, with treatment	0.085	95% CI: 0.07 to 0.20	SEER,2018[102]
5- year probability of death for regional cervical cancer, with treatment	0.429	95% CI: 0.34 to 0.72	
5-year probability of death for distant cervical cancer, with treatment	0.827	95% CI: 0.67 to 0.96	
RR, survival without treatment	1.03		Assumption in Chuck, 2004[68]

RR = relative risk; SEER= Surveillance, Epidemiology and End Results

Diagnostic Accuracy

The characteristics of each screening test (e.g., sensitivity and specificity) were taken from the clinical review. In brief, diagnostic test accuracies were based on pooling sensitivity and specificity based on a bivariate model that assumed perfect reference standards.(Appendix 9). The output of the analysis included the HSROC curve which described the joint distribution between sensitivity and specificity in order to support probabilistic analysis while preserving the correlation between these two diagnostic test accuracy parameters (Table 21).

Given the low proportion of unsatisfactory samples, the model disregarded non-confirmatory outcomes given that such a finding would mean a return for a repeat screen in which the cost of an additional screen would be minimal.

Table 21: Diagnostic Test Accuracy†

Test	Point Estimates		hsROC Parameters (standard deviation)
	Sensitivity	Specificity	
Cytology	0.715	0.905	Beta: 0.011 Theta -0.854 (0.636) Alpha: 3.554 (0.752)
HPV tests	0.901	0.866	Beta: -0.287 Theta -0.255 (0.286) Alpha: 4.329 (1.226)

† Source: Clinical review (reference Appendix)
hsROC= hierarchical summary receiver operating curve

The distribution of cervical abnormalities among Canadian women undergoing cytology was inferred from pooling the findings of multiple published clinical studies and reported in

Table 22. For instance, within the general population (i.e., primary cytology and cytology triage screening strategies), individuals with CIN1 in whom abnormal cervical lesions were observed, 40.5% would be categorized as an ASCUS, 42.6% would be categorized as LSIL and 16.8% would be categorized as HSIL by cytology. [119-121] The distribution of cervical abnormalities by cytology would be different within a subset of hrHPV+ individuals. For instance, amongst hrHPV+ individuals with CIN1 in whom abnormal cervical lesions were observed, 38.1%, 50.7% and 11.2% would be categorized by cytology as an ASCUS, LSIL and HSIL respectively.[56,122]

Table 22: Distribution of cytological and histological findings

		Histology		
		Negative	CIN1	CIN2+
Cytology (general population)[102,120,121]	ASCUS	0.680	0.405	0.169
	LSIL	0.231	0.426	0.242
	>HSIL	0.088	0.168	0.590
Cytology (hrHPV+ women)[56,122]	ASCUS	0.855	0.381	0.291
	LSIL	0.110	0.507	0.203
	>HSIL	0.035	0.112	0.506

ASCUS= atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papillomavirus; HSIL= high-grade squamous intraepithelial lesion; LSIL= low-grade squamous intraepithelial lesion

Adherence & Coverage of Screening Programs

There are three sources of nonadherence within a screening program: 1) non-participation to programmatic screening, 2) screening less frequently than recommended (i.e., under-screening) and 3) loss to follow-up of abnormal results. The economic model captured all three aspects together.

For the first source of nonadherence, age-stratified screening rates were utilized and reflect the combined participation rate of cytology amongst those eligible for screening (i.e., corrected for hysterectomy), reported in the provinces of Manitoba and British Columbia.[123] Although these rates reflect the years of 2011 to 2013, it was assumed that cervical cancer screening participation would remain stable as has been observed when comparing the participation rates from 2004 to 2006 against the rates reported from 2010 to 2012.[124,125] In addition, the target participation rate (80%) set by Canadian Task Force on Preventative Health Care was tested in sensitivity analysis.[124]

For the second source of nonadherence, amongst individuals who did not participate in the year they were supposed to be screened (i.e., missed screens), the model permitted these individuals to return to routine screening in between the time intervals of their next scheduled screen. As there were limited data on the rates of return to screening in those who had missed their scheduled screen, it was assumed that the rates of screening in these patients would be similar to the above-mentioned age-stratified screening rates in the general population. Upon return to screening, their next screening period would be shifted by the time interval dictated by the screening program. Sensitivity analyses were conducted to explore alternative assumptions to the return of screening in individuals who missed screening.

Lastly, in terms of failure to follow-up, it was assumed that there would be no loss-to-follow-up when conducting the triage test (i.e, undergoing HPV with cytology triage or cytology with HPV triage). This assumption was based on the fact that, if LBC samples were collected, it would permit both tests to be performed without an additional clinical visit as HPV DNA test requires only the residual liquid following extraction of the LBC sample. For patients whose follow-up procedure after PAP involved repeat testing (e.g., ASCUS or LSIL results), a systematic review noted lower adherence for additional repeat testing. In particular, in an RCT performed in Netherlands, only 66.3% of individuals with ASCUS/LSIL were found to have completed repeat testing.[126] Age-specific follow-up rates to direct referral for colposcopy immediately after cytology were taken from a national report that summarized the performance of cervical cancer screening in five Canadian provinces.[127] In particular, the report noted that over 70% of individuals in Canada had undergone a colposcopy within a year of an abnormal cytological examination (i.e., AGC, ASC-H, HSIL) except in individuals aged 60 to 69 years old (69%).

Vaccination

To model the potential impact of HPV vaccination in conferring immunity to certain HPV strains and thereby, reducing cervical cancer risks, vaccination was modelled as follows. Cohorts born from 1994 onwards have been part of Canada's publicly-funded vaccination programs that was introduced in 2006.[90] In these cohorts, the uptake of vaccination was assumed to reflect the reported average rate of 55.92% .[90] It was further assumed that vaccination would confer lifelong immunity and reduce risk of HPV infections by 95.5%.[128]

Utilities

The health effects of cervical cancer screening programs were expressed in terms of QALYs. Baseline age-specific utility values from a general Canadian female population, based on EuroQoL 5-Dimensions-3-Levels questionnaires, were taken from Johnson et al.[129]

Given that, in the literature, no single measurement tool was found to have elicited utility values for all health states associated with screening, diagnosis and treatment of precancerous lesions and cervical cancer that are relevant to the current economic evaluation, two sets of health utility weights were considered (Table 23). The following assumptions were made in estimating utilities in the model. Individuals vaccinated or who have undiagnosed health conditions (i.e., HPV infection, cervical dysplasia or cancer) would have a similar utility weight to the general population. Disutility for short-term events such as repeat screening due to low-grade cervical dysplasia or undergoing colposcopy evaluation for a false-positive test results were not considered in the model. A sensitivity analysis was conducted that incorporated a utility weight to abnormal screen results that led to repeat screening or referral to colposcopy.

In the model, relevant health state utilities from screening or from a diagnosed condition were adjusted by an age-specific general utility values using a multiplicative approach.

Utility Weight – Reference Case

Utility weights associated with histologically confirmed CIN1 or CIN2+ were based on an Australian study. In this study, utility weights associated with different screening outcomes in 43 women undergoing cervical cancer screening were elicited by a two-stage standard-gamble technique.[130] Median utility values reported in the publication were incorporated into this economic evaluation.

Few studies were identified from a literature search that have elicited utility for cervical cancer based on a standard-gamble technique in female-only participants. As such, utility weights elicited from a general Korean population (including male and females) that used the standard gamble technique were taken. The study elicited utility weights for different treatment approaches of cervical cancer.[131] To map the treatment approaches to cancer staging, it was assumed that patients with stage I cervical cancer would be managed by surgery only (i.e., cone biopsy or hysterectomy), patients with stage 2 to 3 cervical cancer would be managed by radical hysterectomy+radiotherapy±chemotherapy) whereas patients with stage 4 cervical cancers had utility values corresponding to chemotherapy. Although this Korean study also reported utility weights relating to cervical neoplasia, it was not incorporated into the model given more appropriate utility values elicited specifically in females were available. However, incorporating utility weights from this study is likely to have a negligible change in the interpretation of model findings as the median utility values for CIN1 and CIN2+ (both equal to 0.9) was similar to the utility weights that were tested in the sensitivity analysis described below.

Utility Weight- Sensitivity Analysis

One conference proceeding was identified that reported health state utility values based on the time trade-off approach in US women[132] Utility weights for screening-related outcomes in the model were substituted with the mean utility weights for a variety of cytological and histological health states, where appropriate.

Table 23: Description of Utility Weights within the Economic Model, estimated by Standard Gamble technique

Description		Reference Case	Sensitivity Analysis
		Simonella, 2014[130]	Myers, 2004[132] (n=150)
Baseline utilities [129]		Age-specific	
Utility (applied by multiplicative function)			
Screening Outcomes	CIN 1	0.9997 (0.0026)	0.91
	CIN 2+	0.9996 (0.0233)	0.87
Disease-related outcomes, applied upon diagnosis[131]	Stage I cervical cancer (simple or radical hysterectomy)	0.85	
	Stage II and III cervical cancer (radical hysterectomy+radiotherapy±chemotherapy)	0.78	
	Stage IV cervical cancer (chemotherapy)	0.43 (0.32)	
Cervical Cancer survivor		0.94 [133]	
Death[†]		0	

ASCUS= atypical squamous cells of undetermined significance; CIN= cervical intraepithelial neoplasia; HPV =human papillomavirus; LSIL= low-grade squamous intraepithelial lesion; PAP = Papanicolaou test

[†]Assumed

Costing

All costs were based on Canadian data and converted to 2017/2018 dollars using the general Consumer Price Index for the year of data collection.[134] Based on the perspective of the analysis, only medical costs paid by the Ministry of Health were considered. Costs in the analysis are outlined in Table 24.

Direct screening costs included those for consumable supplies, office visits, outside hospital diagnostic procedures and professional services.The unit costs of cytology and HPV tests, and related fees were extracted from a variety of sources including Ontario Schedule of Laboratory Fees and a previously published economic evaluation.[80]

The average costs of colposcopy with or without biopsy and LEEP included the physician's professional fees and associated costs of the procedure including any laboratory fee for the biopsy specimen. Physician fees, including those of related to pathology, were taken from the Ontario Schedule of Benefits[135] while procedure-related costs were obtained from the Ontario Case Costing Initiative that assumed these procedures would be performed in an ambulatory setting.[136] It was assumed that biopsies, if required, would be conducted concurrently with the colposcopy procedure and this may have underestimated to the actual cost as, in some cases, biopsy is performed subsequently.

Upon the presentation of symptomatic cancer, it was assumed that a colposcopy examination would be performed to confirm diagnosis. The average cost of treatment for cervical cancer were derived from a cost-analysis conducted in British Columbia that reviewed resource patterns of 563 patients between January 2004 to December 2009 in terms of patient-level resource patterns from diagnosis to death or at 5-year discharge.[100] Cancer-related medical costs were applied up to the cancer survivor's lifetime.[137]

2085 **Table 24: Cost parameters in economic evaluation**

Description		Cost ($)	Distribution	Reference
Screening Tests				
Primary Cytology (LBC)	Physician visit (A003): $77.2 Physician sample collection fee (E340): $11.55 Tray: $12.56 Lab fees: $7.52	108.83	NA	OSoB,[135] Popadiuk, 2006,[80] OSLF[138]
Primary Cytology (LBC) with HPV triage	Physician visit (A003): $77.2 Physician sample collection fee (E340): $11.55 Tray: $12.56 Cytology lab fees: $7.52 HPV lab fees: $49.26, if applicable	108.83 (without HPV triage) 158.09 (with HPV triage)	NA	OSoB,[135] Popadiuk, 2006,[80] OSLF[138]
Primary HPV tests	Physician visit (A003): $77.2 Physician sample collection fee (E340): $11.55 Tray: $12.56 HPV lab fees: $49.26 Cytology lab fees: $7.52, if applicable	150.57 (without cytology triage) 158.09 (with cytology triage)	NA	OSoB,[135] Popadiuk, 2006,[80] OSLF[138]
Procedure				
Colposcopy, without biopsy[1]	Ob/Gyn Consult (A205): $101.7 Physician procedure fee (Z731): $50.9 Procedure (non-physician) costs[2]: $232	384.6	Medical procedure: Gamma (α: 1.2, β:199.2)	OSoB,[135] OCCI,[136] OSLF [138]
Colposcopy, with biopsy	Ob/Gyn Consult (A205): $101.7 Physician procedure fee (Z731): $50.9 Procedure (non-physician) costs[2]: $291 Lab technical fee (L720), 2 blocks: $18,75 per block Pathologist fee for surgical specimen (L864): $48.65	529.75	Medical procedure: Gamma (α: 1.2, β:199.2)	
LEEP	Ob/Gyn Partial Assessment (A204): $26.36 Physician procedure fee (Z766): $78 Procedure (non-physician) costs[2]: $525 Lab technical fee (L720), 4 blocks: $18,75 per block Pathologist fee for surgical specimen (L865): $103.2	807.56	Medical procedure: Gamma (α: 4.2, β:123.9)	
Hysterectomy	Ob/Gyn Surgical Consult: $160 Physicians' procedure fee: $640.31 [incl. 6 units of assistant fee ($12.04/unit) and 7 units of anaesthesia ($15.01/unit)] Procedure (non-physician) costs[2]: $5,501 and $4,768 for in-patient and out-patient settings respectively	6141.1 [inpatient] 5408.31 [outpatient]	Inpatient procedure cost: Gamma (α: 3.7, β:1478.6) Outpatient procedure cost: α: 5.5, β: 861.7)	
Cervical cancer	Stage I	16,916	Normal (st dev: 4,800)	Cromwell, 2016[1003]
	Stage II	22,989	Normal (st dev: 3,279)	
	Stage III	25,042	Normal	

Description		Cost ($)	Distribution	Reference
			(st dev: 7,255)	
	Stage IV	42,726	Normal (st dev: 10,813)	
	Survivor (5 years after cancer)	5,565	Normal (st dev: 1,074)	Pendrith, 2016[137]

GP = general practitioner; HPV =human papillomavirus; LBC = liquid based cytology; LEEP= loop electrical excision procedure; NA= not applicable; OCCI = Ontario Case Costing Initiative; OSLF= Ontario Schedule of Laboratory Fee; OSoB = Ontario Schedule of Benefits

[1] Assumed biopsy only performed if abnormal cervical lesions detected during visualization

[2] Procedure cost include both direct (e.g., nursing, diagnostic imaging, pharmacy and labs) and indirect costs (overhead expenses)

[3] Canadian study (B.C.) that captured resource utilization and costs associated with chemotherapy, hospitalization, RT, brachytherapy, medical services covered by provincial insurance, and prescription medication

Statistical Analyses & Sensitivity Analyses

The reference case reflects the probabilistic results based on running 10,000 individuals through the model over 10 runs. Six specific single birth cohorts (i.e., ages 9, 20, 30, 40, 50 and 60) were evaluated. The probabilistic results characterize the extent to which parameter uncertainty impacts the cost-effectiveness estimates in the model. Standard distributional forms were taken to describe the probability distribution functions relating to input parameters: transition probabilities and relative risks were characterized by beta and normal distributions, utility were characterized by beta distribution and costs were characterized by gamma distributions. Where possible, the diagnostic test accuracies of the screening tests (i.e., sensitivity and specificity) were sampled from the joint distribution function described by the hsROC curve.

The incremental cost-utility ratio (ICUR) was calculated according to convention and, in most cases, the sequential ICUR was presented unless otherwise specified. Strategies that were dominated (i.e., another strategy that has lower expected costs and higher expected QALYs) or 'extended dominated' (i.e., at least one possible combination of two treatment strategies exist that would be less costly and results in higher QALYs) were identified. Results of the probabilistic analysis are presented on a cost-effectiveness acceptability curve (CEAC) which highlights the screening programs on the efficiency frontier (i.e., the set of optimal strategies that, for varying costs, produce the highest health benefits). This graph presents the probability that each screening program is optimal given different willingness-to-pay values for an additional QALY gained.

In addition, the model's predicted impact in terms of health care resources (e.g., number of colposcopy performed) required under each specific screening program was estimated and presented. Similarly, clinical outcomes associated with each screening program were reported.

Further sensitivity analyses were conducted to evaluate the degree to which uncertainty in the model parameters (i.e., parameter uncertainty) and uncertainty in its assumptions (i.e., structural uncertainty) would impact the results. These include:

Vaccination uptake: The uptake rate of vaccination came from a pooled estimate from a Canadian review. However, within the same review, it was noted that the uptake rate can range broadly within Canada ranging from 12.40% to 88.20%.[90] Sensitivity analyses were conducted across this range.

Discount rate: The reference case was based on a discount rate of 1.5%,[92] with sensitivity analyses conducted by applying a higher discount rate of 5% and an undiscounted scenario (i.e., discount rate = 0%).

Incidence rate of HPV infection: Incidence of acquiring an HPV infection was based on Ontario study by Sellors et al.[105]

Missed screening: the reference case analysis assumed patients who miss screening in the index year can return to screening between screening intervals according to reported age-specific screening rates.[123] A sensitivity analysis was conducted that assume patients would not return to screening until their next scheduled screening period.

Screening participation rate: Screening participation rate was based on observed data. A sensitivity analysis was conducted in which participation rates were set to the current targeted rate of screening (80%)that was set by the Canadian Task Force on Preventative Health Care.[1]

Alternative utility weights based on a different elicitation tool: The reference case's health state utilities were elicited by the standard gamble approach. A sensitivity analysis was conducted in which utilities weight for diagnosed cervical lesions (i.e.,CIN1, CIN2+) were elicited by the time trade-off method.[132]

Disutility from abnormal screening results requiring repeat testing or false positive findings: In the reference case, no disutility was associated with screening results that led to repeat testing or additional follow-up visits if no cervical abnormalities are detected by colposcopy and biopsy. Rather, age-adjusted baseline utility values were applied in such instances. A sensitivity analysis was conducted that applied a lowered utility weight in patients with screening test outcomes that led to repeat testing or entry into colposcopy management regardless if the initial screening tests was a true positive or false positive finding. Mean utility score for the following screening outcomes were applied: Cytology findings equal to or under LSIL (0.9996), Cytology findings equal to or under LSIL with normal colposcopy (0.9985), HPV positive with normal cytology (0.9986), HPV positive with normal colposcopy (0.9987), CIN1 (0.9989) and CIN2+ (0.9983).[130] These were applied in the year of the screening results.

HPV costs: Current costs for HPV testing were estimated from a Canadian economic evaluation in which the difference in lab costs between HPV and cytology was $41.74. However, as no real-world Canadian data were found that accurately estimated the associated lab fees for HPV testing per patient, several sensitivity analyses were conducted. A previously published economic evaluation conducted under the province of Quebec suggested that, based on their own personal communications HPV lab fees could be only an additional $9 more compared to conventional cytology.[85] A sensitivity analysis was therefore performed in which HPV lab fees were assumed to be $16.52. Furthermore, a threshold analysis was performed to determine the cost of HPV lab tests whereby the cost-effectiveness of HPV-based screening would be under $50,000 per QALY.

Validation

The model structure and inputs were presented to two Canadian clinical experts to ensure that the model, its parameters, and its assumptions reflected Canadian clinical practice and the available body of literature (i.e., face validity). Internal validity was assessed by ensuring that the mathematical calculations were performed correctly and were consistent with the model specification and that logical discrepancies were assessed by evaluating the model under hypothetical and extreme conditions. The model further underwent external technical peer review. External validation was conducted by comparing model outputs against independently published studies.[118,139-141]

Assumptions

Table 25 lists the assumptions in which the reference case of the economic analysis was based upon.

Table 25: Assumptions used to populate the economic model

Assumption	Strategy in which applicable:	Sensitivity Analysis Description
The cost and health impact from the sequelae of low-risk HPV strain were not modelled.	All	None
Resolution of hrHPV infection results in clearance of an individual's CIN lesions.	All	None
Biopsy would always be performed in patients with abnormal colposcopy findings or symptomatic cancer.	All	None
No risk of cancer recurrence	All	None
Performance of screening tests are assumed independent	All strategies involving triage (Strategies B and C)	None
The impact of unsatisfactory sample was not modelled given the low rates of unsatisfactory samples (<1%) reported in the clinical review.	All strategies (applies specifically to cytology)	According to current clinical guideline recommendations, individuals with unsatisfactory specimens would be requested to repeat PAP every 3 months until a satisfactory specimen could be obtained.
Outcomes pertaining to cytology were mapped to the histopathological nomenclature: CIN1 assumed to correspond to low-grade lesions (LSIL) CIN2+ assumed to correspond to HSIL	All strategies (applies specifically to cytology)	None
Physician or patient preferences to specific screening techniques were not considered (i.e., no diagnostic-test related utility applied). Utilities were applied to the final outcome of screening (e.g., no abnormal screening outcomes, diagnosed CIN1 or diagnosed CIN2)		
Disutility for undergoing evaluations for a false-positive test results were not considered in the economic model.	All	None
Disutility from hysterectomy was assumed negligible	All	Test?
Colposcopy and biopsy are the diagnostic gold standard for confirming the presence and grade of CIN, and the presence and severity of cervical cancer. It was assumed to have perfect test accuracy.	All	None
Discounting was set at 1.5%	All	Discount rates of 0% and 5% were explored.

Results

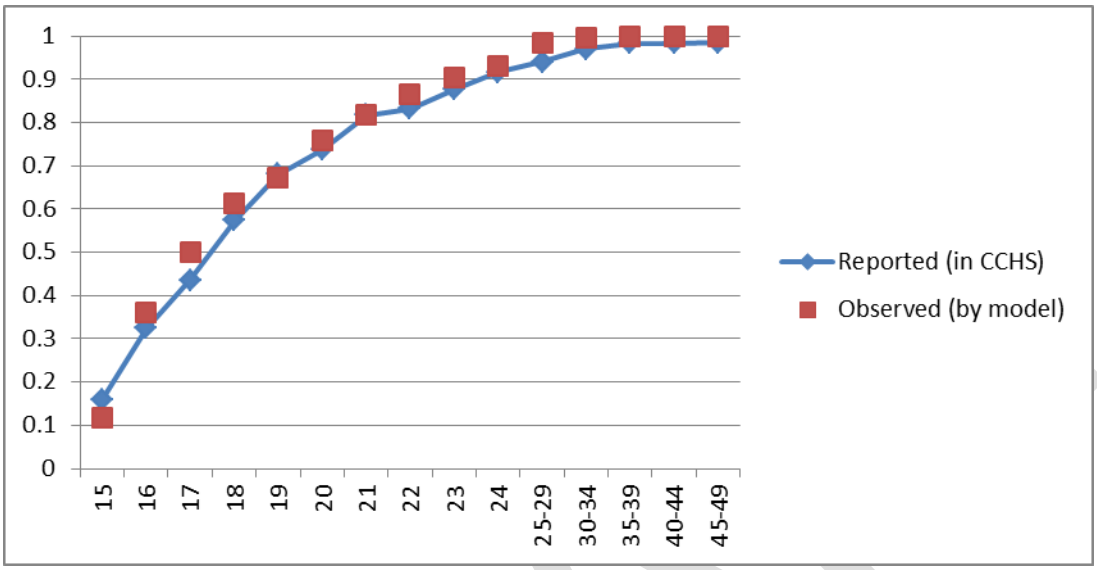
Validation

A series of external validation tests were conducted, comparing results with independent studies that had not informed the development of the economic model to assess to what extent the model was able to predict observed outcomes. Table 26 summarizes the key findings from this exercise.

The deterministic model predicted age-specific onset of sexual activity within a plausible range (Figure 13). Assuming the current screening involving cytology every 3 years between the ages of 21 to 69 and real-world adherence to

screening, the model predicted an absolute lifetime risk of developing cervical cancer of 0.61% which is aligned with the reported Canadian lifetime risk of cervical cancer between the ages of 0 to 74 (i.e., 0.6 to 0.66%).[142] Age-specific incidence is mostly aligned within the range expected.[118] However, the peak of cervical cancer was predicted to occur later in the model with a median age of 54 years old for cervical cancer.[85,123] This is higher than Statistics Canada reports in which individuals in their early forties were the highest risk age group for cervical cancer with a median age of diagnosis at 47 years old.[118]

Figure 13: Modelled and reported proportion of sexually active women, by age



Hysterectomy rates (18.6%) in the model were underestimated. There may be a variety of causes for this. Firstly, the model specifically captured hysterectomy due to non-benign conditions whereas the reported data represents all-cause hysterectomy. Furthermore, the available hysterectomy rates were from the province of Quebec which has one of the lowest rates of hysterectomy.[139]

Table 26: Results from Validation

Parameter	Model predicted	Data observed in Canada (95% CI unless otherwise stated)	*Reference*
Sexual Initiation			
Percentage of 15-year old who have had sexual intercourse	21.9%	21%	*ICO Information center*[142]
Median age at first sexual intercourse	18	16	*ICO Information center*[142]
HPV			
Cumulative lifetime risk of HPV (US values)	85.0%	84.6 (range: 53.6 to 95%)	Chesson, 2014[140]
Cervical Cancer			
Cumulative lifetime risk of cervical cancer (between age 0-74)	0.61%	0.6 to 0.66%	*ICO Information center*[142]
Median age at diagnosis	54	47	*Stats Can*[118]
Cumulative lifetime risk of mortality from cervical cancer		0.2%	*ICO Information center*[142]
Median age at death		59	*Stats Can*[118]
Hysterectomy			

Parameter	Model predicted	Data observed in Canada (95% CI unless otherwise stated)	*Reference*
Prevalence of Hysterectomy	18.6%		*Stankiewicz, 2014*[139]
40 to 49	9.5%	12.4 (10.9 to 13.9)	
50 to 59	12.9%	21.2 (19.4 to 23.0)	
60 to 69	14.3%	34.0 (31.8 to 36.1)	

Reference Case

The analyses reflect 10 Monte Carlo simulation of 10,000 individuals each.

The model was used to generate data regarding the disease history of HPV infection and cervical cancer in Canada, and to profile the effectiveness of the current cervical cancer screening program. Assuming that the current risk factors for HPV infection remains stable and there is no programmatic screening (i.e., screening coverage in model is set to 0), the absolute lifetime risk of cervical cancer would be 2.56% (Table 27). These projections would reflect the risk of cervical cancer in women who are not involved in any programmatic screening for cervical cancer, a subpopulation that continues to exist even despite existing routine screening programs, as noted in the implementation review. Without participation in routine screening, cervical cancer lesions can only be detected if cervical cancer is symptomatic. As a result, in the "no screening" strategy, the expected cost only includes the medical costs associated with cervical cancer treatment (including diagnosis upon symptomatic cervical cancer) and cancer survivorship.

Screening programs were found to reduce the burden of the disease. Compared to the most common screening program in Canadian jurisdictions (i.e., PAP cytology every 3 years between the ages of 20 to 69), the lifetime risk of cervical cancer reduced to 0.82 and this represented a 69.0% reduction in cervical cancer rates compared to a no screening strategy. This reduces the risk of developing cervical cancer from 1 in 40 (no programmatic screening) to 1 in 122 (with programmatic screening). Given incremental QALYs of 0.029 (Table 27), this would indicate that the current screening program could increase, on average, 10.6 days in perfect health (discounted) over an individual's lifetime.

The current screening program was expected to cost $1,531 per person over their lifetime; and compared with no screening, the cost difference was $27.(Table 27) The expected lifetime costs associated with programmatic screening was composed of two elements: i) screening and its associated diagnostic costs (e.g., routine screening, management of for abnormal results- e.g frequent screening- colposcopy/ biopsy) and ii) treatment costs for pre-cancer lesions and cost of managing cervical cancer.

Table 27: Results comparing No screening programs to the current screening program (unvaccinated cohort, starting age 9)

Strategy			Expected cost ($)	Expected QALYs	Lifetime average number of programmatic screening test*	Lifetime risk of developing cervical cancer	
	Frequency	Targeted age range				%	1 in
No Screening			1,504	39.706	0	2.56	40
A1- primary cytology	every 3 yrs	21 to 69	1,531	39.735	12.7	0.82	122
Incremental			27	0.029			

In considering all screening strategies of interest, primary HPV testing with cytology triage every five years starting from the ages of 25 to 69 was found to be the least costly but also the least effective strategy across all cohorts evaluated. In a future incidence cohort (i.e., population with a starting age of 9 years), this strategy was associated with expected costs of $1,471 and resulted in 39.956 QALYs over a lifetime. The next strategy on the efficiency frontier (the set of optimal strategies that, for varying costs, produced the highest health benefits) was a screening strategy based on primary cytology every three years starting from the ages of 21 to 69. The primary cytology strategy would produce an additional 0.005 QALYs at an incremental cost of $551, resulting in an ICER of $112,717 per QALY gained. This strategy reflected the most intensive screening program amongst the screening strategies being evaluated as it was associated with the most frequent and longest screening duration. Indeed, compared to the reference strategy (C3) in which, on average, patients participated in 5.8 screens over their lifetime, this strategy was associated with an average of 11.5 screens over a lifetime (even when factoring participation and adherence to screening). All other strategies were either extendedly dominated (i.e., at least one possible combination of two treatment strategies would be less costly and results in higher QALYs) or dominated (i.e., another strategy has lower expected costs and higher expected QALYs). It is important to note that the incremental QALY between screening strategies were low (<0.01). For instance, between the reference strategy (C3: C-5yr-25) and the most clinically effective strategy (A1: A-3yr-21), the difference in expected QALY over a lifetime was approximately 0.005 which equates to approximately 1.8 days of full health gained per patient.

The screening strategies on the efficiency frontier differed between the age cohorts evaluated. Different cohorts had different vaccination status. The future incidence cohort, with a starting age of 9, incorporated a partly vaccinated population based on current rates of participation in HPV vaccination programs in Canada whereas the prevalent cohort reflected an unvaccinated population with a starting age of 30. As such, a different set of strategies appeared on the effiency frontier. While primary HPV testing with cytology triage remained the lowest costs strategy, shifting from a five year to three year screening frequency would produced an additional 0.002 QALY for an added cost of $463, resulting in an ICER of $194,777 per QALY. All other strategies were either extendedly dominated or dominated.

As the clinical review noted, HPV testing is more sensitive and less specific. In the economic analysis, this clinical utility translates to a lower lifetime risk of developing cervical cancer for strategies in which primary HPV testing is introduced to the broader population eligible for screening rather than implementing primary cytology screening. However, from a cost-only perspective, in comparing approaches to screening with all other characteristics of the screening program held constant (e.g., strategies A2, B1, C2), strategies with primary cytology were found to be less costly than the equivalent strategies that involve primary HPV testing (e.g., C2). The higher costs associated with primary HPV with cytology triage were driven by the increased needs for repeat screening by HPV testing and/or cytology and the slightly higher rates for colposcopy.

With respect to the screening frequency, a trade-off was observed between costs and clinical benefits. This was most notably observed in the primary HPV with cytology triage strategies. Increasing the time interval between screens from a three year to a five year interval was found to lower costs (due to lower numbers of screening-related procedures performed) but resulted in a higher lifetime risk of cervical cancer as some cases of cervical cancers would not be detected by screening since screening became less frequent. The impact of extending the targeted age range less clear. The expected costs were identical in the prevalent cohort given that the majority of patients entering the model were eligible for programmatic screening at the model start whereas, in the future incidence cohort, patients would not eligible for screening at the model start given the actual start age of screening would be conditional on the eligible start age for programmatic screening and the individual's sexual activity status. Although the average number of programmatic screening tests were higher with a lower start age, it was not always clear whether this would translate to clinical benefits in terms of reducing the impact for repeat testing or averting cervical cancer.

2267 **Table 28: Probabilistic Base Case Results**

Strategy			Expected cost ($)	Expected QALYs	Average				Lifetime risk of cervical cancer (%)	Incremental Cost ($)	Incremental QALY	Incremental cost-utility ratio (ICER)
	Frequency	Targeted age range			Programmatic screening test*	Additional Cytology	Additional HPV test	Colposcopy				
Future Incidence Cohort: starting age 9												
C3	5	25 to 69	1,471	39.956	5.8	1.1	0.8	0.9	0.39	Reference		
A1	3	21 to 69	2,021	39,961	11.5	3.0	0	1.5	0.33	551	0.005	112,717
Dominated Strategies												
B2	3	30 to 69	1,580	39.956	9.7	0.9	0.2	0.7	0.37	109	0.000	Ex. dom
C4	5	30 to 69	1,601	39.957	6.6	1.3	0.9	1.0	0.39	130	0.001	Ex. dom
B1	3	25 to 69	1,744	39.957	11.0	1.1	0.2	0.8	0.38	273	0.001	Ex. dom
A3	3	30 to 69	1,847	39.958	8.1	5.7	0	1.2	0.33	376	0.002	Ex. dom
A2	3	25 to 69	1,855	39.958	10.6	2.6	0	1.3	0.32	384	0.002	Ex. dom
C1	3	30 to 69	1,857	39.959	9.3	1.7	1.2	1.3	0.34	387	0.002	Ex. dom
C2	3	25 to 69	2,065	39.960	10.5	1.4	1.4	1.5	0.31	594	-0.001	Dominated
Incidence Cohort : starting age 20												
[to be completed]												
Prevalent Cohort: starting age 30												
C3/C4	5	25 to 69 30 to 69	2,241	31.546	6.1	0.8	0.8	0.9	0.74	Reference		
C1/C2	3	30 to 69 25 to 69	2,704	31.549	9.8	1.0	1.3	1.1	0.63	463	0.002	194,777
Dominated Strategies												
B1/B2	3	25 to 69 30 to 69	2,381	31.546	10.2	0.8	0.2	0.7	0.84	139	-0.000	Dominated
A1/A2/A3	3	21 to 69 25 to 69 30 to 69	2,427	31.544	10.0	1.4	0	0.8	0.78	186	-0.003	Dominated

2268 Ex. Dom = extendedly dominated; QALY= quality adjusted life year

Sensitivity analyses

The results of the sensitivity analyses indicate that the scenarios and parameters in which the cost-effectiveness model responded most sensitively to differed by the population evaluated. The results presented below are therefore ordered by the population being analyzed.

Future Incident Population

The model was sensitive to the following sensitivity analyses that was conducted on the future incident population:

Rate of vaccination uptake: Although the screening strategies forming the efficiency frontier remained identical to the reference case, the expected vaccination uptake rate impacted the estimated ICER values. In cases when the rate of vaccination was set to the lower bound of the reported 95% confidence interval (12.40%), the overall lifetime risk of developing cervical cancer increased. As such, the expected cost associated with each strategy increased while the expected QALYs reduced. The impact on incremental QALY was larger than the impact on incremental costs, resulting in the ICER for primary cytology (every three years, age 21 to 69) decreasing to $60,345 per QALY gained (Table 29). The results highlight that, with lower rates of vaccination, more intensive primary cytology screening program may be more appropriate. The contrary observation could be made when the vaccination uptake rates were higher than the reference case values.

Discounting: If no discounting was applied, (i.e., neutral time preference with respect to present and future costs and benefits), the ICERs reduced for the strategies on the efficiency frontier with more intensive screening (i.e., reducing the frequency, extending the duration) becoming more economically attractive. Specifically, the ICER associated with strategy A1 (primary cytology, every three years, age range 21 to 69) reduced to $76,279 per QALY gained. When a higher discounting rate was set, primary cytology no longer formed part of the efficiency frontier. Rather, strategy A1 was found to be dominated by strategy C2 (primary HPV with cytology triage, 3 years, 25 to 69) (i.e., strategy A1 was more costly and less effective than strategy C2), which was associated with an ICUR of $318.294 per QALY gained (Table 29).

Missed screening: In assuming that patients who missed their programmatic screening would not return to screening until their next scheduled screening period, this made more intensive screening programs appear more favorable. Although the strategies on the efficiency frontier remained identical, the ICER for strategy A1 (primary cytology, every 3 years, age range 21 to 69) primary cytology reduced to $80,599 per QALY gained (Table 29).

Disutility from abnormal screen: When a one-year disutility was applied for abnormal screen results (i.e., true positive and false positives), this was found to reduce the expected QALYs across all screening strategies. The overall impact of incorporating such a disutility was less for screening approaches that entailed primary cytology with HPV triage compared to other approaches to screening. This was expected as, even in the reference case, this approach was associated with the lowest rates of repeat screening (Table 28). Furthermore, given the small differences in QALY between strategies, incorporating a minor disutility from abnormal screen results (< -0.001) could have an impact on which strategies formed the efficiency frontier. Alhtough the reference strategy remained identical to the reference case analyses (i.e., primary HPV with cytology triage), primary cytology with HPV triage replaced all other screening strategies. In the future incidence cohort, the ICER associated with B2 (primary cytology with HPV triage, every 3 years, age range of 30 to 69) reduced to $19,547 per QALY gained whereas, in the prevalent cohort, the ICER associated with B1/B2 (primary cytology with HPV triage, every 3 years, age range of 25/30 to 69) was $14,681 per QALY gained (Table 29).

Table 29: Sensitivity Analyses Results for the Future Incident Cohort.

Analysis	Strategy[a]	Expected		Incremental		Sequential ICER
		Cost($)	QALYs	Cost($)	QALYs	
Reference Case	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,471	39.956	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	2,021	39,961	551	0.005	112,717
Vaccination Uptake (12.40%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,665	39.944	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	2,241	39.953	575	0.0100	60,345

Analysis	Strategy[a]	Expected		Incremental		Sequential ICER
		Cost($)	QALYs	Cost($)	QALYs	
Vaccination Uptake (88.20%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,356	39.966	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	1,868	39.968	512	0.001	428,893
Discount Rate (0%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	2,689	63.606	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	3,473	63.616	784	0.010	76,279
Discount Rate (5%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	447	19.462	Reference		
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	684	19.463	237	0.001	318,284
Missed screening	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,349	39.953	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	1,823	39.959	473	0.006	80,599
Disutility from abnormal screening results	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,471	39.946	Reference		
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	**1,580**	**39.951**	**109**	**0.006**	**19,547**

Ex. Dom = extendedly dominated; HPV = human papillovirus; QALY= quality adjusted life years; TTO = time trade off

[a] Strategies not presented here are either extendedly dominated or dominated.

Prevalent Cohort

The economic evaluation was found to be more sensitive to change under the prevalent cohort population. Across all sensitivity analysis performed, the reference strategy (i.e., the strategy with the lowest expected costs) remained identical (i.e., strategy C3/C4 -primary HPV with cytology triage, 5 years) and in most cases, strategy C1/C2 (primary HPV with cytology triage, 3 years) was the most expensive and most effective intervention, the efficiency frontier often included other screening programs. Many of the same trends noted above in the future incident population could be applied to the prevalent cohort although there were additional sensitivity analyses in which the model was sensitive to under this modelled cohort:

Alternative Incidence Rate: With a different set of HPV infection incidence rates, all four screening programs emerged on the efficiency frontier (i.e., no screening program was dominated or extendedly dominated). Although the expected costs and QALYs for each screening program were similar to the reference case, this analysis highlights the sensitivity of this cohort to even minor changes in the expected results. Although strategy C1/C2 and strategy C3/C4 remained both the cheapest and least effective, and the most expensive and most effective strategies respectively, primary cytology and primary cytology with HPV triage both emerged on the efficiency frontier in between the primary HPV with cytology triage strategies.

Utility from TTO: Due to the small incremental QALY difference between strategies in this cohort, minor changes to utility sources impacted which strategies formed the efficiency frontier. When utility weights were derived by the time trade-off method, primary cytology with HPV triage emerged to be on the efficiency frontier. Specifically, the ICER for B1/B2 (primary cytology with HPV triage, every 3 years) was found to be $43,789 per QALY gained while the ICER for C1/C2 (primary HPV with cytology triage, every 3 years) remained similar at $144,978 per QALY gained.

Cost of HPV: When the cost of HPV testing lowered, primary HPV with cytology triage became increasingly attractive as the expected costs for these strategies reduced. These strategies therefore formed the efficiency frontier if lab costs of HPV were to reduce. Under a willingness-to-pay threshold of $52,634 per QALY, strategy C3/C4 (primary HPV with cytology triage, every five years) would be preferred; above this value, strategy C1/C2 (primary HPV with cytology triage, every three years) would be preferred.

Table 30: Sensitivity Analyses Results for the Prevalent Cohort.

Analysis	Strategy[a]	Expected		Incremental		Sequential ICER
		Cost($)	QALYs	Cost($)	QALYs	
Reference case	C3/C4 Primary HPV w/ cytology triage (5 yrs;)	2,241	31.546	Reference		
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,704	31.549	463	0.002	194,777
Discount rate (0%)	C3/C4 Primary HPV w/ cytology triage (5 yrs;)	3,093	44.320	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	3,311	44.328	218	0.0084	25,885
	A1/A2/A3: Primary cytology (3 yrs)	3,394	44.330	83	0.0022	37,250
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	3,703	44.335	309	0.0046	67,749
Discount rate (5%)	C3/C4 Primary HPV w/ cytology triage (5 yrs)	1,172	17.292	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	1,298	17.293	126	0.0013	99,627
	A1/A2/A3: Primary cytology (3 yrs)	1,381	17.294	83	0.0004	224,807
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	1,538	17.294	156	0.0005	324,379
Alternative Incidence Rates	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,171	31.281	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,352	31.286	182	0.0047	38,510
	A1/A2/A3: Primary cytology (3 yrs)	2,438	31.287	86	0.0011	79,666
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,686	31.289	247	0.0024	105,202
Missed screening	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,023	31.272	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,199	31.280	176	0.0076	23,199
	A1/A2/A3: Primary cytology (3 yrs)	2,269	31.282	70	0.0027	25,583
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,481	31.286	212	0.0036	59,652
Alternative Utility Values (based on TTO)	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,171	31.271	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,352	31.275	182	0.0041	43,789
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,686	31.277	333	0.0023	144,978
Disutility from abnormal screening results	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,171	31.266	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,352	31.278	182	0.0124	14,681
HPV costs	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,031	31.281	Reference		
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,460	31.289	429	0.0081	52,634

Ex. Dom = extendedly dominated; HPV = human papillovirus; QALY= quality adjusted life years; TTO = time trade off

[a] Strategies not presented here are either extendedly dominated or dominated.

Additional details on the sensitivity analyses in which the model findings were found to be robust can be found in Appendix 16.

Summary of Results

The economic evaluation presented herein demonstrates that programmatic screening of individuals with a cervix remains highly effective for the prevention of cervical cancer with lifetime cancer risks estimated to reduce from one in 40 to one in 122 individuals in existing screening programs (i.e., primary cytology every 3 years, between the age of 21 to 69). The Clinical Review concluded that HPV tests are associated with a higher sensitivity but lower specificity than cytology. At a programmatic level, comparing primary cytology to primary HPV with cytology triage over a cohort's lifetime, this translates to a lowered risk of developing cervical cancer in strategies that involved primary HPV testing. Holding all other characteristics of a screening program constant (i.e., frequency, interval), lifetime costs were found to be higher for primary HPV testing than for the equivalent strategies that involves primary cytology whereas QALY differences between these strategies were small. Expanding to consider other aspects of a screening program, the analysis found that, by reducing the frequency of screening from every three to every five years for primary HPV with cytology triage screening, incremental costs were lower than primary cytology every 3 years given that fewer programmatic screening tests would be performed while utilities remained comparable.

Although more frequent screening was found to better detect more lesions, there is a tradeoff between overscreening and cancer prevention. Indeed, lifetime QALY difference between screening strategies were found to be small, being at most 0.019 uder the reference case (which represents an additional seven days of perfect health per individal) and sensitivity analysis found that the economic model was most sensitive to whether a disutility was applied to abnormal findings. Specifically, more frequent screening may become less favourable as it increases the number of abnormal findings that require clinical management and may lead to overtreatment. Indeed, in comparing between primary HPV with cytology triage strategies in which the screening frequency was varied, the reference case found that screening every five years produced slightly lower QALYs than screening every three years; however, when a disutility was applied for abnormal findings, the contrary was observed (i.e., screening every five years produced slightly higher QALYs than screening every three years). This indicates that there are considerable differences between screening programs in the number of repeat testing that would be expected to be performed. Even in assuming small one-time disutilities (->0.001) for abnormal screening results, this can have a major impact in the economic findings.

Expanding the screening interval does advert cases of cervical cancer although it comes at the cost of detecting transient infections that may lead to unnecessary clinical management and overtreatment. Indeed, the economic analysis only evaluated a starting age of screening of 21 for primary cytology; otherwise, the starting age evaluated for all other screening approaches ranged from 25 to 30 years old.

Sensitivity analyses were conducted to test assumptions and alternative parameter values informing the economic model. In nearly all circumstances, the model conclusions remained robust. As noted above, the model was most sensitive to the addition of a one-time disutility for abnormal screening results given the small QALY difference between screening strategies.

The economic evaluation reflected, as much as possiblem, Canadian guidelines on the management of screening outcomes, which was extensively validated by clinical experts involved in this review. However, variations in the management may impact the overall cost-effectiveness of a screening program. This was considered outside the scope of this review which was more focused on comparing different types of tests. Furthermore, this analyses did not compare between different commercial assays of the HPV tests nor the impact from the increasing practice of HPV genotyping to inform clinical management.

2397

Patients Preferences, Perspectives and Experiences: A Qualitative Evidence Synthesis

This review addressed Research Question 4: What barriers, facilitators and preferences about cervical cancer screening are reported by women living in Canada and countries with comparable healthcare contexts? How do these differ across social identity groups?

This question was refined after the initial literature search, with the input of the other HTA authors and clinical experts. A summary of revisions to the protocol were previously outlined.

Methods

A systematic review and qualitative meta-synthesis of the empirical qualitative literature relevant to the research question on patients' experiences and perspectives was conducted. The protocol was written a priori and followed throughout the research process, with iterative adjustments to the research question and search strategies detailed below. This iteration was prescribed by the a priori protocol in order to accommodate findings about the availability and usefulness of qualitative research evidence. The methods reflect the intention to synthesize results of published studies to address the research question and policy question in a way that yields.

Literature Search Methods

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the Peer Review of Electronic Search Strategies (PRESS) checklist.[29]

Information related to patients' experiences was identified by searching the following databases: MEDLINE (1946–) via Ovid; Embase (1974–) via Ovid; PsycINFO (1967–) via Ovid; the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO; PubMed; and the Social Sciences and Humanities segments in Scopus.

A hybrid qualitative filter was applied to limit retrieval to qualitative studies. The validation of this filter has been published.[143] The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords.

Two searches were conducted: 1) an initial search for qualitative research related to HPV testing or screening, completed January 20, 2017; 2) a broader search for qualitative research related to any form of cervical cancer screening, completed February 6, 2017. The search was broadened because the initial search retrieved only 12 eligible papers. For the initial search on HPV testing, the search was not limited by date. Retrieval for the broader search on related forms of cancer screening was limited to documents published since January 1, 2002 to align with the other sections of this HTA. For both searches, conference abstracts were excluded results and results were limited to English- and French-language publications. The complete search strategy is presented in Appendix 1. For the second search, eligibility criteria were tightened to include papers that focused on cervical cancer screening and exclude those which discussed the topic in a minor way, for example alongside other types of cancer screening, or in a discussion of general health system engagement. Only studies conducted in Canada and countries which have comparable health care systems were included (i.e. USA, Australia, New Zealand, European Economic Area).

Regular alerts were established to update the searches until the completion of the stakeholder feedback period of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the *Grey*

Matters checklist, which includes the websites of health technology assessment agencies, Internet search engines, and professional associations.

Selection Criteria

Eligible reports were those published in English or French of any qualitative design that explored perspectives of women eligible for cervical cancer screening. Perspectives of women's partners, family members, clinicians were also included if they co-occurred with women's perspectives. We did not include studies on family member or clinician perspectives alone. The following types of publications were excluded: theses and dissertations, data presented in abstract form only, book chapters, editorials, letters to the editors. Selection criteria are as follows:

Inclusion Criteria

- English- and French-language full-text publications
- Studies published after January 1, 2002
- Primary qualitative empirical research (using any descriptive or interpretive qualitative methodology, including the qualitative component of mixed-methods studies)
- Studies involving adult women (21-70 years of age) and studies involving women outside of this age group who are eligible for cervical cancer screening in the jurisdiction in which the study was conducted.
- Peer-reviewed, published research work
- Studies conducted in a comparative health care context (i.e. Canada, the United States, Australia, New Zealand, United Kingdom, European Economic Area).
- Studies addressing any aspect of women's perspectives on cervical cancer screening, regardless of the particular screening intervention or program, or the process of screening
- Studies that are explicitly relevant to women's experiences with cervical cancer screening, as indicated by a title which includes a concept related to cervical cancer screening or testing

Exclusion Criteria

- Animal and in vitro studies
- Editorials, case reports, or commentaries
- Studies addressing topics other than cervical cancer screening
- Work that has not been peer-reviewed, or is not published (e.g. theses, editorials, letters to the editor)
- Work that is available in abstract form only
- Work that is available only as a book chapter
- Studies that did not include the perspectives of women eligible for cervical cancer screening
- Studies labelled "qualitative" but that did not use a qualitative descriptive or interpretive methodology (e.g., case studies, experiments, surveys or observational analyses using qualitative categorical variables)
- Studies involving the perspectives of elderly (aged 71+ years), adolescent, or pediatric populations.
- The quantitative components of mixed-methods studies were excluded.

Screening and Selecting Studies for Inclusion

At least two reviewers independently screened the titles and abstracts of all citations retrieved from the literature search, and excluded reports that clearly do not meet the eligibility criteria. The full texts of all potentially relevant reports were retrieved for review. Two reviewers independently reviewed the full-text articles based on the detailed eligibility criteria. Any disagreements among reviewers were resolved through discussion. All eligible articles were included in the analysis.

Data Collection and Extraction

Researchers extracted two types of data from each primary report: study characteristics and study results relevant to the research question.[144] One reviewer extracted descriptive data about features of the study using a standardized form . The second type of data relevant to this study is the qualitative results of each included study. Relevant results were extracted into the qualitative data management software N-Vivo 11 (QSR International Pty Ltd Version 11, 2015). Extraction of both types of data was subsequently verified by a second reviewer.

Descriptive data included items such as first author, article title, study objectives, participant characteristics, characteristics of study design and methodology, date of publication, and nation in which the study was conducted. Specific information about participant characteristics collected include: age range, sex or gender, and participant profiles when identified as sampling criteria in the study (e.g. low income Appalachian women). Appendix 11 provides information about each included article.

The data extracted into N-Vivo was the main source of information for our analysis. Reviewers extracted findings from each study that are relevant to the research topic for further analysis. Qualitative findings are "data-driven and integrated discoveries, judgments, and/or pronouncements researchers offer about the phenomena, events, or cases under investigation."[145] In addition to the researchers' findings, reviewers also extracted original data excerpts (participant quotes, stories, or incidents) to illustrate or communicate specific findings. Given that discrepancies have been noted between results presented within abstracts and main reports,[146] only results presented within the main report were extracted. N-Vivo 11 (QSR International Pty Ltd Version 11, 2015) was used to extract and manage this data.

Methodological Assessment

Qualitative meta-synthesis researchers typically do not exclude qualitative research on the basis of independently appraised "quality," an approach that is common to multiple types of interpretive qualitative synthesis.[145,147-153] However, in order to assist readers in assessing the trustworthiness of our conclusions, we conducted an appraisal of quality for each study. For this purpose, we used the CASP Qualitative Checklist.[154] Each study was assessed by two reviewers. Results of this assessment are included in Appendix 11, which reports the agreement or disagreement of the reviewers on each component of the checklist.

Given the lack of consensus in the field of qualitative research as to methods and standards for critical appraisal of research quality,[147] we did not use the CASP tool to exclude studies from consideration. Instead, we included all topically relevant, accessible, and published research using any qualitative interpretive or descriptive methodology. By nature of qualitative data analysis, information-rich and higher quality studies tend to receive more attention in the analysis because they provide more information relevant to the research and policy questions.

Data Analysis

Descriptive Analysis

A descriptive analysis of study and patient characteristics was conducted, with the goal of characterizing the set of included studies in terms of important study and patient characteristics (e.g. sample size, sample type, national context, year of publication).

Concerning study design, there is significant heterogeneity in the reporting of qualitative research methods, and some authors may report a design, while others name only an analytic approach. Reviewers extracted and described whatever information about study design was made available by the authors, focusing on design where one is provided and describing analytic approach if that is the only information available. Reviewers did not impute information about study design and methodology, but relied on the information the authors provided through explicit statements about study methods. As a result of the variable approaches to reporting qualitative methods, our summary of this information (Appendix 12) includes both study designs and analytic approaches.

Tables summarizing study characteristics are available in Appendix 12 through Appendix 19. A table that describes the features of each individual study is available in Appendix 12.

Thematic Analysis

Published qualitative research was analyzed using techniques of integrative qualitative meta-synthesis,[145,149,155] also known as qualitative research integration. Qualitative meta-synthesis summarizes research over a number of qualitative studies with the intent of combining findings from multiple articles. The objective of qualitative meta-synthesis is twofold: first, the aggregate of a result reflects the range of findings across studies while retaining the original meaning; second, by comparing and contrasting findings across studies, a new integrative interpretation is produced.

Analysts used a staged coding strategy adapted from Grounded Theory.[156] This approach involves the comparison of research findings across primary included studies, categories, and co-investigators' interpretations of the studies. All analytic interpretations are negotiated during regular meetings with the whole research team. The analytic team consisted of four members (MV, UM, SK, NA) who each have MSc or PhD qualifications and expertise in qualitative research, particularly in the techniques of Grounded Theory and Qualitative Meta-Synthesis.

The goal of qualitative meta-synthesis is to produce a report which produces succinct findings that accurately reflect both the aggregated results but also the interpretive depth of the component studies, providing the reader a sense of the complexity and richness of the original work.[157] At the same time, mindful of the context of health technology assessment, analysts strive to keep the work relevant to the policy concern, offering descriptive and interpretive findings which are useful in the context of health technology assessment. Reported findings include both themes and contrasting perspectives. The results outline findings which are significant for reason of prominence as well as those which may be less prevalent but are still insightful or relevant to the policy question. We have included findings related to all stages of the lifecycle of a technology, including women's preferences related to implementation.

A note on the terminology of coding for qualitative meta-synthesis: we consider the codes, themes, and categories offered by the author of each study AND develop our own codes, themes, and categories to synthesize the information across studies.[158] We consider a "code" to be the initial unit of qualitative analysis. A code can capture any type of level of idea. It is a label which allows us to apply both descriptive and interpretive level summaries to a piece of data. Codes can be grouped and re-grouped to form categories. Themes are the most abstract level of analysis, and are identified in the data by looking across both categories and codes.[156,158] Sometimes we move in a linear fashion from code → category → theme, but sometimes the process of identifying categories and themes happens simultaneously, especially in the middle and later stages of coding. Sometimes analysis requires de-construction and re-constitution, for instance when thinking about a theme catalyzes the de-construction of a category, and re-coding to identify or organize the data in a different way. This is all part of the iterative nature of analysis.[156]

Initial coding

Using a staged coding process similar to that of grounded theory,[156,159,160,159,160161,162161,162161,162155,156155,156155,156] findings of individual studies were broken into their component parts (the author's key themes, categories, concepts) and then regrouped across studies according to themes and categories inductively-developed by our research team. This was done through a staged process beginning with line-by-line open coding to identify meaning and content. The process of initial coding was completed by multiple coders working separately on the same body of data (approximately five studies to start), and then meeting to discuss their emerging insights. At this stage, we are mainly conducting descriptive coding, although we started to see some "focused coding" work accomplished as the initial codes were condensed and grouped into categories through discussion with all coders. The same group of coders individually coded five more papers, and met to discuss the list of categories and potentially identify initial themes, suggesting a direction for refinement and evolution. At this point, we were confident that the coding of individual analysts was sufficiently aligned, so coding for the rest of the dataset proceeded with one researcher acting as the primary coder and another verifying the coding.

Focused and theoretical coding

Focused and theoretical coding are second-cycle stages of coding, and occurred both together or separately.[156] The objective of focused coding is to group the initial codes into salient categories. The objective of theoretical coding is to account for the relationships between other codes or categories, to provide a uniting primary theme (maybe called a core or central category) that helps to order, understand and explain the relationships between other categories.[156,158]

While many methodological texts explain these as separate processes, in practice they often develop simultaneously, either in tandem or alternating sequence. As the analyst develops familiarity with the data through immersion in analysis, she typically begins to crystallize ideas about different concepts, sometimes pushing one idea quite far theoretically while others remain at an initial coding stage. It is artificial to expect coding and analytic thinking to proceed in a linear fashion, although it is easier to describe it this way in a Methods section.

The dataset for this study was very large, so we iterated between the initial, focused, and theoretical coding stages. We completed initial coding on a subset of approximately 50 papers, and then developed a focused coding schema. We then went back to apply that focused coding schema to the rest of the dataset, refining and adapting the schema as needed and then re-coding the original papers.

Focused or theoretical coding began with a research team meeting to review the initial coding and discuss potential directions for further analysis. At this point, the research team reviewed the initial codes and memos that each analyst had written describing ideas for preliminary categories or themes. The team discussed the relationship between these

items and decided upon a theoretically-relevant direction to proceed. By "theoretically-relevant", we mean a direction that is supported by the initial analysis, judged likely to be rich for further inquiry, and relevant to the research question and policy concern facing decision-makers. These categories form the foundation of the interpretive analysis, allowing us to organize and reflect on the full range of insights across the body of literature.[145,150]

We worked as a team on this large data set by working independently and meeting regularly to discuss: 1) whether the developed list of categories was sufficiently abstract to include all of the initial descriptive themes and to answer the policy question and 2) whether theoretical coding aligns between analysts. At times where we did not agree on both points, we refined the list of categories, themes and their relationships and then re-applied the schema to the data independently before meeting to re-assess sufficiency and alignment. Once we were confident with our analytic scheme, we were able to work more independently, coding larger sets of data before meeting to discuss.

Throughout all stages of analysis, we met regularly to discuss emerging results, and preliminary analytic ideas. To facilitate these discussions, we kept explicit notes using the memo and annotation features in N-Vivo to record decisions made regarding coding and theme development, as a means to help ensure rigour in the analysis. In all stages of coding, analysts pay attention to the transferability of results across different contexts as a way to determine whether some results might only apply to certain sub-groups.

Results

A total of 4,864 results were returned from the electronic database searches, alerts, and search updates. Of these, 117 studies were determined to be eligible after full-text screening, and all were included in the analysis. The study selection processes are presented in a PRISMA flow diagram (see Appendix 16). A list of excluded studies is available upon request. A table describing each of the 117 included studies is provided as Appendix 11, the master table of studies.

Descriptive Analysis

Study characteristics

Of the 117 included studies, all were primary empirical qualitative research studies. A summary of the reported study designs or methods in the included studies is presented in Appendix 12. Most of these studies did not identify a specific methodology, with 28 studies offering no further description beyond "qualitative", and 57 studies offering no further description beyond the use of analytic strategies such as thematic analysis (32), content analysis (15), or framework analysis (10). Of those studies which did identify a specific methodology, 16 reported using Grounded Theory and adapted Grounded Theory approaches or constant comparative analysis, six reported using Qualitative Description, three Ethnography, and seven identified other methodologies (e.g. Interpretive Description, Community-based participatory research, Case Study).

A summary of the reported data collection techniques is presented in Appendix 18. All studies collected data using interviews (52), focus groups (42) or interviews and focus groups (13). Some studies supplemented these data collection techniques (10) with other methods such as open-ended surveys,[161] online focus groups,[162] talking circles,[163] case histories,[164] community meetings,[164] or the analysis of fax messages.[165]

Most of the included studies were conducted in the United States and US territories (63) with an additional 18 studies from Canada. The remainder of the studies were conducted in the United Kingdom (15), Australia (8),Sweden (5), New Zealand (3), Romania (2), Norway (1), Portugal (1), and Poland (1). See Appendix 13 for more details.

These studies included data from 4,835 women, 258 family members or unpaid caregivers, and 433 clinicians. Sample sizes in each study ranged from 1 to 547. See Appendix 14 for further detail.

102 studies recruited participants based on particular aspects of their social or demographic identity. While some of these 102 studies focused on one identity feature, many focused on multiple identity features. 64 studies recruited women who belonged to a minority ethnicity or culture, 13 studies recruited women of low socioeconomic status, ten studies focused on Indigenous women, six focused on women who lived in rural areas, seven focused on women who are lesbian, bi-sexual or transgender, three focused on older women, and 11 studies focused on other aspects of identity (e.g. obese, incarcerated women, homeless women, HIV positive).

Summary of Quality Assessment

Overall, the quality of the included studies was assessed as reasonable. Some studies had more quality concerns than others, often that particular information asked for by the CASP tool was not included in the study report. The sixth CASP criterion (Has the relationship between the researcher and participants been adequately considered?) was very infrequently addressed in published manuscripts. As with many other *a priori* quality criteria for qualitative research, the absence of a factor may reflect word limit constraints in publication rather than methodological constraints. Others have noted that qualitative health researchers conventionally under-report these types of procedural details, and that the quality of the findings tends to rest more on the prowess of the researchers than on methodological processes.[166,167] We did not exclude any study based on critical appraisal, and have published a detailed critique of this practice elsewhere.[168]

Qualitative Meta-Synthesis

The following sections explore the results related to the meta-synthesis. We begin with a description of the theoretical framework we developed to organize the findings of this analysis. After describing the structure of this framework, we will discuss findings related to each element of the framework in the context of cervical cancer screening in general (HPV testing or Pap smear and any other modality included in our studies). Finally, we will detail findings specific to the subset of papers that explicitly addressed HPV testing, comparing and contrasting to the findings on all types of cervical cancer screening

A note on terminology: we are using the words women, woman, and female to describe participants and targets of cervical cancer screening. Four of our studies included the perspectives of transgender men, who have cervixes and are therefore eligible for cervical cancer screening, but do not identify as female.[161,169-171] In this analysis we address the particular experiences of this group separately, to illustrate their unique perspectives and circumstances.

Framework

We have identified a number of factors that act as incentives or disincentives to women's decision-making about participation in cervical cancer screening. In the descriptions of women's experiences, perceptions, and preferences for cervical cancer screening we identified the following factors that can act alternately as push and pull factors to screening participation: Emotions, Cultural and Community Attitudes and Beliefs, Understanding Personal Risk, Logistics, Multiple Roles of Women, Relationships with Health Care Providers, Comfort and Inclusion in the Health Care System, and Knowledge (Appendix 19). We will discuss each factor in turn, detailing how it could act as encouragement or discouragement for screening. Many of these factors are closely related. For example, a woman's understanding of her own risk of developing cervical cancer was closely related to her knowledge of genetic and lifestyle risk factors of cancer. Some categories were more closely connected than others, and Appendix 20 shows a conceptualization of this schema. The studies we analyzed for this report focused on disincentives to cervical cancer screening more frequently and deeply than incentives and our analysis reflects this. These findings have implications for implementation of HPV screening at the levels of policy, and clinician and patient education.

Many of the studies examined perspectives on cervical cancer screening from women sampled for a particular characteristic, including race, income, age and sexual orientation. Our analysis considers the impact of these social identities on the way different factors are experienced. For example, women in most studies found attending a medical appointment a barrier to cervical cancer screening because these visits may require time off work, navigating through inaccessible transportation, child care and more. These factors were strong barriers for women who held precarious employment, who had jobs that did not permit time off for medical appointments, those who could not afford to lose income in order to attend a medical appointment, those who did not have access to a car or convenient transportation, those who lived in rural areas with poor public transportation and more. Some women may face none of these exacerbations whereas others may need to navigate through several of them. As a result, a woman's social location was highly influential on the way she experienced the incentivizing and disincentivizing factors we describe. In Appendix 20, the influence of social location is represented using a physical metaphor: the fulcrum on which the scale balances. First, a brief explanation of this metaphor, drawn from physics and requiring only basic understanding of force and levers. As the fulcrum moves away from the middle of the scale, the weight on the far side exerts more force; in order for the scale to balance, more weight must be placed on the short side. Applying this physical metaphor to our analysis, we conceptualize that for women with significant social and material resources, the fulcrum shifts to the left, and the disincentives exert less downward force. Fewer incentives or less strong incentives are

needed to tip the balance in favour of screening. Therefore, it is easier for them to engage in the screening process. On the other hand, for women who experience social and material deprivation, the fulcrum moves to the right and the disincentive factors are heavier, and more incentives or more powerful incentives are needed to overcome these barriers. As a result, the balance is more tenuous and participation in cervical cancer screening is more difficult.

The magnitude of the factors as represented as Appendix 20 is for illustrative rather than conceptual purposes. We identified that the factors which become most influential, or most prominent differ for each individual. For example, a belief that she is at high risk for cervical cancer may be such a strong motivator that a woman finds ways to overcome other significant barriers. For another individual, a past negative experience of sexual abuse may be so traumatic that she is unwilling to subject herself to a cervical cell scrape, no matter how convenient and important she believes cervical cancer screening to be.

Appendix 21 illustrates how this framework may operate for an individual. A disadvantaged social location may move the fulcrum to the right, meaning that the disincentive factors are now exerting more weight. This exemplar individual may experience incentivizing factors, for instance, recognizing herself at potential risk for cervical cancer, a positive relationship with her health care provider and an understanding of what cervical cancer screening entails. However, the combination of her social location and the disincentivizing factors she experiences tips the scale in towards foregoing participating in cervical cancer screening. Not all factors are at play for all women, and as illustrated by the omission of two factors in Appendix 21. Factors may cluster in different relational groups, for different women. For example, sometimes Knowledge may be most closely related to Relationship with Health Care Provider. For others, it may be more closely aligned with Cultural and Community Attitudes and Beliefs.

As described in the methods section of this report on patient preferences, many of the studies we analyzed addressed cervical cancer screening modalities that do not include HPV testing. We included these perspectives because they are often relevant to HPV testing (e.g. embarrassment of providing a cervical cell sample, inconvenience of attending a medical appointment), even when the data describes another type of cervical cancer screening, and they are relevant to the policy concern motivating this HTA. In order to facilitate the policy decision considered by CADTH, in the second part of this report we highlight findings that are particularly relevant to HPV testing.

Factor 1: Emotions

This theme discusses emotional discomfort deriving from modesty, shyness and embarrassment concerns and how vulnerability, shame and powerlessness influence women's screening behaviours. Moreover, women commonly reported fear, in particular, of the test, pain and discomfort associated with the test, test results and cancer more generally. Emotional responses were mediated in some women by fatalistic beliefs about cancer that discouraged active participation in screening, or on the opposite end of the spectrum, strong preventive health orientations that strongly encouraged preventative action even in the face of difficult emotional responses

Emotional discomfort and distress

Women reported *emotional discomfort* and *embarrassment* as common barriers to screening.[164,170-186] Modesty and shyness were major sources of these emotions for many women during the screening procedure.[175,177,187-191] Women felt embarrassment from the test procedure,[171,174,178,186,187,189,190,192-204] and by exposing their bodies to a stranger.[181,182,189,193,197,198,201,205,206] Due to women's perception of the link between sexual activity and need for HPV testing, embarrassment was also a consequence of women's anticipation of their communities discovering that they engaged in screening[181,184,185,198,207] which, for some women, amounted to shame from their community.[208,209] Some women anticipated embarrassment upon diagnosis of HPV because of its perceived association to sexual infidelity.[210] For some, experiencing embarrassment was a sufficient reason not to attend screening.[184,211,212] For others, however, embarrassment was not a disincentive[165] because these concerns did not outweigh the importance of screening and maintaining their health.[189] Findings related to the stigma of HPV diagnosis and sexual infidelity or promiscuity will be discussed more fully in the last section of our results.

Other aspects of emotional discomfort include *vulnerability*, *shame* and *powerlessness*.[170,171,185,193,196,209,213,214] Some women felt vulnerable because of the male gender of the sample taker.[182,215,216] Others experienced a sense of powerlessness from how the cervical cell sample was obtained,[170,185,193,215] especially around a lack of privacy during this procedure.[171,181,209,211,216] In general, women emphasized the importance of privacy and the need for sensitivity around screening.[171,181,183,187,190,195,198,205,209,217] The emotional distress of cervical cancer screening was exacerbated for women who had previously experienced sexual assault[186,193,199,200,202,209,218,219] and those who don't or hadn't yet experienced penetrative sex.[161,172,207,220] Transmasculine people discussed the potential for experiencing emotional distress due to the dissonance between their gender identity (male) and participation in an intimate exam involving penetration of a body part associated with women.[161,169-171] For some women who were survivors of sexual assault, abstaining from screening was a choice made to protect oneself from reliving traumatic experiences of sexual abuse and violation.[163,209] Indigenous women in two studies considered pap smears to be an extension of colonization, with reminders of sexual abuse experienced in the residential school system.[163,209]

Fear

Some women reported *fear* while engaging in screening, which included *fear of the test*, *fear of pain and discomfort*, *fear of the test results* and *fear of cancer*. *Fear of cervical cancer screening* was a commonly reported concern, regardless of the screening modality.[171,174,182,187,191,198,201,212,219,221,222] This was derived from fear of cancer treatment,[223] fear of waiting for the test in doctor's office,[174,187] and fear from the unfamiliarity of procedure.[201,219,222] Women who engaged in routine screening *feared pain*,[171,172,177,178,180,181,183,186,189,194,202,212-214,217-219,222,224-226] and *discomfort*[174,177,181,189,192-194,202,213,216,226-230] that may result from the screening procedure. Discomfort, in particular, was perceived as a consequence of the care provider,[194,198,219,222] the way the procedure was performed,[194,222] inappropriate sizing of the speculum,[194,214] bleeding from the test,[178,201,212,216,226] and the invasiveness of test.[178,191,194,207,209,214,219,221,226,230,231] For many, the pain and discomfort from the test were strong reasons to not attend screening.[165,172,173,181,193,204,212,216,222,224,228,230-232] Women used strong language when describing the pain and discomfort of the test. We found metaphors of sexual assault and rape used to describe this experience: "During focus group discussions, some women described feeling as if they were 'molested' during the examination" (p.1121 in[193])[193,199,200] Women's experiences of cervical cancer screening ranged from unpleasant to intensely traumatic, and may be linked to past experiences of sexual assault.[193,199,202,209,218,219] For some this fear may be alleviated either through emotional support,[198] adequate and clear information,[233] and speaking to the doctor.[196]

Women reported *fear of test results*,[172,174,179,181,186,193,198,199,201,212,215,216,218,219,221,222,224,230,231] such as receiving a cancer diagnosis.[172,176,181,188,190,192,193,202,205,211,216,221,225,234] This fear became a significant barrier to engaging in screening behaviours,[187,190,192,212,225,230] which may be allayed through an adequate explanation of the test results.[233] Moreover, closely associated with the fear of test results amongst those engaging in HPV testing was the stigma of HPV positive status.[210,232,233] Stigma, either from their cultural enclave or from the broader society, was a significant barrier to starting and maintaining HPV testing for cervical cancer screening, but was less of a concern for women who were participating in cervical cancer screening with Pap smear.[174,176,186,235] For others, however, stigma did not discourage screening behaviours,[236] and could be dissipated from properly explaining the diagnosis, management of HPV, associated risk of cervical cancer, availability of treatment for cervical cancer.[233] These women reported relief and reassurance as their prime motivators for screening.[197-200,237] Women sought to put their mind at rest,[197,200] and reassure their health status through screening.[232,238,239]

Finally, women commonly reported *fear of cancer*,[171,177,181-183,187,198,204,205,222,223,225,240] in particular, an intense fear that cancer inevitably results in death.[182,188,198,223,225,241,242] Some women derived their fear from being HPV positive, and efforts to describe that most HPV does not lead to cancer did not alleviate women's concerns.[234]

Personal values and emotional orientation

An important theme that is relevant to several factors is women's personal values and their emotional orientation to concepts of illness, cancer, risk, and medical intervention. Many women reported a sense of *fatalism* related to screening.[187,193,198,200,211,212,216,224,225,229,237,241,243,244] This fatalism resulted from a sense of powerlessness that if the screening test came back positive, they could do anything to remediate their situation.[193,198,211,225,241] For example, women in one study described fatalistic feelings about HPV screening due to the lack of treatment available for HPV.[233] This sense of fatalism was described by women as a barrier to initiating and maintaining their screening behaviours, related to a diagnosis of cancer and not a specific screening modality.[198,200,203,212,224,229,243]

Positive emotions about screening were typically described as a preventative health orientation and self-efficacy. These women had a propensity to prevent cancer,[172,176,187,199,202,208,211,216,219,222,224,243,245,246] which propelled them to proactively seek screening, treatment or relevant knowledge.[175,177,189,190,207,210,219,220,222,233,234,237,245-247] Some women perceived their engagement in screening as a moral obligation to uphold one's health.[165,190] These beliefs may be strengthened, especially for initiating and maintaining screening, through encouragement from their families, peers and health care providers.[176,177,194,198,202,222,237,239,243,245,248,249] These beliefs were closely linked to acknowledgment of the importance and benefits of screening,[177,189,198,222,234,237,239,243,245] which increased their motivation and self-discipline to pursue screening while acknowledging its barriers.[177,189,237,245,248] Conversely, the lack of a preventative health orientation contributed to inaction and apathy towards engaging in screening,[178,190,196,197,202,205,249] and in some cases, denial of the need and importance of screening.[196]

Factor 2: Cultural and Community Attitudes and Beliefs

The attitudes and beliefs a woman holds related to those of her culture or community significantly influenced how she perceives cervical cancer screening, as well as related concepts of health, illness, and the health care system. Women identified cultural practices and beliefs that were barriers and facilitators to screening. In particular, some women reported difficulty in aligning the values and beliefs of their culture with that of the health care system. This cultural incongruency could function as a disincentive to screening when it resulted in the perception that health care system did not respect culture values. The importance of culture and community was also apparent in many studies that describe cultural dialogue and community support as integral to establishing and maintaining screening behaviours. This dialogue was especially important for conceptualizing the risk factors of cervical cancer, which influenced women's personal understanding of their risk and the reasons to pursue cervical cancer screening.

Cultural practices and beliefs

Women from many different types of communities identified their community's culture as a barrier to screening.[175,177,182-185,187,194,195,197,198,201,208,225,230,243,250,251] The practices and beliefs embedded in community life were significant obstacles to screening.[173,182-185,187,194,197,198,201,207,220,223,230,235,242,250] For example, several authors documented a belief in the lesbian community that women who have sex with women do not need to participate in cervical cancer screening because they do not have sex with men.[252] Women in communities where female genital mutilation is commonplace may forego screening because they anticipate judgment and shame from Western health care providers.[182,183,207,230]

Cultural beliefs could also influence a woman's perceptions about the need or importance of screening. Many women derived a preventive health orientation from cultural and community beliefs, which served as facilitators to screening.[163,182,195,200,207,222,229,235,244] On the other hand, some women relegated the need for a preventive approach to their healthcare because they believed that their religion served this purpose.[182,183,223,225,229,230] Fatalistic beliefs and beliefs in predestination were widespread in some communities and presented significant barriers to pursuing screening options.[176,182,184,195,200,208,224,225,229,253]These beliefs stemmed from community practices but manifested in personal emotions and beliefs revolving screening.

Cultural (in)congruency

Many women reported difficulties with aligning with the values and practices of the health care system, which became disincentives to screening.[163,175,176,182-184,188,191,195,198,201,207,209,220,229,242,250,251,253] Some women identified virginity as a point where their values diverged from that of the health care system. Women equated the privacy, sanctity, and sacredness of their body to preserving their virginity. However, the same women perceived the health care system to not value virginity because of the invasiveness of the procedure that does not promote their cultural values and beliefs.[182,184,207,220,229,250] This understanding may derive from the belief of some women that virginity is linked to physical penetration. Moreover, other women may believe that loss of virginity is a consequence of any sexual contact. Health care professionals must be equipped with diverse conceptualizations of health, especially in relation to medical procedures that may be considered intimate and impinge on the values and beliefs of certain cultural groups. Concerns about speculum use and penetration were found in papers that solicited views from women identified as Muslim, Mexican-American, lesbian.[172,182,220,226] Other women reported alienation from the health care system,[163,209,220] often catalyzed by interactions with culturally insensitive care providers.[176,183,195,201,207,220,242,251] For

example, Indigenous women reported alienation from the health care system when they interacted with clinicians who did not understand the implications and history of abuse associated with the colonization of the Indigenous peoples.[163,209]

Women reported cultural congruency as an incentive to pursue screening.[163,175,198,220,222,225,227,229,230] Receiving positive health messages from culturally congruent care providers from within their communities,[163,220,225,230] moving care from a sterile medical setting into a welcoming, comfortable community space,[163,222] and combining both Traditional and Western healing were important ways to balance their cultural values with the practices of conventional health care.[163,175,198,229]

Community discussion

Many women were motivated to pursue screening due to a community dialogue on cervical cancer and Pap testing.[163,164,194,198,201,205,207,219,220,222,225,229,235,240,243] These women identified the dialogue as a way to navigate through their community's infrastructure barriers to screening.[194,220,229] An increase in community awareness of screening supported women to not just start but also continue participating in screening programs.[163,220,225,229,240]
Social support was a notable incentive to pursue screening.[163,176,198,205,207,208,220,222,225,229,230,235,237,243,244,250,254,255]
Social support from the following groups was described as helpful and desirable: mothers,[198,219,220,244] friends,[198,205,207,208,219,222,229,230,243,244,255] family,[191,198,208,222,229,230,250,255] partners,[176,198,205,208,229,230,235] health professionals,[163,198,230,235,254] faith leaders,[225,229] survivors of cancer,[240,255] and the community.[163,208,219,229,237] When support was not available from these sources, participation in screening was less likely.[175,184,185,191,198,201,208,250] In particular, an unsupportive partner could be a major barrier to continuing screening.[172,201,225,247,254] Women were concerned about the jealousy of their partner,[172,201,225,254] and feared their partner's reaction upon disclosing a positive HPV status as barriers to maintaining screening.[247] In some ways, the fears mentioned above were derived from the absence of a community dialogue[173,175,176,184,185,187,195,198,201,207,208,217,220,225,227,230,235,240,242,244,250,253] about female reproductive and sexual issues,[173,187,195,198,207,220,230,235,242,250] cervical cancer,[173,176,198,207,208,225,235,240,244] and pap testing.[201,208,227,240,250] The lack of a community dialogue and understanding about these issues could also be related to an emphasis on cultural privacy in the community, which some women identified as a barrier to screening.[163,164,184,185,195,204,208,209,220,225,230,244,250]These women considered their bodies as a private topic to discuss with their immediate family only.[185,195,220,250] They resisted interference from external members such as health care professionals, especially in small communities,[163,185,204,209] in order to maintain their "cultural safety".[164]

Community understanding of risk

Women's perception of their personal risk for cervical cancer may be derived from or built upon foundational cultural beliefs. In particular, several studies from different communities described perceptions that women who are sexually inactive are not at-risk for cancer and HPV, and therefore, do not require screening.[173,184,185,190,207,217,220,235,244,256] On the other hand, communities thought that women who are married or sexually active should pursue screening.[173,184,185,207,217,220,235,244] Moreover, communities maintained that the absence[188,208,225] or presence[188,195,208,244,250] of physical indicators of health were significant incentives or disincentives to pursue screening. When women discussed "symptoms", they typically referred to regular menstrual cycles, and lack of symptoms associated with STIs. Finally, women named their community's inaccurate or incomplete perception of risk[200,207,208,225,243,244] due to their lack of knowledge or confusion with their current understanding of screening practices and guidelines.[225] Cervical cancer screening using any modality was closely associated with sexual activity by many communities,[173,174,176,184,185,190,198,207,217,230,240,250,254] which raised the stigma for those who chose to pursue screening, and added another barrier to maintaining screening behaviours.[163,174,176,207,225,230,240,254]

Factor 3: Understanding Personal Risk

The way in which women identify their own personal risk for cervical cancer, including beliefs and perceptions of vulnerability, influences their decisions and behaviours concerning screening practices. Although these factors are interwoven with their knowledge of personal risk (i.e., general understanding of cervical cancer and its risk factors, screening procedures, and link between HPV and cervical cancer), and how they see themselves in relation to these factors, there are specific elements that are important to acknowledge. Specifically, the appraisal of one's personal

risk draws on a person's understanding of their family history of cancer (biological risks), lifestyle factors (physical and behavioral risks), age-related risks such as menopause, and general well-being and being asymptomatic.

Biological risks

Many women used the absence of a family history of cancer to position themselves as being at low-risk for cervical cancer, which was used as a justification for not participating in cervical cancer screening.[184,187,191,199,212,216,222,228,232,237,241,244,248,252,256] This is not congruent with biomedical understandings of cervical cancer etiology, especially with regards to the link between cervical cancer and HR-HPV, which is not hereditary.[257] In addition to this disincentive to obtaining check-ups, it also removed some worries and anxieties around cancer diagnosis.[256] Overall, the notion of "cancerous genes" was important to the way women understood the significance of cervical cancer screening to their lives,[256] and some women perceived a biological link as more impactful than behavioural or physical risks.[252] This factor also worked as an incentive: women who had close family members who had been diagnosed with cervical cancer expressed a strong commitment to screening participation.[181,196,228,238,244,246,248,251,256,258]

Physical and behavioural risks

Several studies noted women's decision to not participate in cervical cancer screening due to their perception that they were at low-risk of cervical cancer because they did not engage in lifestyle behaviours that would predispose them to cervical cancer.[165,169,173,178,181,184,185,187,190-192,195,200,201,205,212,224,232,235,241,243-245,248,252,254,256,258] These perceptions of risk were primarily based upon on whether they were in a long-term monogamous relationship or were active with multiple sexual partners. Some lesbian women perceived themselves to be at lower risk of cervical cancer because they do not have sex with men.[252] Women also reported an array of risk factors related to their lifestyle such as smoking, unstable housing, poverty, unhealthy diet, lack of hygiene, use of intrauterine devices, douche solutions, certain types of toilet paper, birth control, HIV infection, changes in menstrual patterns, drug use, and promiscuity, which may serve as drivers or disincentives to screening participation depending on emotions or an orientation towards preventive health care.[165,169,172,174,180,184,185,188,190,212,219,224,227,228,232,239,241,243,245,246,248,254,256,258-261] Some individuals also suggested that anyone with a cervix, despite their gender identity, behavioural or personal lifestyle choices, should engage in screening.[169]

Age and life stage related risks

Some women perceived that cervical cancer risk reduces with age and therefore, screening was less important or not needed as frequently for older women.[192,207,212,216,224,235,238,244,245,262] "Older" was defined variably (and sometimes not at all) in different studies but was often linked to menopause, rather than a particular age. Moreover, women reported that a series of several previous cervical smears displaying normal results gave them a sense of security in their assessment of themselves as low-risk.[216] It was noted that the challenge of navigating through the social norms associated with the physical changes that come with aging and menopause may divert some post-menopausal women away from engaging in screening practices.[216] For other women, this understanding led them to adopt a preventive health orientation and allocate more time and attention to their health by engaging in screening initiatives.[244]

General well-being

General well-being and feeling asymptomatic, such as a lack of pain and having regular menstrual cycles, were substantial disincentives to cervical cancer screening.[165,169,178,181,183,187-189,192,193,195,199,200,204,207,211,216,217,222,224,229,230,237,238,247-250,260] Some women who were motivated to participate in screening drew their motivation from a desire to reassure themselves of their cancer-free health status despite the lack of symptoms.[163,169,173,181,199,201,216,238] Moreover, these women were incentivized to engage in screening because they believed that an early diagnosis may provide them with a better prognosis, and a negative screening result may give them the sense of security and relief they want.[163,169,173,181,183,199,216,238] Finally, some studies reported that the awareness of one's individual body such as being alert of bodily changes and having a preventive orientation towards their health care were significant incentives for women to participate in screening.[169,187,197,211,228,249]

Factor 4: Logistics

Logistical challenges acted as a strong disincentive to screening. A general lack of time was commonly reported by women, which required them to strike a balance between multiple priorities, such as family and work commitments, with cervical cancer screening. While the logistical barriers detailed in this section are possible to remediate individually, these efforts may not counter the tendency of women to prioritize other commitments over preventative health care. A more holistic approach that encourages the early socialization of screening by integrating community and social groups may be needed.[165,172,174,193,222,231,237,249,263]

Balancing priorities

Women juggled work and family commitments,[171,172,174,176-178,180-183,186,187,189,190,193,195,196,203,204,207,211,213,216,218,219,221,222,225,231,235,238,249,250,264,265] childcare responsibilities,[165,174,176,178,180-182,187,189,200,207,211,212,216,217,220,222,225,250,264,265] and navigated through transportation challenges to attend screening appointments.[174,179,180,189,196,200,207,211,217,218,220,222,225,228,231,242,244,249,219] Appointments at clinics that were far from their home or at inconvenient locations were taxing because of the travel time involved; women living in rural areas faced more challenges in this area because clinics are likely to be located farther away and there is typically less public transportation available.[204,211] Women suggested that providing cervical cancer screening in local community hubs or other convenient locations would facilitate attendance.[174,181,193,222,231,249,260] Long wait times in the clinic exacerbated the challenge of attending screening appointments and decreased women's willingness to attend screening in the future.[172,176,183,185,193,194,213,228,231,244,264-266]

Scheduling appointments

Most cervical cancer screening programs, regardless of the screening modality, require in-person attendance at a medical facility. Women reported a lengthy list of logistical barriers to participating in screening, for example, the scheduling of appointments was challenged by inflexible clinic hours that made it difficult to remember and schedule appointments.[178,186,187,194,211,218,221,224,228,250,267,268] Reminders and encouragement from the clinic and health care provider would help overcome the challenge of remembering to schedule and attend infrequent medical appointments.[182,183,186,193,217,224,231,249,251,264] Many women suggested that having appointment times outside of traditional working hours would alleviate many of these logistical barriers.[173,174,193,202,204,213,231,235] Moreover, women appreciated the efficient use of their clinic appointments by combining cervical cancer screening with other services; contraception, other cancer screening, general health care were mentioned as potential candidates for combining with cervical cancer screening.[174,193,213,222,224,231,238,249,252] Self-sampling at home may alleviate some of the logistical barriers to attending in-person appointments, although this screening modality was not unanimously accepted.[203,204,220,233] Scheduling medical appointments by phone were often named as a locus of communication challenges for women, especially those who did not speak the majority language where they lived.[175,178,185,189,204,230,235,244,265]

Communication

Communication challenges were also mentioned as barriers to screening. Women described communication barriers as arising from a lack of time, effort and respect from the clinical staff that prevented person-focused communication between patients and care providers.[164,172,176,183,190,191,194,201,224,230,231,253,265,266] Most frequently, communication challenges arose when women spoke a different language than their care provider.[173,175,176,183,184,187-189,191,194,201,207,212,220,222,223,230,235,244,250,264,265] These challenges could also occur for women with mental health issues, and those who are deaf.[221,263] Women who faced communication challenges struggled to understand the need for cervical cancer screening including its procedure and follow-up protocol.[173,175,176,186-189,194,201,207,212,220,222,223,230,235,244,250,253,264,265] Women reported logistical and other concerns with interpreters such as not having cultural knowledge and appropriate medical terminology.[176,180,212,235,263] A lack of social distance in rural and culturally close-knit communities may mean that women are hesitant to use interpreters fearing that they may disclose confidential health information to others in the community.[164,194,218,244,250]

Finances

Women in American studies often mentioned health insurance and the cost of screening as a logistical barrier, although this theme was not prevalent in countries that cover costs of cervical cancer screening through a universal health care system.[172,176,179,185,187-191,195,196,203,207,211,218,220,221,225,230,244,247,249,253,264,268] For these women, covering the costs of cervical cancer screening was a strong incentive to participate.[172,222,230,238,249,253,260,268]

Factor 5: Multiple Roles of Women

Familial responses

Many women reported placing the needs of children, partners, and in-laws above their own, which often resulted in women foregoing timely and appropriate health care. Managing time amidst familial obligations was perceived to be a barrier for accessing preventative care because of the demanding nature of domestic responsibilities,[163,164,173,176,181,186,187,193,204,211,219-221,231,242,250,264] for example, women's roles providing child and elder care, or in supporting the family finances through paid employment and budget management. When participation in cervical cancer screening has a financial cost (e.g. time off work, parking fees, fees for the service itself), it may be de-prioritized by a woman, who may choose not to forego paid employment or to allocate family resources to children's activities.[163,187,195,213,221,230,264] In addition, women who have obligations with a family business or caring for children or grandchildren are also challenged to attend medical appointments for cervical cancer screening.[186,187,264] Offering appointments outside traditional business hours would assist women in balancing their personal, domestic and employment activities.[173] Women in many studies expressed that their own health was a lower priority: "their children, husband, in-laws, household duties, cultural obligations and work outside the home came before their own needs: 'My health … it's not important'" (p. 182).[250]

In addition, the family structure in some cultural groups can significantly influence a woman's ability to seek health care from a male physician, thus posing additional barriers for accessing care.[250] On the other hand, a strong sense of familial responsibilities provoked women to self-care in order to remain healthy such that they are able to properly care for their family. This belief was more prevalent in cultures that associated self with family kinship such that caring for oneself is the same as caring for their family.[172,195,209,219,222,232,237,244-246,250]

Communication

Some women highlighted the significance of communication between mothers and daughters, and the need to nurture strong connections among various groups and communities of women. In Indigenous cultures, for example, many women commented on how the understanding of women's embodiment and sexuality were changing in younger generations, which made it difficult to establish and enhance the relationship between mothers and their daughters. Women made a strong and purposeful effort to connect with their children and speak to them about these sensitive issues in order to remediate the lack of dialogue with their own mothers.[209]

Factor 6: Relationship with Healthcare Providers

Healthcare providers (HCP) had a significant influence on the screening practices of women because they are well placed to engage their patients in screening practices.[170,171,182,183,185,198,222,230,233,239,248,249,251,261,268,269] Many studies reported that patients approach their primary HCPs as the first source of medical information.[182,183,185,196,222,233,237,239,244,249,254,270] This relationship was mediated by women's trust in their HCP, and was one of the strongest factors that enhanced the patient-provider relationship.[182,183,213,248,262,265,268]

Satisfaction with HCP communication

The HCP's communication style and bed side manner had a significant effect on their relationship with patients which in turn affected women's decisions about when and how to engage with the health care system, including participation in cervical cancer screening. When women felt included in making decisions about their health, they positively perceived recommendations for cervical cancer screening from their primary health care provider.[182,185,193,198,201,204,206,209,211,216,219,228,233,238,239,244,245,251,255,262,265,269,271] The practice of patient-centred care nurtured the trusting relationship between patient and provider, and when not present led to barriers in patient care.

Women gave examples of HCP behaviour related to cervical cancer screening that eroded trust: not receiving a satisfactory response after sharing vulnerable information,[171,268,272,273] when the HCP did not understand their individual situation,[161,169,171,252,268,273] or did not allow them to ask questions concerning their health.[183,185,186,195,212] A lack of trust with the HCP also influenced women feelings of concern for their privacy and confidentiality,[183,201] which was not a concern for women who were satisfied with the care they received.[165,176] Overall, women were less likely to participate in cervical cancer screening when they were not in a trusting relationship with their care provider,[170,183,199,219] or when they felt taken for granted and isolated;[215] forgotten or neglected,[172,185] or degraded and disrespected.[165,171,183,186,191,195,199,206,207,212,218,222,237,243,262,268,269,271,273] These types of negative experiences often negatively impacted future screening with different providers. Previous negative experiences acted as a barrier to engaging with the health care system in general, not just the particular health care provider.[164,171,172,176,183,191,194,201,224,230,231,265,266]

Women were more likely to accept cervical cancer screening when offered by their care provider, especially when they had a trusting relationship.[170,171,174,176,185,186,193,219,222,231,238,268] When women were satisfied with the medical care provided, they felt empowered,[171,182,199,222,228,268] and comfortable with their decision to start and continue screening.[162,171,182,219,269] Some women recognized the value of medical encounters with HCPs because they encouraged communication about their health.[235] An important feature of this experience was having the HCP explain the screening procedure, which enabled women to make informed decisions about participation.[171,182,185,186,199,213,214,219,228,243,244,272]

Personal characteristics influencing experience of care

An individual woman's personal characteristics (e.g. culture, ethnicity, religion, literacy, health status, socio economic status and sexual orientation) could influence the patient-provider relationship in a way that may disincentivize screening participation. Women reported negative interactions with health care providers related to personal characteristics such as female genital mutilation,[212] weight,[177,211,249] or sexual orientation.[161,171,273] Other women felt that HCPs perceived them to have lesser knowledge based on their socio-economic status and race,[219,230,253,264] or blamed them for their health status,[177,253] or medical condition. A language mismatch or lack of proficiency in English language exacerbated communication issues in this group of women.[176,184,189,192,207,222,223,230,235,237,243] Women also reported that HCPs were insensitive to their values and beliefs, which became a strong disincentive to screening.[171,176,241,252,273] Women overcame these barriers when their HCPs personalized the medical encounter for women with different backgrounds, beliefs and values.[169,170,185,186,244,268] Similarly, preferences for HCP with similar ethnic, cultural backgrounds or life experiences were recommended,[175,200,220,228,237,244,250,262,273] as well as provision of culturally sensitive services in accordance to religious beliefs.[176,185,250]

Gender

The gender of the HCP acting as a sample taker was an important, recurrent theme in multiple studies.[162,164,174,175,182,183,185,190,191,193,196,199,200,207,209,212,217,219,222-224,229,231,232,235,237,238,244,265,269,273,274] Women generally preferred screening by a female HCP.[164,174,182,191,200,219,222-224,235,237,268,269,272,274] This preference was influenced by multiple factors, for example, feelings of embarrassment and exposure that accompanied having a male HCP.[172,182,183,185,199,215,217,269] In some cases, women's partners did not allow screening by a male HCP[170,185,205,268] due to values and beliefs concerning privacy of women and the intimate relationship between two individuals. Lack of availability of a female care provider could be significant barrier to screening participation,[183,222,231] sometimes resulting from a woman's reluctance to request a female care provider.[212,223] When female providers were available, women cited this as a major facilitator of cervical cancer screening participation.[162,183,190,193,196,199,200,207,209,217,222,229,231,232,237,244,265,273,274]

Initiation by HCP

Many studies reported that HCPs play a significant role by initiating a discussion on cervical cancer screening with women, many of whom first attended screening due to these discussions with their HCPs.[171,182,185,186,212,219,233,248,261,268] Women's HCP also encouraged them to participate regularly,[175,182,185,186,190,193,198,200,224,231,233,237,239,244,249,251,255,275] especially for those who felt embarrassed or fearful of screening.[196,199] Reminders by HCPs or clinic staff played an important role in maintaining regular screening over

time.[171,175,186,189,200,204,222,230,245,249,251] These results indicate that a HCP's active outlook towards screening practices translated into women's positive reaction and engagement in screening. The lack of such recommendations by HCPs became barriers for women to partake in screening.[189,192,212,223,241,253,273]

Studies of transmasculine people described the reluctance of health care providers to initiate cervical cancer screening with these men. This reluctance is perhaps due to the lack of evidence or provider ignorance about the need for screening in trans men,[169] and perhaps due to the sensitivity of the health care provider reluctant to cause emotional distress by initiating a discussion that would remind the man about the dissonance between his sex assigned at birth (female) and gender identity (male).

Factor 7: Comfort and Inclusion in the Healthcare System

Women's comfort and relationship with their primary health care provider influenced their feelings of trust and inclusion in the health care system. Some women expressed doubts in the competence and beneficence of their health care provider, worrying that "the health care system or the doctor was not perceived to be reliably operating to their benefit" ([207] p.726) [172,207,224,239,245,249,251,253,265] These negative perceptions emanated from their experiences with the health care system. As further explored in the section about the importance of relationships with health care providers, the "apparent spillover benefit of a provider's communication style to encompass medical competency was noticeably linked to women's perceptions of trust of both their providers and the medical care system."[251]

Relationships

While some women indicated that a trusting relationship with a health care provider who cares for them as an individual person[165,169,171,186,244,253,268] fostered comfort with screening and health care in general, other women were more comfortable in a setting that was more anonymous, to facilitate sharing personal details and receiving intimate care.[165,227] Many women interpreted reminders and encouragement from health care providers to engage in screening as a show of care and concern,[175,190,200,225,233] although some perceived these invitations as unwanted and invasive.[165] Inclusivity is fostered when women can identify or relate to information offered in patient education and recruitment materials.[219,226,252,273]

Many women expressed a preference to receive care in locations and from care providers who understood their experiences.[171,176,226,251,268,273] For example, in a study of lesbian women, participants "articulated a preference to undertake any future screening at a women's health clinic, especially one that specialized in lesbian health. They perceived these clinics to be a safe environment, free from intimidation and judgement, which would enhance their chances of accessing future screening."[226] Demonstrations of cultural awareness were important facilitators of trust and inclusion in the health care system, especially for newcomers who may come from starkly different health care systems and need to orient themselves to screening programs.[171,183-185,200,222,227,235,268] For example, for immigrant groups from some countries, cancer might not be a familiar concept, and the concept of screening for cancer in absence of symptoms might be quite new and confusing. Pratt and colleagues note that "Some [Somali immigrants] felt that cancer was a US disease, and not one they had been aware of in Africa. As a result, having screening felt very uncomfortable, especially when the purpose of the test wasn't clear." (p. 7)[229] Other immigrant groups may prefer the health systems or traditional knowledge of their place of origin. For example, Chinese immigrant women in several studies expressed a preference for both traditional Chinese medicine, but also for the Chinese health care system: "participants recounted myriad personal experiences to illustrate the superiority of Chinese medicine across a broad range of health topics". (p. 5)[227] This preference included the Chinese system for cervical cancer screening, described by participants as organized through one's employer, hospital-based, compulsory and efficient.[222,227]

Interactions with the health care system

When women encountered culturally insensitive or stigmatizing treatment in the health care system, they were less likely to engage in future screening,[165,171,176,177,186,197,219,253,256,268] such as those who "had attended in the past but following a bad experience, in which she felt her anxiety and unease had been dismissed by the smear-taker, had ceased attendance." (p. 170)[256] Negative interactions with their own health care provider, as previously discussed, were damaging but so too were negative interactions with other care providers, administrators, and health system

bureaucracy. For instance, women mentioned past instances where they or their relatives had been ignored when they had pain or illness as an experience which made them reluctant to engage with the health care system.[216] More frequently, women discussed their experiences of feeling stigmatized in the health care system as a result of their weight, smoking habits, English-speaking ability, HIV status or socio-economic status. This stigmatization frequently resulted in a disengagement from health care services.[165,176,177,207,211,216,224,232,245,266,171,185,186,219,253]

Screening programs

For some women, organized screening programs were also a cause of distrust in the health care system. Some women did not trust the medical benefits of screening, and were not convinced of the necessity of participating in a population-based preventative screening program such as cervical cancer screening.[165,189,193,207,235,245,253] Others expressed a preference for traditional or alternative forms of medicine, and a general skepticism or wariness of the interventional nature of Western biomedicine.[188,195,216,224,225,227] Others may accept the scientific premise of cervical cancer screening and treatment, but maintain their skepticism concerning the organization and efficacy of the medical system and its ability to deliver prompt, reliable, sensitive and specific results, and facilitate access to effective treatment if needed.[190,216,222,237,239,242,244,253] A small number of women expressed opinions that population-based programs were coercive, encroached on private aspects of life, or treated women like objects.[165,245]

Factor 8: Knowledge

This domain describes the role of knowledge and information in incentivizing the screening process. Women identified many aspects of acquiring and using knowledge about screening. In particular, women reported that there was a lack of access to accurate, complete and useful information about cervical cancer screening, which became a disincentive to screening. Misconceptions, misinformation or too much information compounded this experience. Specifically, women reported confusion and a lack of understanding concerning the purpose and need for cervical cancer screening. Women sought logistical information about screening such as locations, testing procedures and results. These women identified educational campaigns as significant motivators to screening, in particular, it enabled them to understand the different aspects of cervical cancer and HPV screening and be more informed and confident in making health care decisions.

Access to information

Knowledge is an essential domain for understanding the incentives and disincentives to screen. In particular, women reported lack of access to information related to cervical cancer screening[175,182-185,188,190,191,204,211,214,225,232,242,247,253,265] such as symptoms, treatment, cell sampling procedure, the necessity of cervical cancer screening and the implications of a positive pap smear or HPV test.[175,182-185,190,191,204,211,225,242] For some, this translated to a lack of awareness of screening, and limited access to sufficient and accurate information for making health care decisions.[182-185,190,225,232,242,243] Furthermore, women reported many misconceptions of screening, which for some, lead to abstaining from screening.[175,183,184,242,253,265]

Women were unaware of cervical cancer screening programs, and their purpose and the target population.[181,193,213,230,245,253,255] While many programs exist to accommodate women without health insurance or those who experience other challenges to screening participation, women in those target groups were mostly unaware of these programs.[172,176,218,230,249,253]

Women identified educational interventions or campaigns as important sources of information and motivation to participate in screening.[172,182-185,196,204,217,219,240] These interventions were perceived as accommodating if they occurred at a convenient location in the local community or clinic.[172,182,185,225,240,253] Across many groups, trust in screening programs and the health care system was facilitated by education programs designed to widely inform women about cervical cancer screening and normalize the screening process.[185,213,235,252,253] The participation of other women in these programs was motivating for some women to partake in screening, and helped them to find a sense of belonging within the healthcare system. Other women mentioned clear, accurate information and reminders from primary care providers,[175,183-186,214,219,222,225,243,253] increased availability of written information,[240] community examples,[225] and information from the media,[180] as incentives to screen. Women recommended designing

educational materials to meet the accessibility needs of women who communicate in different languages and those with low literacy levels.[182-185,217,267,268]

Understanding of purpose of screening

Overall, most women did not understand or were confused about the purpose and need for cervical cancer screening.[172,174,183-185,188,190,199,200,214,222,232,242,243,253] On the one hand, some women believed that screening was either a test for sexually transmitted infections (STIs) or a diagnostic test for cancer.[182,188,199,200,253] On the other hand, certain women correctly identified cervical cancer screening as a test for cancer, in particular, its early detection.[172,199,200,232] These women reported a need for education on the purpose for cervical cancer screening,[172,182,185,258] and information related to the procedure of test.[172,182,185,190,204]

General knowledge about HPV

Concerning information related to HPV, women desired general knowledge about HPV such as its source, transmission, treatment, health and social consequences, risk factors, its relationship with cancer and STIs, the time between contracting HPV and developing cervical cancer, practicalities of screening options (e.g., how long it takes to obtain and interpret test results, what the next steps after diagnosis are), reliability of HPV testing compared to Pap testing, the purpose of screening tests, and relationship between HPV screening and HPV vaccinations.[181,185,200,203,204,210,213,233-235,241,246,247,267,276]

There is great value in enabling women to coherently link these individual pieces of information together. Brown and colleagues[210] differentiated between two groups of women. On the one hand, some women who were knowledgeable about the different aspects of screening were not empowered to maintain their screening behaviours because these aspects were not coherently linked to each other. That is, while they understood the "facts", they did not draw the connections between these pieces of information needed to grasp the implications of the knowledge. On the other hand, women who did understand the implications and were able to make the link, different pieces of screening-related information showed greater motivation towards screening and an orientation towards preventive health.[210]

Screening interval

Women were not always clear on who should engage in cervical cancer screening, who is exempt from it and when it may be stopped. Opinions about these issues reflected women's personal understandings of risk rather than evidence-based guidelines.[187,219,220,239,241,245] Several authors noted a gap between beliefs about optimal screening intervals and personal practice about engaging in screening,[239] reinforcing the overall conclusion that knowledge and beliefs are not the most important determinants of screening.

Regarding the onset, cessation and interval of screening, knowledge gaps about the risk and nature of HPV as a sexually-transmitted infection influenced women's thoughts on when and how often screening should occur. For instance, explanations about optimal cervical cancer screening intervals were often explained in reference to sexual activity and relationship status (i.e. monogamy). Many women objected to screening programs beginning for women in their mid-twenties because it did not coincide with the age of onset of sexual activity in their communities.[172,187,239,243,245,263] Other triggers for screening to begin were the onset of menses or upon reaching a certain age (16 to 20 years).[239,245]

Opinions on optimal intervals ranged from 6 months to five years,[172,187,219,239,241,243,245,250,263] but many women relied on the "heuristic that all screening is good and thus that more screening is better screening" (p.30).[239] Any change in the frequency or duration of screening was met with hesitance about the health implications, and skepticism about whether the change was for financial reasons, or truly in women's best interest.[245]

HPV-Specific Factor 1: Attitudes and Beliefs Concerning HPV

Women expressed various attitudes and beliefs about HPV. In particular, women discussed their perceptions of the association between HPV and cervical cancer. Although most women were unaware or uncertain of the link, those that were aware associated fatalistic beliefs with a HPV diagnosis. Moreover, the majority of women experience and

perceive a stigma associated with the STI dimension of HPV, which significantly influence women's screening practices. To remediate these concerns, women require knowledge about HPV prevention and transmission.

The link between HPV and cancer

For women, understanding the relationship between HPV and cancer was essential for understanding their personal level of risk. Several studies demonstrated that without specific education, few women consider HPV to be a risk factor for cervical cancer.[180,212,224,234,248] Those who were aware of the relationship between HPV and cervical cancer tended to overestimate the causal relationship and equate a diagnosis of HPV with an inevitable diagnosis of cancer and the strong possibility of death from that cancer.[190,228,233,234,236,241,247,248,252,276] Most studies reported that women were uncertain of the link between HPV and cervical cancer,[162,169,172,173,200,203,210,213,228,233-235,239,241,244,246-248,252,259,277] which led women to feel confused about the risk factors, prevention strategies, treatment approaches and the meaning of test results.[172,173,182,210,226,239,245,247,253,259,267,276,277] This is significant because as outlined above, these can be key motivating factors that encourage participation in cervical cancer screening.

HPV as an STI

The majority of studies in this review identified a stigma associated with sexual transmission of HPV.[209,217,224,233,246,276,278] For example, women felt fear and embarrassment from the stigma associated with HPV, especially when disclosing their HPV-positive status to partner, family or community.[210,233,234,276] However, some women were not discouraged by this stigma to pursue screening,[210] and did not attribute shame or moral judgement concerning sexuality to those who engaged in screening.[235] Interestingly, women who were unaware of the sexually transmissible nature of HPV and believed that STIs were an inevitable part of sexual activity, as well as those who internalized the high prevalence of HPV did not feel a stigma associated with a diagnosis of HPV.[233,276,278]

Women in several studies exhibited knowledge gaps about the purpose of HPV testing,[161,164,184,224,231,241,248,253,258] and commonly held the misconception that Pap tests screened for multiple sexually-transmitted infections.[199,224,231,241] Women were concerned about acquiring knowledge about HPV as an STI, mainly related to the risk factors and prevention of HPV transmission.[161,172,173,180,210,212,234,235,246,247,252,258,259,276-278] Notably, some women felt that men were the focal point of HPV transmission, especially those who were not circumcised.[161,180,217,246,252]

HPV-Specific Factor 2: The Screening Process

This section discusses women's concerns associated with different screening modalities. A comparison is made between HPV testing and Pap testing on the basis of the stigma associated with STDs. Following this is a discussion on how women perceive the accuracy of screening in relation to their personal emotions and the logistical challenges of seeking it. Finally, this section ends with a discussion on self-sampling by contrasting two positions. While some women expressed that self-sampling tests could overcome physical and emotional discomfort associated with screening and some logistical barriers, other women were concerned about the accuracy of self-collection technology and were more confident in physician-administered screening.

HPV testing vs. Pap testing

Some women may prefer the Pap test over HPV testing because it avoids the stigma associated with contracting a sexually-transmitted disease. This preference is not applicable to women who do not experience this stigma. Participants in McCaffrey[276] and Brown[210] expressed a difference on the issue of preference between HPV testing and Pap testing. Whereas McCaffrey's[276] participants were reluctant to choose HPV testing because of the stigma of promiscuity and infidelity associated with a STD diagnosis, Brown's[210] participants preferred HPV testing because the results were perceived to be more definitive, and actionable concerning sexual transmission. These understandings may be due to differences in cultural values and beliefs between groups of women, or the specific information provided in the context of the research study.[210]

Women expressed concern about whether undergoing HPV testing would result in undue worry given the lack of treatments and strategies to prevent HPV transmission.[186,233,234] Some women wondered if HPV could be detected through serum screening to avoid the embarrassment and discomfort of the procedure.[172,180] In one study, women strongly preferred traditional cytology tests. HPV testing was described as most acceptable if offered as part of triage for low-grade abnormal cytology results.[233] Women who characterized themselves as proactive about preventative health were more comfortable with HPV testing as a population-based screening modality.[214,233]

Accuracy of screening

The perceived accuracy of screening influenced women's testing preferences, although the interpretation of accuracy may vary depending on their level of understanding and knowledge about HPV and Pap testing. Women expressed concerns about repeat screening visits to the clinic, and perceived that this would be lessened if HPV testing was the primary cervical cancer screening modality.[170,178,180,210,267] Moreover, women in one study recounted their habits of declining repeat pap testing after receiving abnormal cytology results because it prevented the anxiety associated with waiting for test results, and the need for multiple, inconvenient visits to the physician; the option of using the original specimen for adjunctive HPV testing was appealing to these women.[210] However, women who were comfortable with Pap testing were reluctant to abandon a screening method they accepted and perceived to be highly effective.[214,233,245]

Self-sampling

Several studies explored women's perceptions of HPV self-sampling. All compared HPV self-sampling with women's previous experiences, typically health care provider-performed pap smears. In the majority of studies, women expressed mixed feelings. Some preferred the convenience of participating in self-screening due to its privacy and protection from stigma associated with HPV, whereas others preferred the accuracy of a healthcare provider completing a Pap test.[170,173,179,180,182,186,203,204,214,217,234,267,274]

Women who preferred self-sampling over other screening modalities emphasized its ability to overcome the psychological and logistical barriers associated with screening. In particular, self-sampling provided increased convenience, anonymity and comfort, reduced the time, pain and embarrassment associated with screening, obviated the stigma attributed to HPV as STI testing, simplified the testing process, did not require childcare, and assisted in avoiding the challenge of accessing a complicated health care system.[173,179,180,182,186,203,204,217,234,267,274] Self-sampling could ease many of the physical, emotional, and logistical discomforts of a cervical cell smear, and provide a more accessible screening option for under-screened women.[186,204,214]

Some women expressed a need to learn more about HPV testing and self-collection before feeling confident enough to use self-sampling technology.[180,204,217] Other women preferred to delegate sample collection to their health care providers. The choice between HPV self-sampling and HCP-facilitated Pap smear collection was fueled by perceptions of the accuracy and reliability of self-collected samples, fear of not performing the self-collection properly, contamination and infection, limited awareness of self-sampling amongst marginalized women, forgetfulness, the lack of acceptance in the health care system, more comfort with HCP-collected samples, undue worry over mailing self-test devices and collected samples, and pain and discomfort associated with self-collection procedures.[170,173,179,180,182,203,204,214,217,234,267,274] Women in one study remarked that self-sampling would be more accurate and beneficial than Pap tests because it would not be rushed, would enable women to learn about their bodies, empower them to take control of their health, and provide an avenue to familiarize themselves with their genitalia.[267] In relation to cost, women disagreed on the acceptability of costs associated with self-sampling kits, with some American and Canadian women finding the added cost unacceptable[179,203,267] and other Canadians judging it to be acceptable, using the analogy of paying for the convenience of a home pregnancy test.[267]

Another emerging theme was the need for a compromise between self-sampling and clinician-administered testing by providing the option for self-sampling at the doctor's office.[217,267] The second option eased the concerns around accurately completing the test, prompted regular screening, and provided easy access to a health care provider.[217,267] Women also suggested that the self-collection of samples could serve as a reminder for screening deadlines, and encourage collaboration between women and their health care providers in the uptake and maintenance of cervical

cancer screening.[267] Women discussed the necessity of educational materials and detailed instructions for self-sampling kits,[179,203,217,274] which included step-by-step diagrams, more information about sample storage, and the recommended actions after sample collection.[203,274]

In a study of women and clinician views of self-sampling, the clinicians mentioned a concern that women with physical limitations or dexterity challenges may not be able to perform a self-sample; this concern was not mentioned by any of the women participants.[203]

Summary of Results

This review aimed to describe women's experiences with cervical cancer screening and their resultant perspectives on barriers, facilitators and preferences for the same. Given the relatively small qualitative literature on HPV screening, we included factors relevant to other modalities of cervical cancer screening which are transferable or relevant to the policy decision of replacing Pap testing with HPV testing.

Some of the strongest patient preferences will not be affected by a change in screening modality from pap smear to HPV. For example, both require a cervical cell smear, and therefore the potential for embarrassment, pain, and logistical inconvenience of that procedure is unchanged. There is a reasonable body of literature on self-sampling strategies for HPV testing which indicate that it may be widely, but not universally accepted. The opportunity to choose self-sampling may encourage participation from women who would otherwise find the barriers of having a clinician take cervical cells to be a disincentive to screening participation. The importance of the relationship between patient and health care provider will also continue to be important. Sensitive, clear communication from the health care provider that emphasizes the importance of cervical cancer screening is likely to improve participation.

Our review outlines a number of HPV testing specific factors that may impact women's preferences and participation. Few women understood the link between HPV and cervical cancer, which resulted in misunderstandings about the nature and importance of HPV testing. A lack of understanding of this link is also related to the way that women assessed their personal risk of cervical cancer in relation to their sexual activities. As demonstrated by our review, women who judge themselves to be at low risk of cervical cancer are less likely to participate in cervical cancer screening; when HPV is understood as a sexually transmitted disease, many women understand their risk to be related to having multiple male sexual partners. As a result of this misunderstanding, many women may underestimate their personal risk and decline to participate in screening. If Pap cytology is replaced by HPV testing as the primary cervical cancer screening test in Canada, patient education that focuses on the etiology and risk factors of cervical cancer may improve participation rates.

From a clinical perspective, perceptions of the sensitivity and specificity of HPV testing compared to pap smear is notable. Women did not often discuss perceptions of test accuracy, potentially indicating that women may not be aware of the clinical evidence informing the change in cervical cancer screening modalities.[210] However, several studies document women's preferences for a screening modality which was less likely to require return visits for further testing, a strong point in favour of HPV screening and one which speaks to a preference for a more accurate test.[178,180,210,267]

Our review is highly concordant with a recent systematic review and synthesis of primary qualitative research on women's perceptions and experiences of cervical cancer screening. Chorley and colleagues emphasized two primary themes: "should I go for screening" "and screening is a big deal".[279] The first theme, "should I go for screening" describes women's considerations of the relevance and value of cervical cancer screening. Chorley's description of this theme is highly resonant with our factor of how women assess their personal risk, with a discussion of women's understandings of the etiology of cervical cancer balanced against their assessment of their familial and behavioural risk factors. Both our review and Chorley's emphasize women's assessment of their risk of cervical cancer as related to their sexual behaviour, family history, and current health state. Women's perceptions of the value of screening were related to reassurance of health after a negative screening result was received. As in our review, Chorley and colleagues noted some misunderstandings of the purpose of screening, with many women describing cervical cancer screening as a test for infections or a reproductive check-up. Chorley's review also found a minority group of women who were skeptical of organized screening programs and the beneficence of physicians who offered screening.

The second major theme of Chorley's review was "screening is a big deal". In this theme they discuss the physical and emotional consequences of screening. Similar findings across both reviews were the anxiety and distress caused both by the physical procedure and the possibility that cancer may be diagnosed. Embarrassment, shame, and vulnerability are strong themes in both reviews. Both reviews discussed the potential of community stigma related to screening participation and sexual activity, and practical (logistical) barriers to screening participation. Chorley briefly mentions that "for some, screening was considered harmful because it could lead to further investigation or unnecessary treatment" (p.166). They offer no citation for this statement, so it is not possible to trace this back to particular studies included in their review. Under the guidance of clinical experts, we were alert to themes of overdiagnosis in our literature, but found only very minor mentions in one or two papers. Female sample takers and clear, sensitive communication from health care providers with whom they have a trusting relationship are mentioned by both reviews as strong facilitators of screening.

Ethics

What ethical issues are raised by HPV testing for cervical cancer screening and how might they be addressed?

We conducted a systematic review to determine the ethical and legal issues that have been identified as raised by HPV as a primary cervical cancer screening test. Given the paucity of results from a search for research addressing this question directly, we performed to a second search to determine the ethical and legal issues that have been identified in cervical cancer screening, as planned in our protocol.

Purpose and background

Screening for cervical cancer precursors is widely considered a preventive medicine success, cutting disease-specific mortality by 70-80% and the incidence of invasive cancer by over 50%[280,281] according to observational studies. However, cervical cancer screening, like all cancer screening, has no documented effect on overall cancer mortality or on all-cause mortality[282,283] and, like all cancer screening, its benefits come at the cost of the psychological and physical burdens and harms of false positives, false negatives, follow-up diagnostic testing, and overtreatment, in addition to the opportunity costs to individuals and the health system.[284]

Population-wide cancer screening programs increasingly raise controversies.[285-287] Many members of the public and many health professionals believe strongly that early detection saves lives—that screening fulfills the clinical duty of **beneficence**. Recommendations to change the intensity of screening or the population invited to screen in order to limit the harms of screening—in order to fulfill the duty of **non-maleficence**—can be controversial. They may be seen as motivated by cost considerations even when they are based in a clinical analysis of harms and benefits. Issues in evidence and ethics are closely linked in cancer screening.[286]

Screening is undertaken on a public health basis, with a focus in communication on improving uptake rather than fostering **informed choice** and an understanding of the limitations of screening.[288] **Legal risks** to programs and providers have historically arisen when false negatives, inevitable to any screening program, are a surprise to patients.

Equity issues arise in several dimensions. First, failure to prevent a preventable cancer death may be an equity concern when vulnerable populations are unable to access screening or follow-up treatment. Second, changes in test characteristics effect population subgroups differently, supporting a clinical judgment (based on beneficence and non-maleficence) to change the population invited to screen. These changes can raise fairness questions. Third, because screening programs are population wide programs for conditions that lead to a significant disease burden, a favourable QALY may translate into a large budget impact at the implementation level, raising equity questions in priority setting for healthcare more broadly.[289]

Screening for cervical cancer precursors has been more successful in lowering disease specific mortality than other cancer screening practices, and as a result the current screening controversies have not focused on cervical

cancer.[290] Nonetheless, concerns both about de-intensification[291] and about overdetection and overtreatment[292] in screening for cervical cancer precursors do arise.

This ethical review and analysis focuses on **equity**, **non-maleficence**, and **autonomy** issues in relation to a proposed change in screening for cervical cancer precursors, from cytological testing as the primary screening tool to HPV testing for persistent infection with high-risk oncogenic HPV strains as the primary screening tool with cytology used to triage results. It also discusses **liability concerns** for pathologists and cytologists that have arisen from cytology. Its analysis is consistent with Parker et al.'s recent argument that "avoiding harm and supporting autonomy are under-prioritized in cancer screening policies and practices".[287]

There is no existing detailed ethical and legal analysis of these questions in the specific context of HPV as a primary test for cervical cancer screening and in the context of cervical cancer screening in general. Hence this report synthesizes sources identified in the systematic review (see Appendix 22) with novel ethical analysis.

In cytology-based screening (the traditional "pap smear" or the newer liquid-based cytology), a sample of cervical tissue is collected by primary care providers and read by cytologists. Abnormal screen test results lead to diagnostic testing: visual inspection of the cervix for lesions (colposcopy). Abnormalities seen at this stage may be further dis-confirmed or confirmed by biopsy. If confirmed, patients are offered excision (by LEEP or other excision or ablation technique). There are some variations and controversies in practice in management of findings, particularly CIN2.[293] Although management questions are outside the scope of this review, note that the harm-benefit balance of adopting a given screening technology can rest on cytological practice and on clinical decisions. These may be guideline-concordant and/or may be influenced by clinician, technician, and patient factors. Follow-up and treatment that is more intensive than guidelines recommend can make a screening program that would have a favourable harm-benefit tradeoff in an ideal world of good guidelines and good guideline concordance into a program with an unfavourable harm-benefit tradeoff.

The proposed new technology, HPV testing as a primary screen for precancerous cervical lesions, starts by detecting an even earlier precursor: the high-risk oncogenic HPV infection that starts the process of cell mutation that leads in some cases to lesions, which in turn lead in some cases to cancer. Where this precursor HPV infection is found, the cells already collected are screened ("triaged") by cytology for precancerous lesions; patients then enter the pathway described above.

Evidence supports the claim that HPV-based screening ***changes the test characteristics***, making possible the achievement of the **beneficence** goal of cancer prevention, but raising concerns about ***non-maleficence,*** arising from the test's greater sensitivity. Insofar as the test is more sensitive, this sensitivity may increase the false positive rate and the use of diagnostic colposcopy. Furthermore, these false positives would be transformed in their nature and significance by the use of HPV as a primary screening tool (see discussion of nature of screening test).

To avoid the burdens of excessive diagnostic referral for the health system and to fulfill duties of ***non-maleficence*** to patients, changes in screening interval (to as long as 5 years) and screening population (with an age of initiation as late as 30) are typically part of adoption of HPV testing as a primary screen. Such changes to screening programs raise questions about the benefits patients enjoyed under the old screening schedule and population, for example if persons in their 20s are no longer invited to screen for cervical cancer. Clinicians and health policymakers may perceive this tradeoff as appropriate in order to avoid the harms of overtreatment for persons in this age group, but others may perceive it as the withdrawal of a benefit and as a fairness question.

HPV-based screening would also constitute a change in the ***nature*** of the screening test, not just a change in test characteristics. The HPV test is a test for a high-risk oncogenic sexually transmitted infection, for which, in itself, there is limited information about effective prevention of transmission.[294] This raises issues unique to the HPV-based screening for cervical cancer precursors. HPV as a primary screen will change the patient experience of a "false positive". A false positive test for a cervical lesion would remain a true positive for high-risk oncogenic HPV infection. This may have an effect on acceptability of the test, its harm-benefit tradeoff, and ***patient information needs*** both in the process of informed choice and in the interpretation of test results.

The nature of the test also opens up the possibility of self-collected screening samples, which it is hypothesized might address barriers to access and so ***equity*** issues insofar as these arise from poor access to screening. At the same time, the nature of the test as an STI test may be less acceptable to some already under-screened groups.

Search strategy

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist - an evidence-based checklist for the peer review of electronic search strategies.[29]

Ethics related information was identified by searching the following databases: MEDLINE (1946–) via Ovid; PsycINFO (1967–) via Ovid; the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO; and PubMed.

Philosopher's Index and Heine Online were hand-searched for ethical and legal literature not captured in health sciences databases.

The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Two searches were conducted: 1) an initial search on HPV testing and key terms for ethics concepts, completed February 9, 2017; 2) a broader search on cervical cancer screening and key terms for ethics concepts, completed March 3, 2017. Updated searches performed from April 2017 through July 2018 are reflected in this report.

For both searches, no methodological filters were applied to limit retrieval by study design. Results were limited to English- and French-language publications. Retrieval was not limited by date. The detailed strategy is presented in Appendix 1.

Regular alerts were established to update the searches until the completion of the stakeholder feedback period of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the *Grey Matters* checklist,[3] which includes the websites of HTA agencies, Internet search engines, and professional associations.

Selection criteria

4,305 articles were reviewed. Our initial selection criteria were to include articles if they:

- Provided normative analysis of an ethical or legal issue arising in cervical cancer screening *programs or practices*;
- Presented empirical research directly addressing an ethical or legal issue arising in cervical cancer screening *programs or practices*;
- Explicitly identified but did not analyze or investigate empirically an ethical issue arising in cervical cancer screening.

Articles that identify issues that have an ethical or legal dimension where this dimension is not specifically identified and analyzed as such were excluded, as this category would include most of the literature on cervical cancer screening.

In the progress of the review, we found that the third criterion would also generate an enormous and repetitive literature of low quality, and so we abandoned it and retained the first two, required explicit normative analysis or empirical investigation of an ethical or legal issue in cervical cancer screening. We also clarified the inclusion criteria to specify that research ethics pertaining to cervical cancer screening (e.g. the acceptability of the Indian RCT, ethics review of the audit of screening practice in New Zealand) are excluded. We also excluded a small number of articles that had no relevance to on-going or emerging issues, such as articles pertaining to legal issues arising from automated technology for checking cytology screening samples.

We excluded letters but did not exclude editorials and commentaries. We found no relevant abstracts or theses. We excluded analyses and studies that were performed in and relevant only to screening in low and middle income countries.

In the first round (specific to HPV as a primary screening test), 698 papers were identified. Two reviewers reviewed abstracts and titles for inclusion and met to resolve differences.

- 36 papers were retrieved for review;
- 1 paper met inclusion criteria.[295]

In the second round (all cervical cancer screening) and in subsequent iterations of both searches, 3,667 papers were retrieved (4,134, with 467 duplicates). One reviewer reviewed abstracts and titles and consulted with the second reviewer to resolve uncertainties.

- 192 papers were retrieved for review;
- 43 papers met inclusion criteria.

By hand-searching, 13 additional papers were identified and reviewed and 6 additional papers met inclusion criteria.[287,296-300]

Hence, the formal literature review encompasses 50 papers (see Appendix 22). The prisma diagram is also presented in Appendix 22.

Results

Non-maleficence: minimizing the harms of screening and balancing these with benefits

Ethical issues in screening differ from those in clinical medicine. In adopting a screening program, society is encouraging persons who are otherwise healthy in relation to the disease of concern to undergo a clinical intervention that they would not have undergone but for the promotion of screening. This step is not neutral: apart from the financial costs and the opportunity costs involved in all medical interventions, medical testing carries risks of harms. In the context of testing, these are called the "cascade effects of medical technology"[301] or the "screening cascade."[284]

Debate about harms related to cancer screening has grown in the last decade, largely due to controversies in breast and prostate cancer screening.[284,290,302,303] These controversies centre in particular around the concern about overdiagnosis: the identification of cancers that would never have become clinically significant and would never have been diagnosed but for screening program participation. However, public understanding of these concerns is not strong. For example, evidence suggests that only 3% of the public understand the concept of overdiagnosis.[304]

Cervical cancer screening was the pioneer screening program. The process of re-assessing the harms and benefits of screening has followed rather than preceded its implementation.[286] New data are emerging of women's physical and psychological experiences of colposcopy, for example.[305,306] Some of the issues now under scrutiny (harm-benefit tradeoff, role of informed consent, opportunity costs) were raised in the early days of cervical cancer screening.[59,299,307,308]

A basic framework for thinking about harms or burdens and benefits of screening is to consider the orders of magnitude involved: **to prevent cervical cancer deaths in the low single digits, an order of magnitude larger (in the 10s) women undergo the burden and risks of the preventive intervention (colposcopy); another order of magnitude larger (in the 100s) experience a false positive result (formerly a "pure" false positive but with HPV as a primary screening test, a true positive status for high-risk oncogenic HPV); and another order of magnitude larger (~1000) participate in screening in order to achieve that benefit.**

So in cervical cancer screening, of ~1000 women undergoing (biannual) screening for 10 years to prevent cervical cancer, one woman avoids a death from cervical cancer.[309] Over a lifetime, ~3 cancer deaths will be prevented, and all-cancer mortality will not be lowered. Of those 1000 women, according to one recent Finnish registry study (screening 30-65, with 5-year intervals), 340 will have a positive screen test result at some point in their life and be offered more intensive surveillance or confirmatory testing; 54 will have a colposcopy with or without biopsy (with attendance risks of infection and risks to future pregnancies),[292] and 22 will have histologically confirmed findings.[310] (The particular study was not designed to ascertain the precise number of excisions by LEEP or cone biopsy were performed.)

There is no agreed consensus for what would constitute an unacceptable balance of such harms for a life saved.

With these orders of magnitude in mind, Harris et al.'s recent analysis of the harms of cancer screening classifies harms and burdens to individuals as psychosocial, monetary, medical, and opportunity costs.[284] (Costs and opportunity costs here are distinct from the health system's costs and opportunity costs.)

Some harms and burdens arise in the process of sample collection; some occur in the process of follow-up of abnormal test results, including communication of results, waiting for follow-up, and diagnostic testing. The process of surveillance, designed to avoid the harms of overtreatment, can lead to distress.[311]

Harms may also arise from false negatives: false reassurance may lead to abandoning preventive behaviours, or may cause patients and providers to delay acting on clinical symptoms when they do emerge, and may change the experience of diagnosis.

A systematic review specifically looked at psychological outcomes post-colposcopy in the context of cytological screening, including biopsy and/or LEEP: anxiety, depression, distress, cancer and fertility worries or fears, and sexual or psychosexual functioning were investigated in the 16 studies (23 papers) reviewed.[312] All studies found effects, but heterogeneity prevents conclusions about the extent or persistence of these effects.

Abnormal results (including false positives)

The harms and burdens of abnormal test results include psychological distress (anxiety, depression, heightened fear, psychosexual dysfunction) in the interval between notification and diagnostic testing or after the confirmation or disconfirmation of initial test results. This distress may be moderate or substantial; it may be transient or persistent.[313,314] It may be an emotional response with variable behavioural manifestation—it may shape future health-related behaviours.

Cervical cancer screening has minimized harm to perinatal morbidity by offering monitoring instead of immediate treatment where this is feasible in women in their child-bearing years. The possibility of achieving a similar or better level of avoidance of perinatal morbidity with HPV testing may depend on the vaccination coverage of the screened population.[315]

One systematic review indicates patient preference for active follow-up instead of observation by repeat testing, consistent with the general problem for screening that the salience of the risk of a missed cancer leads to over-intensive follow-up and treatment, although reassurance of low risk may affect this preference.[316]

Overdiagnosis

Overdiagnosis is the identification and treatment of abnormalities that, if never detected or treated, would never have advanced to be clinically significant or to cause mortality within the patient's lifetime.[290] For the overdiagnosed individual, the harms of treatment are a net harm rather than a net benefit: they would never have experienced the clinical intervention but for their participation in screening. However, this individual and their clinician never know that they have been overdiagnosed. Overdiagnosis is inferred from population level statistics, when the incidence rate for a condition rises but the eventual mortality never decreases or does not decrease proportionate to the preventive intervention. For this reason it has been called a "utilitarian" concept.[317] It is a topic of substantial research including conceptual clarification[286,318] and ethical[317] and policy debate[285] in relation to cancer screening.

Some argue the term should be reserved for the overdetection and subsequent overtreatment of histologically confirmed cancers and not used for overdetection and overtreatment of cancer precursors,[319] but it has been used in the context of cervical cancer.[320,321] Whatever the harm is called, the basic concept applies: it is possible to cause more screen-related harm, particularly obstetric harms,[322] if a change in technology leads to detecting and treating more precursor conditions. Colposcopy rates are used in cervical cancer prevention research as a surrogate for these screening harms.[323]

Features of HPV-based screening raise concerns about two forms of what might be called "overdiagnosis". Insofar as HPV-based screening is more sensitive, it will detect more precursor lesions that may not progress to cancer. Insofar as it is a test for high-risk oncogenic HPV, it will detect an order of magnitude more cases of HR HPV infection that will not progress to cancer precursor.

One study in the cervical cancer context found that information about overdiagnosis may be interpreted differently for cancer than for other diseases, suggesting that cancer (rather than the harms of overtreatment) remains the most salient risk for patients to avoid.[320]

Minimizing harms; weighing harms

The question of what constitutes an **acceptable balance** of burden and harm with benefits has arisen throughout the history of cervical cancer screening,[289,295,299,324] often in the context of controversy of screening intervals.

Kinney & Huh argue, claiming rhetorically that public opinion is on their side, that no reduction in cancer mortality that is less robust than the reduction provided by an annual cytology screening schedule (a US practice) is ever justified.[295] This view is not shared widely in countries with a robust public health sector: even a three-year interval was argued to be too intensive in the UK,[289] and a study from the Netherlands demonstrates that their less intensive screening schedule achieves similar mortality reduction to that of the US with 1/3 to 1/2 the harms (including in the rate of preterm delivery after excision of precancerous lesion).[325] Massad suggests there are problems in specificity, public acceptability, complexity, and cost (with negative effects on equity) that tell against HPV testing.[326] Austin weighs in twice with the view that cost considerations, not reduction of harms, are the true motivating factor behind widening screening intervals.[327,328]

These six papers identified in the systematic review report and interpret clinical and cost-effectiveness data. Note that they are not included or evaluated in the ethics systematic review for these data; rather, this ethics review captures the range of normative stances on what the harm-benefit trade-off should be. These include the view that *only* cancer mortality reduction is ethically valuable (**beneficence**),[295,327,328] that reduction of harms to screened persons also counts (**non-maleficence**)[325] that opportunity costs matter (broader conception of **beneficence** and **equity**),[289] and that impact on equity matters.[326] Williams, Carter, & Rychetnik argue that the understanding of "harm" and "benefit" differ so widely across different positions in screening that standard utilitarian techniques such as decision analysis and economic analysis will do little to resolve these controversies.[296]

Ethical issues in evidence

These differing views also illustrate the claims of Carter et al.:[286] values influence the interpretation of evidence in cancer screening debates.

Grimes et al. argue that standards of evidence should be higher for preventive interventions than for clinical interventions, given that the health system promotes the uptake of health services by people who are otherwise healthy in relation to the disease of concern.[59]

Ethical issues in screening for HPV evidence also include bias in the evidence base introduced by commercial interests: cost-effectiveness studies in, by underestimating the sensitivity of the standard intervention.[300]

There is no disagreement in principle on a responsibility to minimize harms. Cervical cancer screening programs have historically sometimes responded to evidence of screening-related harms to **minimize** harms, in accordance with the duty of non-maleficence. For example, Canada was an early voice for de-intensification of cervical cancer screening, with a Task Force recommendation in 1976 for screening intervals of 3 years for women after two negative test results.[329] Clinicians and pathologists later collaborated to reclassify cervical intraepithelial neoplasia as a low-grade lesion in order to encourage less aggressive management of the findings of cervical cancer screening.[303] More recently, guidelines have recommended that the age of onset for screening with cytology be delayed to 25 or 30 to avoid identifying the many transient lesions women develop in their 20s.[16]

A key question for HPV as a primary screen for cervical cancer will be the minimization of harms from false positives and overdiagnosis.

Significance of HPV test characteristics

HPV-based screening for cervical lesions would directly and indirectly affect the balance of benefits and harms in cervical cancer screening through its different test characteristics. Ideally a new screening test will be more accurate, so that fewer cases of cancer will be missed. The sensitivity of cytology is low, and so a test with better sensitivity is a desideratum for cervical cancer screening.[38] However, improvements in sensitivity of a test (reductions in false negatives) may worsen specificity (increase false positives). The HPV test's increased sensitivity and lower specificity could lead to increased harms from diagnostic colposcopy and biopsy and could lead to overdiagnosis.[330-332]

The question of whether or not to adopt HPV as a primary screen is likely to depend not just on the evidence and strength of evidence that it reduces the incidence of advanced cervical cancer and cervical cancer mortality, but also on important questions about screening intensiveness and the balance of treatment and surveillance in follow-up and provider compliance with recommendations for follow-up.

Jurisdictions adopting HPV as a primary screen change the screening population and reduce the frequency of screening[321] to fulfill the duty of non-maleficence (reduce harm). Cytology continues to be used for post-HPV-testing triage to increase specificity,[332] screening intervals are lengthened to reduce overdetection for all participants, and the lower end of the age-range for screening is raised to avoid overdiagnosis of transient HPV infections in young persons.[332-334]

Editorials identified in the formal literature review suggest that some clinicians resist delaying onset of testing and lengthening screening intervals, perceiving these as motivated by financial interests rather than by non-maleficence.[295,327,328]

The later onset and reduction in frequency may also be difficult for patients and the public to accept.[335,336] There is currently substantial overuse of current cytology screening where it provides marginal or no benefit in Canada.[337]

Resistance to a later onset of screening is not just a matter of scepticism about the motivation of non-maleficence.

Some women in their 20s derive some benefit from screening with the current technology and are being asked to forego that benefit.[338] The decision to adopt HPV as a primary screen would be a decision to adopt a test that works better for women 30+ and worse for women under 30, such that screening for the latter group would likely be discouraged. The question arises whether cytological screening could continue for women under 30.[339] although evidence for this common practice is weak.[16]

Raising the age of screening initiation could have implications for other health interventions that are commonly delivered at the same time, such as STI testing, as we have already learned with the 2012 guideline changes in Ontario raising the age of initiation to 25.[340] Naimer et al. recommend screening for STIs based on STI risk and not as an add-on to cytology.

Raising the age for beginning screening may be warranted by the overall balance of harms and benefits or by the lack of feasibility of continuing with cytology for under-30s or by the existing weak evidence for benefit for this group. The basis for the decision should be transparent, anticipating a need for public and professional education.

Significance of the nature of the HPV test

The nature of the HPV test has further implications for informed choice and for the harm-benefit trade-off; it may also have implications for equity.

HPV-based screening as an STI test

HPV-based screening involves testing for the HPV infection that is a precursor to the cellular changes sought by cytology. As such, the test will identify many women with this precursor infection for whom the infection would not progress to a lesion. What was previously a false positive test result under screening by cytology will now be both a false positive for cancer precursor lesions and a true-positive for high-risk oncogenic HPV. This constitutes a second kind of overdiagnosis with potential psychosocial effects and burdens for patients.

How significant is this change?

To avoid duplication of the PPE review, we did not include in our systematic review empirical research on patient or provider views of the change to HPV as a primary screening tool. However, the PPE review analyzed results in terms of barriers and facilitators to screening uptake in general, not capturing patient preferences for which screening test should be used. Hendry's recent systematic review[341] of public views on cytology and/or HPV-based screening modalities (including scenarios where either was used for primary screen or triage) indicates that this change raises substantial concerns for some women:

Women had overwhelmingly negative concerns; an HPV diagnosis was daunting, had associated problems of disclosure of a sexually transmitted infection (STI), impacted on relationships and provoked fear of stigmatisation. Nevertheless, many thought HPV testing could be a preferable alternative to repeat cytology [reflecting inclusion in

this meta-analysis of HPV testing as a post-cytology triage]. Knowledge was poor; women struggled to interpret limited information in the context of existing knowledge about STIs and cervical cancer.[341]

The change in nature of technology raises the question of patient information needs, both in respect of informed choice and in respect of mitigating the burden for patients of knowledge of STI status (non-maleficence). It also suggests that communication of test results may need to take into account patient confidentiality concerns which are always important but likely to be heightened around an STI.

How substantial is this concern?

Recall the discussion of orders of magnitude above (pp. orders_of_magnitude). Under cytological testing, 10s of women (out of ~1000) may or may not infer from their positive cytology results that they have a high-risk oncogenic HPV infection. Under HPV as a primary screen, 100s of women (out of ~1000) will be informed that their screening test result was a false positive for cervical cancer and its precursor lesion, leaving them with the diagnosis of a high-risk oncogenic HPV infection.

This is a change in the screening experience for a large proportion of the population. The Hendry et al. review supports the view that, despite their substantial concerns, people are not on balance opposed to HPV as a primary screen if and when the evidence of cancer prevention outcomes and the ability of the test to deliver more reliable negative test results supports it. However, an important limitation of existing research on acceptability of HPV testing (as captured in Hendry's review[341] or published since[210,312,342]) is that it explores the scenario of HPV and cytology co-testing in the US context or HPV testing as triage after cytology elsewhere, rather than HPV testing as a primary screen with cytology as triage, which is the focus of the present report. While screening participants report that HPV testing appropriately managed as triage for primary cytology is acceptable, they did not discuss the population level implications of HPV testing as a primary screening test, where an order of magnitude more women are informed of their high-risk oncogenic HPV status.

Hendry et al.'s systematic review[341] is nonetheless informative for the information needs of those who test positive for high risk oncogenic HPV.

For patients, questions about their own responsibilities to sexual partners could extend beyond ethical and relational concerns to legal concerns, given Canada's criminal law regime around STI disclosure. One paper was identified by hand search analyzing the legal duty to disclose a high-risk oncogenic HPV diagnosis to sexual partners in the US: it argues that tort litigation is unlikely.[343] In Canada, partner disclosure for STI is governed by criminal and not tort law; this is extensively debated in relation to HIV/AIDS[344] but the reach of criminal law is not limited to HIV/AIDS. We were unable to identify a Canadian legal analysis of this question and our research strategy was not designed to produce primary analysis of legal risk.

Educational needs identified in the Hendry et al. review included the distinction between the virus being high-risk and individuals bing high-risk and the relationship between oncogenic HPV and the HPV strains associated with genital warts. Women had concerns about fertility, relationships and their disclosure responsibilities, stigma, and cancer risk. Reassurance was provided by knowledge that the impact of the virus on men was negligible and (perhaps surprisingly) by the fact that condoms do not offer effective prevention, which was felt by some women in these studies to relieve them of the need to disclose to partners and use condoms. The implications of this for women whose partners are not men, or for women in a context where non-disclosure of STIs is criminalized, are not discussed. Women's concerns about cancer were alleviated by the explanation that the path from HPV is long and not all HPV infections produce cancer. Stigmatization is, for some, alleviated by the prevalence of the condition.[341]

Patient education and counselling needs may change. They may look to their primary care providers for advice. Some guidance is available from the Public Health Agency of Canada.[294]

Equity concerns

There is discussion in the PPE report of qualitative evidence that, for some already under-screened groups, the change in the nature of the test could represent a further barrier to screening participation, particularly where extra- and pre-marital sexual relations are stigmatized. Adopting such a test without attention to community acceptability could worsen health inequities. Failing to offer such a test because of perceived unacceptability could have a similar effect.

When faced with variation in values that affects the acceptability of medical treatment, one can consider a number of alternative courses of action. One option is to provide the best medical standard of care to all, regardless of variation in values. This “strict equality” approach appeals to the value of medical beneficence, but insofar as it does not address a barrier to care, it may fail to provide that (ideal) medical benefit. In addition, it may alienate individuals and their communities and expose individuals to risks if test results are communicated with insufficient concern for patient confidentiality.

Another option would be not to adopt the technology or not to offer it to a specific community with concerns. This may respect the values of community, but it may compound health inequities for that community and for the group that would otherwise have benefitted medically within that community, and it may constitute stereotyping where assumptions are made about communities and about individuals identified with communities. Tailoring detection approaches to specific communities may not be feasible in a population wide screening program.

A technological fix (such as self-testing) may be attractive. It may be seen as more simple than inter-cultural dialogue and culture change. Evidence would be key to such a solution. Within a community where some forms of sexual activity are highly stigmatized, the home may be an unsafe setting for an STI test and the physician’s office a safe setting for de-stigmatization.

Working with communities to learn the nature and importance of their values in relation to HPV testing for cancer prevention could enable the identification and amelioration of specific concerns that communities have. This approach would respect values, prevent stereotyping, and be consistent with values of informed choice and patient centered care. It may require attention and time.

Informed choice and cervical cancer screening

Seven issues pertaining to informed choice for screening in general and for cervical cancer screening have been discussed in the medico-legal and ethical literature.

The formal literature review revealed that in the early days of screening, discussions entered around the responsibility of the physician 1) to offer screening[307,345] and 2) to communicate screening test results accurately without overestimating the scope of therapeutic privilege.[346,347]

The voluntariness of screening has been emphasized in two papers criticizing coercive screening practices: 3) in a discussion of the applicability of legal standards of informed consent to examinations undertaken for women incarcerated or involuntarily admitted[348] and 4) in a discussion of the coercive clinical practice of making provision of birth control contingent on accepting screening.[298]

As legal liability and quality control issues in screening programs emerged, the role of informed choice in 5) mitigating harms from false negatives and legal risks became significant[349] and informed the UK GMC guidance on informed choice for screening.

More recently, 6) the quality of information provision for informed choice and 7) goal of information provision in screening has come into question: is the goal to promote uptake or to promote informed choice?[288,297,350-352] Williams et al.[352] and Koltoff et al.[351] both argue for higher standards for information provision for a preventive intervention, given that the impetus behind the intervention lies with the provider and not with the patient. Jepson et al. argue that the policy move towards informed choice in screening opens the question how this choice should be conceptualized in public health and measured. Adequacy of information is essential but so is voluntariness (that options exist and the person has effective freedom to choose among options without unreasonable barriers), the person's own desire for active or passive participation in decision-making, and the person's ability to match their decision to their values. Some problems in informed choice must be addressed with information but others must be addressed by removing barriers to access or by enabling patients to clarify their values and manage specific fears or anxieties that may pertain to the decision-making process.[297] Snadden emphasized the role of primary care physicians practicing preventive care in addressing the emotional dimension of screening.[307]

The question of the relationship between improving uptake and enabling informed choice may be intensified when targets for screening uptake become the basis of pay-for-performance systems implemented by insurers or governments. An alternative, more respectful of patient choice, would be to tie clinician incentives to the informed

choice process rather than to the test procedure.[16,352] (Meanwhile, evidence from Ontario suggests that pay-for-performance incentives have not increased screening uptake.[353])

With the caveat that information provision is not the only dimension of informed choice, [297] the systematic review identified four studies that examine the adequacy of information provision for informed consent by content analysis of screening materials (2), by questionnaire of patients (1), or self-report of providers (1).

Slater found that among colposcopy attendees at a single clinic in the UK, 56% received no information sheet (despite the NHS providing one), 59% were not asked for explicit consent, 42% were not given an explanation of the reasons for the test and its limitations, and 72% were not informed that some false negatives and false positives are unavoidable.[354]

Chew-Graham et al. interviewed GPs and practice nurses in the UK, finding variations in practice and beliefs between the two groups. Practice nurses followed a routine in information provision, while physicians varied information provision with clinical context and time available.[350] Practice nurses were persistent in promoting uptake due to their commitment to the benefits of the program; GPs were more skeptical of value of screening and more inclined to accept patients' declining screening. GPs, however, did act to meet screening targets where incentives were involved. Most interviewees of both professions thought informed choice was implied by attendance and did not discuss the purpose and limitations of the test in any detail with patients.[350]

Williams et al. reviewed information about screening from screening programs in Australia and found that benefits were overestimated and harms and limitations understated. Narrative literature review and normative analysis informed their discussion of GPs feeling pressured by targets and limited time to provide inadequate consent.[352]

Kolthoff et al. reviewed screening invitations from 10 different countries and found that a median of 4 of 17 possible information items were provided, that positive information was included more often than negative, statistics when presented were given in terms favourable to screening (e.g. relative rather than absolute risk reduction), that false positives and overdiagnosis were rarely described, and that some screening invitations directly appealed to women to take up screening rather than encouraging them to make their own choices.[351]

The role of informed choice in public health interventions is controversial. Some argue that individual autonomy is overvalued in clinical bioethics and inappropriate in public health.[355] Others argue that individual autonomy remains important in public health ethics, but that public health ethics must attend closely to structural determinants of the opportunity to exercise autonomy[356] and that screening involves both clinical and public health perspectives.[296]

The individual nature of benefit from screening (in contrast to infectious disease measures), the failure of screening to demonstrate cost savings to the system,[357] and the small absolute risk reduction of the targeted cancer that it offers individuals all speak against the claim that in this case the public interest overrides the individual interest in disclosure of material information relevant to their choice. A survey in Australia found the majority of women wanted to be informed and involved in choices around cervical cancer screening.[336]

Furthermore, information provision is not only an expression of respect for persons' autonomy (in that it enables them to make an appropriate choice to take part in screening or not); it is also an expression of respect for them as persons. People may want information even when they don't want to take an active role in decision-making about medical interventions.[336] Providing information enables people to anticipate, prepare, and plan for contingencies. For example, studies of information needs and of the colposcopy experience have found that women undergoing colposcopy may benefit from preparatory information to manage the sensory experience.[305,358,359] Furthermore, patients (and clinicians) who understand the limitations of screening programs and the inevitability of false negatives are better able to respond promptly to clinical symptoms that emerge between screens.[349] As such, providing this information also fulfills duties of non-maleficence. In addition to preventing patient harm, awareness of program limitations can mitigate legal risks (as we shall see in the next section). These considerations led to an emphasis on informed choice in the UK significant.[349]

The above is an overview of the background to why informed choice is increasingly considered important in cancer screening.[360] This trend is independent of test technology.

However, the different nature of the HPV test as a primary screen for cervical cancer creates new considerations for information needs, both in advance of screening (to promote informed choice and meet duties of non-maleficence in relation to false negatives) and in in the communication of test results, including results that are positive for high-risk

oncogenic HPV but negative for cytology (see above). Providers should be prepared to fulfill their duties of non-maleficence and respect for persons by providing them with information necessary and in such a way as to mitigate the burden of this new category of results.

Massad proposes mitigating the concern with HPV as an STI by having "patients accept HPV testing as a cancer risk marker rather than a test for sexually transmitted disease."[326] Given that the HPV test *is* a test for an STI, it would be difficult to operationalize this proposal within existing legal and ethical standards for informed consent and transparency in screening program policy. Patients will learn the nature of the test from their own research, and legal and ethical standards for the content of informed consent include both the purpose and the *nature* of an intervention.

Legal risks

There is no published legal scholarship on HPV-based screening for cervical cancer. Literature concerning cytology-based cervical cancer screening focusses on malpractice claims resulting from false negative test results, with one article (found by hand-search) on coercive testing practices (included in above discussion of informed choice).

The organization of a screening program is a large social undertaking involving extensive lab services and coordination between these services and primary, secondary, and tertiary care. Coordination and quality issues may arise at any step. In addition, cytology has a low sensitivity; its effectiveness depends on repeat screening. As such, it is possible that the reassurance of a negative test result is in fact a false assurance or that it misleads people to disregard the possibility of developing cancer after a true negative test result. Neither possibility can be ruled out by cancer screening, however high the quality and coordination of testing and its communication.

Through litigation in the US, courts have been asked to weigh in on whether a given case of cancer was the result of negligent errors in quality and communication, or of the inevitable false negatives that will characterize any screening program no matter how high its quality. The poor inter-rater reliability of cytology (a visual inspection test) has contributed to variability in expert witness reports about whether a given negative test should have been read as positive. In the UK, these issues played out in a public inquiry, with implications for how the UK came to emphasize informed choice in screening. There is no literature addressing these issues in the Canadian context; this literature review was not designed to research primary legal sources (legislation and court cases) or provide legal analysis and/or advice based on such primary sources.

Primary care provider negligence has included improper sampling/scraping;[361] improper identification; incomplete history;[362] and incomplete follow-up[363] and failures in legal requirements for disclosure of information.[345,346,364,365] In response, recommendations have been made for risk management strategies for defending against malpractice cases[363] and malpractice insurance coverage.[366]

Lab negligence in the cytology era, by contrast, has been described as litigation "crisis".[364,367-369] With the implementation of cervical cancer screening in the US, pathologists and cytologists went from being among the specialties with the lowest medico-legal costs to among the highest. Laboratory negligence alleged and found in court cases has included improper smear processing; inexperience, overwork or lack of training and supervision of cytotechnologists; erroneous interpretation of results; erroneous comments and recommendations; absence of quality assurance programs; and failure by attending physicians to follow up on recommendations.[370]

In some cases, negligence suits may have resulted from true failures in quality control in the lab setting. However, some suits have arisen from the public's and the courts' lack of understanding of the limits of screening tests. Medico-legal commentators have described this as an "implied linkage between 'error' and negligence" (e.g.[371]) and as mistaking a screening test for a diagnostic test.[326,372,373] Solutions include educating clinicians, patients, and the public of the fallibility of the cytological testing and the unreasonableness of a zero error standard that courts are perceived to have adopted.[369,374-378] These discussions have fed into common arguments against the current legal framework for malpractice; some have called for medical liability reform that could include no-fault compensation (national) insurance pools and limiting compensation amounts in relevant tort cases.[349,365,372,379] Many medico-legal commentators argued that malpractice claims that arose in the early days of cervical cancer screening could threaten the cost-effectiveness of the test and the viability of the relevant screening programs.[364,374,376,379]

Commonly proposed solutions to this crisis have included developing professional practice standards,[365,380] standards for legal review of an alleged breach in duty of care (e.g. expert witnesses, expert panels and other processes to

ensure unbiased, objective review[348,380-382]) and maintaining a database to give defence attorneys access to appropriate expertise in screening practices.[383] Other solutions include risk management practices and guidelines for quality assurance and quality control in practice settings.[366,367,369,375,378,379,384]

Rosenthal argued that the pathology profession needs to "practice risk reduction in addition to crisis control," and focus on the well-being of patients. Tort law is as an important avenue for protecting patients' rights.[349,368,372]

In the end, as Freckelton and others have stated, the cytology liability crisis did not materialize and the notion that the courts had adopted a zero-error standard was exaggerated.[370,375,379]

HPV-based screening is perceived to have substantially better inter-rater reliability and superior sensitivity. Perhaps both factors would provide medico-legal protection for labs and their staff and this would motivate enthusiasm for the switch to HPV-based screening. However, the scenarios for HPV-based screening still include cytology triage, such that subjective visual inspection test remains a step in screening. The number of these cytological screens will be substantially reduced. It does not necessarily follow, however, that the legal risk for those who read cytological samples will be reduced. With fewer cytologists and fewer labs, each remaining lab and cytologist may experience the same legal exposure as in the cytology era.

Equity

Concerns about equity in cervical cancer screening access and outcomes are substantial and long-standing. (See, for example, Walton's argument in the 1970s that the Canadian programs should lengthen screening interval and using the resources saved to reach hard-to-reach groups.[329])

Two studies addressing informed choice commented on equity; one empirical ethics study analyzed equity in cervical cancer screening specifically. In interviews with screening program experts in Australia conducted by Williams et al.,[385] informants made use of different understandings of equity in discussing disparities in cervical cancer screening. Three main views emerged: a utilitarian view that valued high uptake and expected making mainstream services available to communities to translate into access; a view that barriers to access to mainstream services had to be addressed; and a view that services had to be tailored to communities. A single participant argued that disparities may be less concerning because underscreened persons may have other health priorities that are greater priorities for them and that should also be prioritized by the health system. According to this view, equity in cancer screening will come when equity in other conditions causing greater burdens for the target population is achieved.[385]

Williams et al. (in a separate study)[386] raise equity concerns around information not tailored to highest risk groups, e.g. Aboriginal and Torres Island Straight women and equity concerns relating to non-maleficence, i.e. the specific exposure of younger women to harms of overtreatment.[386]

Jepson et al. raise questions about access as the precondition for informed choice, arguing that choice implies the ability to choose an option that matches the person's preferences and values and the ability to act on choices without barriers,[297] highlighting the close connection between equity and autonomy.

The PPE review captures a substantial body of qualitative research into (hence patient and provider perception) of barriers to access to screening; much of this research is conducted with groups that also experience inequities in access to treatment. This rich and informative literature should be supplemented by research into systems features that limit access both to prevention and to treatment, such as quality and availability of care in immigrant communities and access to insurance, that may not emerge through qualitative research of patient experience (e.g. patients may not know that their primary care is substandard).[387-390]

A common proposal in relation to HPV as a primary screen is that it enables self-collection of samples, and this may address access issues for underscreened persons,[391] including (for example) rural and remote, Indigenous, and transgender patients. There is evidence that self-collection as an *add-on* to provider collection, specifically designed to reach persons who are not currently attending screening, may increase screening in these groups. Rozemeijer et al. discuss the trade-off point at which women who would have screened anyway switch to self-collection for reasons of convenience (rather than women who would not have screened anyway adopting self-collection for reasons of access) and that lowers screening program performance because of different test characteristics.[392] Colorectal

cancer screening is done on a self-sampling basis in Canada, with kits provided by mail-out. It has much lower uptake than cervical cancer screening.[393]

Self-sampling could raise questions of coverage in the Canadian environment: either kits would be provided and mailed out (as in current colorectal cancer screening programs) or would be made available for purchase, in which case the cost of these kits could have a negative impact on equity.

Program organization

Many of the issues discussed above pertain not just to patients and their healthcare providers or the public, but to the organization and delivery of cervical cancer screening.

It is widely speculated that a later start to screening and a widened screening interval may reduce screening uptake.[321] Cervical cancer screening practices in Canada are diverse across jurisdictions, incorporating elements of central organization and of opportunistic screening.[386] If HPV as a primary test is adopted with a later initiation of screening and increased intervals, it may be appropriate to revisit the organization of screening, implementing registries, invitations, and reminders. These systems involve navigating privacy and confidentiality concerns between the public health and primary care sectors, as experience in New Zealand has demonstrated.[394]

At the same time, the question of how program targets relate to the value of informed choice and to clinical guidelines must be addressed. In Canada, program targets are not guided by an informed choice paradigm and they are divorced from guidelines: the CPAC's target for uptake is 80% of invitees 21 to 69,[393] despite weak evidence for screening ages 21-29[16] and Periodic Health Exam guidance from the College of Family Physicians for beginning screening at 25.[395] As discussed above, these targets can lead to producing invitation materials and incentivizing physician for screening uptake in ways that are detrimental to informed choice and even to adherence to clinical guidelines that are based on achieving a reasonable balance of harms and benefits.

Parker et al. identify these issues—the balance of harms and benefits in screening and the balance of promoting uptake and promoting informed consent—as having implications for the governance of screening programs: they recommend that committees governing screening programs should justify their recommendations in terms and both values and evidence, distinguishing the interests of individual members, the program, and the public and making their reasoning around these transparent.[287]

The so-called "liability crisis" focused attention on the quality and coordination of care between lab services and primary care. The addition of HPV testing brings a new lab specialty into the process and similar quality and coordination issues will have to be addressed. (See Schneider's contribution to Petry, Wörmann, & Schneider,[333] anticipating that German gynecologists [the relevant primary care providers in that country] may be reluctant to communicate with multiple labs in an era where HPV and cytology are both parts of screening.)

Summary of Results

Screening involves **balancing the benefits of disease detection (beneficence) with harms and burdens of screening attendance, false positives, and overdiagnosis (non-maleficence).** The clinical review provides evidence for whether a shift to HPV based screening for cervical cancer precursors would reduce cervical cancer mortality or failing that long-term measure, reduce the incidence of invasive cancer.

The ethics review provides context and content for understanding the human experience and significance of the nature and test characteristics and the magnitude of the changes that would be implied by adopting HPV-based screening.

The implications of a false positive test result are substantially different for a large proportion of the population under the scenario of HPV as a primary screening test: a third of women would at some point in their lives receive an diagnosis of a high-risk oncogenic HPV infection.

There is no common agreement on the line between an acceptable and an unacceptable balance of harms and benefits in screening. Some advocate that the only acceptable change in this balance would be to prevent more

disease than we currently do; others argue that the harms and burdens attendant on current levels of prevention are excessive and that some reduction in disease prevention would be acceptable if we could substantially reduce the harms of screening.

In addition to test characteristics (sensitivity and specificity; positive and negative predictive value), the change to HPV testing as a primary screen changes the nature of the test and introduces new burdens for a substantial portion of the population.

Furthermore, the balance of harms and benefits depends on patients and providers following guidelines intended to de-intensify screening (start later and extend intervals) and manage the intensity of treatment.

In this context, **patient information needs**—both for **informed choice** and for mitigating the burden of knowledge of high-risk oncogenic HPV status—and the time and resources for primary care to manage these needs would change.

The perceived greater objectivity of genetic testing over cytological inspection may create a perception of greater **medico-legal** comfort with the test. However, the same exposure to risk but for fewer cytologists may be the result, while communication among a larger number of technicians may create new medico-legal risks.

There appears to be mixed, and largely speculative, views about the effects on **equity** of HPV as a primary screen. Some underscreened groups may be especially concerned about the HPV-based screening as an STI test, and this may lower uptake; some groups may benefit from self-sampling as an outreach strategy targeted to those who experience barriers to clinical sampling.

Implementation Issues

This section addressed the following Research Question:

What are the main challenges, considerations, and enablers to implementing HPV testing for primary cervical cancer screening in Canada?

Methods

To understand the issues associated with implementing HPV testing for primary cervical cancer screening, a literature search was conducted and stakeholders were consulted by phone and email. The methods were sequentially designed such that the results of the literature search were used to inform the need and scope of the stakeholder consultations. The planned output was a narrative review.

Literature Search Methods

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist - an evidence-based checklist for the peer review of electronic search strategies.[29]

Information related to implementation issues was identified by searching the following databases: MEDLINE (1946–) via Ovid; Embase (1974–) via Ovid; CINAHL (1981–) via EBSCO; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were cervical cancer screening, and Canada, and key terms for implementation issues (e.g., barrier*, facilitat*, adopt*, socio*, education*, decision aid*, staffing, workflow*, cytologist*, self-sampl*, physician*). A Canada filter was applied. No other methodological filters were applied to limit retrieval by study design. Retrieval was limited to documents published since January 1, 2002. Results were limited to English- and French-language publications. The detailed strategy is available on request.

The search was conducted on March 14, 2017. Regular alerts were established to update the searches until the close of stakeholder feedback. Regular search updates were performed on databases that do not provide alert services. Articles identified in the alerts and meeting the selection criteria of the review were incorporated into the analysis if they were identified prior to the completion of the stakeholder feedback period of the final report.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (www.cadth.ca/grey-matters),[3] which includes the websites of HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with clinical experts. An iterative strategy was used, such that, as the reviewers began to understand the important issues, more targeted searches could take place. For example, a Google and PubMed search was performed to find additional information on cytotechnologist training.

Screening and Selecting Articles for Inclusion

Articles were screened and selected for inclusion by two reviewers. Articles were selected if they reported implementation issues such as factors that influence uptake, barriers faced by clinicians, patients, and laboratory personnel, facilitators that can aid in implementation, and descriptions of previously implemented cervical cancer screening programs. Consensus between reviewers was required for the selection of the first 50 articles into this review, to ensure that common criteria were being used. After that point, each reviewer selected articles individually.

Data Extraction

Data was extracted into a table by one reviewer in a Microsoft Word document. Details and data extracted focused on the context associated with implementation (i.e., setting, geographical, epidemiological, socioeconomic, sociocultural, political, legal, and ethical) and four domains of implementation (i.e., provider, organization and structure, funding, and policy).

Consultations

To augment the data collected from the literature review, consultations were conducted with targeted experts and stakeholders identified by CADTH's knowledge mobilization and implementation support team. Individuals were approached via email and invited to participate in a phone interview or to provide written responses to questions by email, at their convenience. Consultations took place with stakeholders and experts from the Canadian laboratory, pathology, and cancer specialty sectors. Consultations also took place with representatives from countries that are in the process of implementing HPV primary screening, namely England and the Netherlands. To guide the consultations, semi-structured interview guides were developed with questions and prompts to facilitate the conversation. At a high level, questions asked how a change to HPV testing for primary screening of cervical cancer would affect laboratory operations, patients, and health care providers, and what barriers and facilitators exist to adopting the new technology and processes. The interviews were conducted by one or two researchers, as resources and timing permitted. Notes were taken during the interviews to capture information relevant to the research question. If needed, follow-up questions or clarifications were conducted by email. Each consultant was provided with a chance to review their statements before inclusion in the final report, and written permission to include his or her name was obtained.

Data Analysis and Synthesis

Each article identified through the literature search, or information provided through the consultations, was analyzed using the methods of content analysis. Data were sorted into relevant categories using the domains identified within the Context and Implementation of Complex Interventions (CICI) framework from the INTEGRATE-HTA[396] guidance as a framework. Specifically, the CICI framework[396] defines eight domains of context (i.e., setting, geographical, epidemiological, socioeconomic, sociocultural, political, legal, and ethical) and four domains of implementation (i.e., provider, organization and structure, funding, and policy), each contributing differently to how an intervention is implemented, who can access it, and ultimately how effective it will be. The 12 domains of context and implementation of the CICI[396] framework comprised a coding template that was initially applied to all data.

Once all data were read and coded, text coded within each domain was summarized by one reviewer. Because of the complexity of the topic, the final summary of content was organized by topic-specific categories rather than by CICI[396] domains. The categories were program administration and change management; effects on laboratory structure and workflow; effects on screening participation rates; health care provider barriers and facilitators; and geographical, socioeconomic, and sociocultural issues.

When analyzing data, the items coded and summaries written were those most relevant at the health services delivery level. The aim is to provide information to policy-makers regarding the operational requirements and supports

that should be in place or could be used to help facilitate the effective implementation of the recommendations of the expert committee.

Results

The literature search yielded 678 citations, of which we determined 78 articles were eligible to address our research question. Most of the literature was from Canada, supplemented by a few international papers that were highly cited or particularly relevant to a specific topic. The literature included studies published in academic journals as well as organizational reports, guidelines, and news articles identified through the grey literature search.

Many experts (representing 21 stakeholder organizations) were invited to take part in consultations, and approximately half of them agreed. Consultations were performed with three clinical experts, three members of the Pan-Canadian Cervical Screening Network, seven representatives from the laboratory sector, two representatives from the policy sector, and two international experts. Many of these experts have cross-sector involvements and academic/teaching positions, so they were able to provide broad perspectives.

The key issue that emerged can be summarized as follows:

- A switch to HPV testing would be a large operational and culture shift for clinicians, patients, and laboratories. Good planning, funding, and coordination would be needed to make sure implementation runs smoothly.
    - Acceptance of the new type of screening test (i.e. STI screening) by patients and clinicians has the potential to be a challenge — preventing a drop in screening participation rates could be important.
    - A major change to laboratory configuration, workflow, and human resourcing would be required; this change could present a challenge.
    - There are several facilitators that may help with overcoming these barriers; for example: education, step-wise rollout, organized screening programs, good information technology (IT) systems, or self-sampling.

These issues are discussed in more detail in the following sections.

Program Administration and Change Management

If a decision is made to implement HPV testing for primary cervical cancer screening in Canadian jurisdictions, it will affect the administration of screening services and processes. This review identified both challenges and opportunities related to implementation.

A change to the cervical cancer screening strategy would likely require substantial funding, administrative and management resources, planning, and strategic implementation. The change has the potential to take considerable time and may be challenging to implement consistently throughout the country, where each province and territory administers and delivers its own health care services.

Currently, there is variation in structures and practices across the jurisdictions. For example, some provinces have organized cervical screening programs, while others (Quebec and the Territories) rely on opportunistic screening, which is screening that is initiated by the patient or their primary care provider. Screening intervals, start and end ages, and algorithms (management pathways for patients) differ across jurisdictions. There is a mix of public and private labs that process cervical specimens, and approximately half the provinces and territories are still using conventional Pap cytology instead of liquid-based cytology (see Table 31).[23] Because liquid-based cytology enables one cervical sample to be used for both the HPV test and a reflex (triage) cytology test without calling the patient back, a change to HPV-based screening with cytology triage may require the adoption of liquid-based cytology across all jurisdictions.[397,398] This change could be costly[93] and would add an extra step to the implementation process.

There is also the issue of change management to consider. A switch to HPV testing may be disruptive for patients (i.e. screening frequency may change and the number of positive tests may change), clinicians, and laboratory staff,

who are all accustomed to cytology testing. A change in culture and behavior would be required, with clear protocols and education. There are concerns about whether healthcare providers and the public would adhere to the new processes.[399-401]

"Switching to HPV testing for primary screening will be a huge culture shift for labs, clinicians, and other stakeholders. This should be a well thought-out process." (Lori Clarke, Laboratory Medicine Consultant, Department of Health, Government of New Brunswick: personal communication, 2017 December 19).

Table 31: Provincial and territorial differences in cytology detection methods in use in the cervical cancer screening[23]

Jurisdiction	Cytology Detection Methods
Nunavut*	Liquid Based Cytology
Northwest Territories*	Liquid Based Cytology
Yukon	NR
British Columbia	Conventional Cytology
Alberta	Liquid Based Cytology
Saskatchewan	Conventional Cytology
Manitoba	Liquid Based Cytology
Ontario	Liquid Based Cytology
Quebec	Conventional Cytology and Liquid Based Cytology
New Brunswick	Conventional Cytology and Liquid Based Cytology
Nova Scotia	Conventional Cytology and one district using Liquid Based Cytology testing only for Pap tests performed in colposcopy.
Prince Edward Island	Conventional Cytology
Newfoundland and Labrador	Liquid Based Cytology

*Organized screening program not available. Responses refer to opportunistic cervical cancer screening.
NR = Not reported
Table reproduced with permission from CPAC.[23]

If a decision is made to adopt HPV-based screening, resources would be required to plan and implement changes to clinical practices and to laboratory structures and operations — ensuring that all components are linked and communicating well with each other. The effects on the individual components of the system are discussed in more detail in the following sections, but they must also be thought of as an integrated system, with most or all of the components possibly needing to be in place before HPV-based cervical cancer screening could be implemented.

Organized cervical cancer screening programs

In many countries, cervical cancer screening began as opportunistic screening — that is, screening that is initiated by a healthcare professional or patient. This opportunistic screening, as well as local organized screening programs, over time matured into larger, sometimes national, programs.[402] In Canada, there are currently several organized provincial cervical cancer screening programs in place. These organized screening programs have the potential to facilitate the implementation of HPV-based screening because they could play a lead role in centralized data collection and follow-up strategies to improve or manage screening participation.[403] The Canadian Partnership Against Cancer states that organized screening programs are the most important system-level strategy used to date for ensuring optimal screening participation.[1]

Of note, Canada's three territories and the province of Quebec do not have organized cervical cancer screening programs,[23,404] therefore, different implementation strategies may be required there. Some authors have suggested a greater role for HPV self-sampling;[404] while, others feel that for HPV testing for primary cervical cancer screening to be successful, organized screening programs would need to be established everywhere.

"Organized screening programs can help integrate all the data, link test results to patient recalls, and ensure standardized follow-up." (Dr. Manon Auger, Director, Cytopathology Laboratory, McGill University Health Centre; and Professor, Department of Pathology, McGill University: personal communication, 2017 November 24).

Planning, investment, and program administration

The Pan American Health Organization (PAHO) and World Health Organization (WHO) recommend that a decision to introduce HPV testing into a cervical cancer screening program should be taken at the highest level of the public health authority and as part of a public health strategy to improve the screening program. Engaging the main stakeholders (such as provincial health ministries, cervical cancer screening programs, obstetric groups, and cancer organizations) from the beginning of the planning process and building consensus among them are thought to be key components to ensure effective introduction of this new technology.[405]

"It is important to have a unified message. When there are many people and organizations giving different advice about cervical cancer screening, it negates the benefits. We need a consensus statement, one main guideline, and we need to have everyone onboard." (Dr. Marc Steben, Medical advisor, STI unit, Institute national de santé publique du Québec, Montreal, Quebec: personal communication, 2017 December)

In general, when a new screening program is being established, it has been suggested that adequate investment in staff and equipment (for carrying out the screening test, diagnosis of cervical cancer, treatment, and administration of the screening program) is available before the new program begins.[401,406]

Step-wise approach

International health organizations have recommended that a step-wise approach, starting with small pilot sites, could facilitate implementation.[405,406] Different components of the screening program set-up could be tested within the local healthcare system before being introduced into a large population. Based on lessons learned at the pilot sites, a program can be expanded to other geographical areas as resources permit.[398,405,406]

Performance monitoring and evaluation

Performance monitoring and evaluation of a new screening program are believed to be important. It has been noted that the identification of performance indicators included within the development of screening policy and management guidelines may be helpful.[399,405] In the UK, to ensure accountability of the HPV primary screening program, Cancer Research UK has suggested that a clear implementation plan with timelines should be made publically available and that updates about the status of implementation (e.g., data on program reach and uptake) should be published regularly.[400]

A panel of experts on HPV testing convened by the Canadian Partnership Against Cancer has stated that ongoing evaluation of screening, follow-up, and outcomes is critical.[2] The Pan-Canadian Cervical Cancer Screening Network recommends developing multidisciplinary committees to monitor and evaluate quality and utilization of HPV-based screening.[401]

In the laboratory sector, quality assurance of tests could facilitate implementation because it will help ensure that the new tests are working as expected.[406-408] "Quality assurance is particularly important when new technologies and processes are being implemented. For HPV-based screening, quality assurance needs to be done at all levels: molecular, cytology, and histology." (Dr. Manon Auger: personal communication, 2017 November).

Participation in external quality assessment (proficiency testing and confirmatory testing) may enable laboratories to verify that they have successfully implemented HPV detection and typing assays.[18] Inter-laboratory performance might be evaluated by sending proficiency panels to the laboratories.[408] Planning quality assurance methods in advance may help facilitate implementation by ensuring that newly implemented tests or testing pathways (i.e., HPV tests and cytology triage tests) are producing the expected results.[2,406-408]

Overdiagnosis and Overdetection

A concern with HPV testing is its lower specificity and potential to result in increased numbers of positive tests (when compared with cytology testing), overdiagnosis, and overtreatment. This could cause psychological and emotional distress (as indicated in the Patient Perspectives review), inconvenience, and unwarranted colposcopies and cervical treatments (with potential for iatrogenic illnesses).[409] The overdetection of HPV that would never lead to cancer could also result in increased costs and resource use from the increased patient recalls, subsequent follow-up procedures, and unnecessary treatments.[409,410] It has been argued that screening must balance the potential benefits of finding and treating early disease against the harms caused by overdiagnosis and treatment of early abnormalities that would not progress or that would regress if never found.[78,409]

Loss of specificity

The loss of specificity that accompanies the increased sensitivity of HPV testing is an identified barrier to successful implementation.[19,403] This barrier has delayed the acceptance of HPV-based screening in Canada.[411] Lower specificity and a corresponding increase in sensitivity, may lead to a potential increase in referral for colposcopy and any unwanted effects of subsequent unnecessary treatments are major factors when considering primary HPV-based screening.[398,411]

The authors of a recent study found that specificity can also be adversely affected in the context of a triage system where cytotechnicians are influenced by knowing the HPV status of a sample. The heightened attention of the cytotechnicians appeared to have led to more false-positive results.[407] The study authors speculated whether the loss in specificity could be counteracted by a well-organized quality assurance program. Third-party review by a cytopathologist was also thought to potentially improve accuracy.[407]

Optimal screening age and interval

The use of HPV testing instead of cytology testing for cervical cancer screening has the potential to identify transient HPV infections, which are particularly prevalent in those younger than 25, and that are likely to resolve on their own and not lead to cancer diagnoses or the need for further interventions.[78,409,412] Implementing a later start age for screening (e.g., 25 to 30 years old) and extending the screening interval (e.g., to every 4 or 5 years) is expected to mitigate the problem of over-screening and overdiagnosis.[18,409,413]

Triage strategies

It has been suggested that triage following the primary HPV test has the potential to alleviate problems associated with low specificity and overdiagnosis and thus facilitate the implementation of an HPV-based screening program.[2,18,19,122,414] The most widely studied triage test in this situation is cytology.[414] Other triage tests are being studied, including genotyping for HPV16 and other high-risk HPV types, as well as identifying biomarkers of disease progression such as expression of $p16^{INK4a}$ and Ki-67, or DNA methylation.[414] Note that these other triage tests are outside the scope of this CADTH Optimal Use project.

The authors of a paper on the Canadian Cervical Cancer Screening Trial state that appropriate triage of high-risk HPV positive test results to colposcopy is necessary to identify those at immediate risk and to prevent undue harm to those at low to moderate risk.[122] The authors concluded that appropriately balancing the benefits of HPV-based primary screening with informed management recommendations is important to the success of this screening strategy and its widening utilization.[122]

Funding models

Aligning screening recommendations with funding models could reduce over-screening because health-care providers will only be paid for sample collection at appropriate intervals and for eligible patients.[78,401,415] A well-organized and monitored program, in which primary HPV tests taken outside the program are not reimbursed by the government, could help minimize the number of tests taken outside the program, thereby limited the level of over-screening.[78]

Registry system

The benefits of a registry are discussed throughout this implementation section, and it is also thought to be a facilitator to preventing over-screening and overdiagnosis.

The PAHO/WHO states that the information system can be based in each health facility or centralized in an office that serves several health facilities.[405] During the consultations for this report, some stakeholders expressed that a national registry with supporting software would be needed. They advocate that a single registry is needed to communicate results to the screening participant, all her health care providers, and laboratory staff, and to keep track of screening history and eligibility intervals. This kind of system would prevent someone from going to a different clinician to obtain screening if denied by her primary care provider (i.e., because she is not due for a screening appointment), and therefore it could help prevent overdiagnosis and overtreatment.

"A national registry would be ideal because people move a lot. Having a national registry or registries that are well connected would prevent unnecessary testing" (Dr. Marc Steben: personal communication, 2017 December).

Encouraging stewardship

Another facilitator that could mitigate overdiagnosis is to encourage stewardship of appropriate screening practices. For example, Ontario's reimbursement guidelines encourage physicians to consider whether it is professionally appropriate to provide screening services in excess of the limit and to have discussions with patients about why the test is not medically indicated and potential risks associated with unnecessary medical interventions.[416]

The Pan-Canadian Cervical Cancer Screening Network recommends that laboratories need to have a stronger role in being custodians against inappropriate testing and need to be able to send that message back to providers.[401] However, other experts, while acknowledging that labs have a role in promulgating screening guidelines, feel that the primary custodian role should remain with health care providers because, once a specimen arrives in the lab, it is difficult to refuse testing for medical, legal, client, ethical, and practical reasons. Labs frequently receive test specimens without any knowledge of the clinical situation (e.g., if the specimen is from a high-risk individual or if the test is being used for another form of clinical management, such as a test of cure.) (Dr. Terence Colgan: Head of Gynaecological Pathology and Cytopathology, Mount Sinai Hospital, Toronto: personal communication, 2017 January 17)

Education on overdiagnosis

Providing information on overdiagnosis and over-screening to the public could help ensure adherence with recommended screening frequencies.[417] Also, providing information on overdiagnosis in decision aids could increase the number of women making an informed choice.[351] Women should be free to accept or refuse the test.[406]

HPV vaccination

The increasing prevalence of HPV vaccination in the population is anticipated to lead to fewer HPV infections and therefore fewer HPV-positive screening results and fewer cytologic abnormalities. This has the potential to reduce the overdiagnosis and overtreatment of screening participants.[2,80,398,411] In other words, the increasing prevalence of HPV vaccination may be a facilitator that could counteract the potential barrier of overdiagnosis and overtreatment, however as vaccinationated cohorts move through screening ages, vaccination may reduce the need for cervical cancer screening programs. Supporting access to vaccination and supporting the acceptance and uptake of the HPV vaccine could be considered as part of the implementation strategy for HPV-based primary screening.

Effect on Referrals to Colposcopy and Wait Times

An increase in the number of referrals to colposcopy is frequently cited as a barrier to implementing HPV-based screening because this would place a strain on the system, especially in the initial implementation phase. As described in the Clinical review portion of this report, colposcopy referrals are predicted to increase, especially during the first round of screening, and particularly if women younger than 35 are screened. This increase may have an impact on workload in colposcopy clinics and possibly patient wait times.

It is not clear if wait times would increase. One Canadian study observed a reduced wait time from the time of a positive Pap cytology triage result to colposcopy.[397,398] Both the reduced workload of Pap cytology results being read

by cytotechnicians and a heightened sense of urgency that providers felt to refer a patient with high risk results to colposcopy were cited as potential reasons for this reduction in wait-time.[397,398]

Referral rates to colposcopy and wait times may also change after the first few screening rounds of the new program.

"Although colposcopy volumes increase with the first screen, the volumes decrease with the second HPV screen. Hence there will be increased wait times followed by a decrease. There will be a need not only for initial management algorithms but also on-going management algorithms for those patients within a colposcopy environment" (Dr. Robert Lotocki, Manitoba PCCSN member: personal communication, 2017 March 10).

Staggered roll-out

During the consultations, it was suggested that a staggered roll-out (where certain age groups are screened one year and others the following year, etc.) could be a way to manage any initial spikes in referrals to colposcopy, as opposed to screening the whole eligible population at once. In Italy, where many regions have adopted HPV-based primary cervical cancer screening, most cervical screening programs chose to transition to HPV-based testing over the course of a few years to allow for adjustment to the volume of activity in screening.[418]

Effects on Laboratory Structure and Workflow

Several barriers and facilitators were identified related to laboratory structure and workflow.

Human resourcing in cytology

Reduced cytology workload and, therefore, job losses for cytologists, has been identified as a concern related to implementing HPV-based primary screening.[2,419] In Canada, molecular testing for HPV would be performed in a microbiology lab and automated — it would not be performed in a cytology lab by cytologists. As a result, it is believed that there would be significant job losses for cytologists (Dr. Terence Colgan: personal communication, 2017 January).

It is not certain to what extent job losses might occur, but fear about job losses is an implementation barrier, and its effects are already being felt in Canada (even before a decision regarding HPV-based primary screening has been made). During the consultations for this report, it was heard that cytologists (cytotechnologists and cytopathologists) see the change to HPV-based screening happening in other countries and assume it will eventually be implemented in Canada. "Students are afraid of going into this profession because they anticipate HPV testing will replace cytology testing for primary screening, and that computer algorithms will replace human interpretation of samples." (Dr. Manon Auger: personal communication, 2017 November) In recent years there has been a reduction in the number of Canadian schools and programs providing cytology training. (Dr. Peter Bridge, Academic Chair, Medical Laboratory Sciences, The Michener Institute of Education at UHN, Toronto: personal communication, 2018 May 22; and Dr. Manon Auger: personal communication, 2017 November)

During the consultations, it was heard that there is a shortage in the cytotechnologist and cytopathologist workforce in some Canadian jurisdictions. "Historically, it has been a struggle to recruit cytotechnologists as class sizes are small and there is no training program in the province. The greatest challenge has been to fill temporary postings such as maternity leaves." (Brian Timmons, Provincial Technical Director Laboratory Services, Health PEI: personal communication, 2017 December 13) "There is also attrition in the cytology workforce, as many people are retiring." (Dr. Manon Auger: personal communication, 2017 November)

"Hence, it may be more of a question of whether our current method of primary screening with cytology is sustainable." (Dr. Robert Lotocki: personal communication, 2017 March).

Throughout the consultations for this report, concerns were heard that the cytology workforce is becoming too reduced to meet continued demand. If a triage test is adopted that involves cytology testing, there will be a need for cytology staff. Furthermore, while cervical cytology tests are a type of gynecologic cytology, non-gynecologic cytology is usually done in the same lab, so the need for cyto-technical staff will continue to exist in these labs. (Dr. Robert Lotocki: personal communication, 2017 March).

Concerns were also heard about the effect on competency. Small laboratories may not have the volume of samples needed for cytotechnologists and pathologists to maintain competency (Dr. Kristen Mead, Program Medical Director, Pathology, Health PEI: personal communication, 2017 December 13).

Human resourcing issues, including job losses and challenges with staff retention and recruitment, are also expected or are already being seen in countries that are switching from cytology to HPV testing. “In England, job losses for cytology screeners are predicted if the option to centralize HPV/cytology laboratories is taken forward — many people could potentially be made redundant or will need to move to a different specialty." (Janet Rimmer, Senior Implementation Lead, HPV, England: personal communication, 2017 August 23). However, the cytology role will remain important in England, because cytology will be performed to triage HPV-positive samples. “It is important to note that currently there are not enough cytology screening staff in England to maintain turnaround time standards with primary cytology screening. Abnormal reporting rates are expected to remain similar at least in the first few years after implementing primary HPV testing, and there will be a need for pathologists and consultant biomedical scientists to assess and report the abnormal cytology samples. It may be a challenge to ensure sufficient staff, because fewer people may want to pursue this career path.” (Janet Rimmer: personal communication, 2017 August).

In New Zealand, where planning is underway for a change to HPV-based primary screening,[420] uncertainty about job security has caused some laboratory staff to leave. Concerns have been raised that no new trained staff are available, and that it could be difficult to maintain adequate levels of skills and services. These concerns primarily relate to cytology staff, but worries were also noted about potential pathology and histology staff shortages.[421] In response to these concerns, the National Screening Unit within the Ministry of Health is undertaking research to better understand laboratory and staff requirements leading up to and after changing to primary HPV-based screening. The National Screening Unit has also committed to work closely with laboratories and staff, before any changes take place, to identify the best ways to support the workforce.[421]

Retraining, expanded roles, and career transition opportunities for laboratory staff could facilitate the acceptance and implementation of an HPV-based screening system. There is the potential for growth in new skill development opportunities such as molecular training.[401,422] In the Netherlands, where HPV-based cervical screening is being introduced, cytotechnologists are moving to careers in histology, molecular pathology, immunology, and rapid on-site evaluation (ROSE) (Lia Van Zuylan-Manders, Team Leader Cytology, Radbound University Nijmegen Medical Centre, Netherlands: personal communication, 2017 September 8). In England, training tailored to primary HPV-based screening is being developed for laboratory staff for delivery by dedicated training centres (Janet Rimmer: personal communication, 2017 August).In the United States, many cytotechnologists are already practicing with expanded roles; for example, performing ROSE for specimen adequacy of fine needle aspirations (FNA).

In Canada, there are continuing education courses available to enable current cytotechnologists to upgrade their knowledge and skills for a renewed work environment. However, retraining is not without its challenges. “A protectionist attitude from some staff currently in the laboratory environment (pathologists, cytotechnologists, as well as other laboratory technologists) limits the acceptance of cytotechnologists in delivering additional skills.” (Dr. Catherine Brown, Professor and Clinical Liaison Officer, The Michener Institute of Education at UHN, Toronto, personal communication, 2018 June 25). Also, retraining and relicensing take considerable time and effort and require additional resources that may not be readily available.[423] “Retraining and career transition might not be feasible for many current cytotechnologists” (Dr. Catherine Brown: personal communication, 2018 June).

For new students beginning training, new core competencies (e.g., histology, molecular) endorsed by the Canadian Society for Medical Laboratory Science (CSMLS) have been added to training curriculums. Newly trained cytotechnologists completing training from 2017 onward will be educated in histology sample preparation; recognition of normal and abnormal tissue architecture; immunohistochemistry /immunocytochemistry technique and basic analysis; ROSE for FNA; kit-based molecular testing for high-risk HPV, EGFR, and alk genes; and fluorescence in situ hybridization (FISH) techniques and basic analysis. These graduates will be eligible to become licensed in cytology, histology, and molecular work and may be able to perform expanded functions within the lab.[423,424]

While the curriculum changes are promising for new graduates, the loss of some older cytotechnologists – those who are the most skilled and experienced – might still occur. “The expanded scope of practice will produce many ‘jacks of all trades,’ but we will miss the ‘masters.’ It takes many years of experience to become an excellent cytotechnologist

and cytopathologist. We need to sustain those currently trained so that our field is not decimated by mass exodus and layoffs." (Dr. Catherine Brown: personal communication, 2018 June).

Centralization of Laboratories

Current laboratory structure and workflow could pose a challenge to the implementation of an HPV-based screening strategy. Because the HPV test is a molecular test, and because a change from cytology to HPV-based primary screening would likely lower cytology sample volumes and throughput, the centralization of labs (reduction in number of small labs processing samples) may assist in the adjustment to the different sample volumes and thus facilitate a change to HPV-based screening. This configuration change is under consideration in England and has been adopted in the Netherlands when transitioning from cytology-based to HPV-based screening. There are accompanying logistical challenges; for example, with fewer, more centralized labs, there is a challenge to ensure that samples arrive to the labs on time, considering the greater distance they might need to travel (Janet Rimmer: personal communication, 2017 August). "Another challenge is asking staff members to move to a new location. In England, the option being considered is a reduction from approximately 50 labs to 10–15 labs. These 10 to15 labs will be located across England and each one will provide both HPV testing and cytology testing. It will be important to ensure that each lab is sufficiently sized so that there are sufficient numbers of cytologist screeners working at all times (i.e., even when some staff take vacation)" (Janet Rimmer: personal communication, 2017 August). In the Netherlands, there was a reduction from approximately 35 screening labs to 5 labs (one for each region). One of the main challenges was the lengthiness of the process – with the selection of laboratories lasting from the fall of 2015 to June 2016. (Lia Van Zuylen-Manders: personal communication, 2017 September).

It is not clear if centralization of labs would be an appropriate strategy in Canada, considering its geography, population distribution, and health system structure. Each jurisdiction has unique factors to consider. Concerns have been raised about centralization of labs, such as loss of connectivity and communication between cytology and histology (biopsy) testing. "Currently, most cytology labs are in the pathology department — even if they are not housed in the same building, it is possible to walk over to talk to your colleagues." (Dr. Manon Auger: personal communication, 2017 November). "The problem with centralization is that biopsies would be performed elsewhere, because it is unrealistic for biopsies to be all done in the same lab. Biopsy and cytology separation could potentially be dangerous as it is suboptimal to look at samples out of context." (Dr. Manon Auger: personal communication, 2017 November). There are also concerns about the impact of centralization on non-gynecologic cytology. "The demand for non-gynecologic cytology is growing, but having fewer labs and fewer cytologists in general will have a negative impact on non-gynecologic cytology" (Dr. Manon Auger: personal communication, 2017 November).

Laboratory Costs of Transitioning to HPV-Based Screening

Capital costs of purchasing HPV testing equipment and reagents will need to be considered.[405] However, some of the equipment may already be in place, because several jurisdictions in Canada are currently doing HPV triage of cytology-positive cervical samples.[23] It is also expected that some of the costs will decrease with increased volume and vendor competition (Dr. Robert Lotocki, Manitoba PCCSN member: personal communication, 2017 March). Group purchasing and competition among manufacturers could result in lower costs for HPV testing equipment and reagents.[425]

Jurisdictions that have not yet switched to liquid-based cytology will need to do so, which will incur costs (Dr. Robert Lotocki, personal communication, 2017 March). Building modifications may be required in laboratories housing the new equipment, and the funding for those modifications will need to be in place (Brian Timmons: personal communication, 2017 December).

Cost issues are addressed in more detail in the Economic Analysis portion of this report.

IT systems

Throughout the consultations, a common topic that emerged was the need for new or modified IT systems that are more comprehensive in tracking and linking data. With the added complexity of using different testing technologies (e.g., HPV molecular test with cytology triage, instead of cytology alone), IT systems were identified as important facilitators to implementation in the laboratory sector if HPV-based screening is adopted. Current systems may be a

barrier to implementation. For example, in Prince Edward Island, there are concerns about linking multiple laboratory test results related to one patient

"We have an electronic health record (EHR) system here, but the reporting formats vary depending upon the discipline; for example, microbiology and pathology are in two very different sections. In our operations, HPV testing would be performed by the Microbiology laboratory. Reporting systems may have to be modified to ensure the continuity of results between the HPV testing lab and Pathology where the cytology information is housed." (Brian Timmons: personal communication, 2017 December).

"A pathologist should be able to look at the electronic medical record and easily see the patient's screening history, HPV results, colposcopy results, etc." (Dr. Kristen Mead: personal communication, 2017 December).

Similar needs for IT systems were identified in Quebec. "It's important to have one registry that ties all the test results together. It needs to match the molecular results to the cytology results and to the histology results. All the data needs to be integrated, and the test results need to be linked to patient recall. Money will be needed from the province for this IT system because if it's left up to individual institutions, they will choose whatever is cheapest rather than what is optimal." (Dr. Manon Auger: personal communication, 2017 November).

The experience of other countries may be valuable to Canadian stakeholders if there is the decision to implement HPV-based screening. "The Netherlands uses a fully automated system for tracking results called SCREEN IT. This system transfers results from laboratories, to screening programs, and then to GPs. The results are sent automatically, and the system is working well." (Lia Van Zuylen-Manders: personal communication, 2017 September). In England, there is a plan to implement a new call/recall IT system in 2018. The system will invite women and inform them of their results once received from the laboratory. The collection and reporting of statistics is being done separately, with data published for all of England (Janet Rimmer: personal communication, 2017 August).

The Cancer Research UK group states that "Commitment to and introduction of a fully-funded IT system must be included as part of the roll-out plans for HPV primary tests but should not delay its introduction."[400]

Effects on Screening Participation Rates

Screening participation rates may be affected by the organization of HPV-based cervical cancer screening systems, such as increased intervals between screening appointments, availability and quality of invitation letters, availability of education, and availability of self-sampling technology. As identified by the patient experiences review, screening participation can also be affected by patient factors such as age, socioeconomic and sociocultural status, and other individual factors. Clinical trials and countries that are or have already implemented HPV screening may provide valuable information with respect to how a switch to HPV-based screening had an effect on participation rates.

Many barriers and facilitators to screening participation are common to both cytology-based and HPV-based strategies. The following section will primarily focus on those specific to HPV-based screening.

Longer intervals and later start age may cause patient participation drop-off

The longer intervals and later start age may be met with reluctance.[417,426,427] In Australia, where HPV-based screening is being introduced, more than 70,000 people signed an online petition to oppose the changes to the cervical screening program, and it is speculated that some of the opposition was based on potential misunderstanding of the rationale for the change as well as misunderstanding of the effectiveness of screening and the role of HPV as a cause of cervical cancer.[427] In an opinion article, researchers in Australia stated that a reasonable message to take away from the petition was that communication and consultation have not been sufficient or effective.[427] In England, the introduction of a later start age for screening was also not well received — it was perceived by some as "rationing care." A decade later, some people are still exhibiting their discontent, and national media headlines can be seen such as: "Denying young women smear test is a disgrace".[412]

In the Canadian context, participation in the Ontario Cervical Screening Program (OCSP) decreased by 5% between 2009 and 2014.[426] This decrease coincided with the introduction of a longer interval between screens from once a year to once every three years. Before the guideline change, participation had increased in every measurement period since 2003.[426] In the HIV-positive population in Ontario, cervical cancer screening rates also dropped in 2012

and 2013, even though annual screening continued to be recommended for this patient population.[428] One possible reason is that there was a delay in authorizing an alternate billing code for those who were HIV-positive or otherwise immunocompromised to allow for continued annual screening (a 10 month delay from when the original billing disincentive was introduced for the general population in January 2013).[428]

In a survey of participants in a clinical trial in British Columbia, the intention to attend HPV-based screening dropped once participants were advised of the extended screening interval and later start age.[417] It has been suggested that comprehensive education to improve the understanding of the rationale for a change from cytology to HPV testing (and thus the change in screening interval) may mitigate that potential barrier.[417]

Patient education about cervical cancer screening in general

Patient education has been found to increase participation in cervical cancer screening performed by Pap test.[429,430] There is reason to believe that this would also be the case for an HPV-based screening program.

Patient education about HPV and HPV-based screening

Patient communication and education could facilitate the implementation of HPV testing, both in the clinic and through self-sampling.[2,217,391,405]

One of the experts consulted recommended that "communication and educational tools should be developed well before any implementation because they will require input and review by various stakeholders, including clinicians, policy-makers, and screening participants. These tools should exist in various formats (paper handouts, public service announcements, screening program websites, social media, etc.). It is anticipated that a multi-faceted and well-planned approach will have greater reach and improve the chances that stakeholders understand why cervical screening is changing, and therefore, accept these changes to a public health approach that has been implemented for decades." (Laurie Smith, RN(C) BN MPH, Research Manager, HPV FOCAL/HPV Related Diseases, BC Cancer/Women's Health Research Institute: personal communication, 2017 September 8).

Having educational materials available in various formats has been further supported in the literature.[267,431] Other ways to facilitate uptake could include developing materials for varying literacy levels and translating materials into many languages.[405,432] The pan-Canadian forum on cervical cancer prevention and control recommends that education should be specific to age, gender, sexual orientation, and culture.[432]

Vulnerable populations, such as patients who are immunocompromised, may need tailored communication. "Often vulnerable patients are too busy dealing with other pressing health issues to think much about cancer screening. It's important to provide communication and equal access to health services to vulnerable populations such those who have chronic illnesses and to new immigrants and refugees." (Dr. Marc Steben: personal communication, 2017 December).

Patient education on HPV could be facilitated by using many modes of outreach, including by healthcare providers, teachers, youth counsellors, public health educators, and the media.[405,432]

The pan-Canadian forum on cervical cancer prevention and control further recommends that the content of communication and education tools be developed in consultations with clinical experts and with input from the target audience and the health care providers who will be disseminating them.[432]

Information about the types of HPV, its transmission and prevention, the link between HPV and cervical cancer, and the importance of cervical cancer screening could be a facilitator to implementing an HPV-based screening program.[405,432,433] Destigmatizing HPV infection and emphasizing its high prevalence in the population (potentially describing it as the "common cold" of STIs[401]) have been identified as some of the most important messages to convey to patients.[433]

Explaining the differences between cytology testing and HPV testing, and explaining the naturally slow progression of the disease, may increase comfort levels regarding a potentially later start age and extended screening interval.[433] Because a later start age and extended screening interval may be perceived as a cut-back to health care, experts have emphasized the importance of messaging that clearly outline the scientific reasons for the change in programs.[2,417]

Community education

Community education has been shown to be an important facilitator to encouraging participation in screening.[210,217] Many people still have limited knowledge about HPV; it has been proposed that HPV information should be provided to all Canadians, not just those eligible for screening.[210,432] Community education could help destigmatize HPV infections and could help the public understand and accept changes to the cervical cancer screening strategy.[217,412] In an opinion piece,[427] researchers in Australia stated that "meaningful public engagement and communication are neither easy nor cheap, but shying away from them is not an acceptable response." The PAHO/WHO manual recommends involving mass media to promote messages about HPV testing because this can help obtain a greater commitment from the public and health providers when the program is rolled out.[405]

Other countries that are implementing HPV-based cervical cancer screening have provided information online about the change. For example, the UK National Screening Committee (NSC) developed Questions and Answers that are available on their website.[434] Australia's National Cervical Cancer Screening Program website provides information about the new test, answers common questions about HPV and cervical cancer, and features an animated video.[435] New Zealand's National Cervical Screening Programme (NCSP) has also provided information online[420] about its plans to introduce HPV testing for primary screening and it has developed Frequently Asked Questions.[436]

HPV vaccination and its link to screening participation

Cervical cancer screening (via cytology testing) has been found to be more common among HPV-vaccinated females.[437] The authors speculate that females willing to pay for the vaccine may be more health conscious and thus also participate in screening more than those females not willing to pay for the vaccine.[437]

All jurisdictions in Canada are currently offering school-based HPV vaccination to girls, and 10 provinces have begun or announced a school-based HPV vaccination program for boys.[23] HPV vaccines are also available in all provinces and territories outside of the school-based programs, but they usually must be requested and paid for by the patient or their private insurance.[23] Patient counselling on HPV vaccination could be an opportunity to provide counselling on HPV-based screening, and vice versa.[438] "Women getting the vaccine are generally more aware about prevention. Counselling on cervical cancer screening and prevention can be combined with vaccine education." (Dr. Marc Steben: personal communication, 2017 December). Many clinical experts state that it is important for the vaccinated population to continue cervical cancer screening, and this is a message that should be included in communication materials.[403,437-439]

Invitation and recall letters

Invitation and recall letters have been shown to increase awareness and participation in screening.[426,429,430,440,441] The literature notes some key findings on how to further increase participation through invitation and recalls, including sending the invitations by mail, sending a reminder letter after an invitation letter, having the letters signed by a medical director or the patient's physician, and including customized messages (e.g., date of the last test).[440]

The Pan-Canadian Cervical Screening Initiative (PCCSI) network recommends that optimal correspondence would include an invitation to participate in screening, notification of screening results, recall notice for next screening, and follow-up on abnormal results.[440] The network recommends the implementation of all these correspondence elements across Canadian cervical cancer screening programs, but that each province or territory should conduct their own prioritization exercise to determine the approach and correspondence elements appropriate to them, considering capacity, resources, and overall program goals. The network also recommends that letters should be reinforced and supported by other strategies including phone calls, electronic communication, health promotion activities, mass media campaigns, clinician-directed strategies, and targeted activities for those who are more difficult to reach.[440] While these strategies are not unique to HPV-based screening, they may be relevant, particularly because of the extended screening interval.

HPV self-sampling

Self-sampling for HPV testing may be a facilitator to screening participation. In particular, studies have shown that self-sampling increases screening participation rates in women who are under-screened or never screened.[22,391,430,442-444] As found in the Patient Preferences and Experiences section and in the literature identified in

this Implementation Issues review, self-sampling can also be more appealing to individuals who fear speculum examination conducted by a health care provider or who have concerns about privacy and modesty.[431,445,446] A self-sample kit that can be used at home offers the benefit of increased convenience and eliminates the need to book time off work, arrange for childcare, or travel to a clinic.[22,217,391] Attitudes toward self-sampling tend to be positive with high acceptance or willingness to try this method.[431,442,447]

In the Netherlands, those not responding to the screening invitation will receive a self-sampling kit for HPV testing and those with an HR HPV+ result will be referred to their physician for sample collection for cytology triage.[18] However, studies have shown that automatically mailing kits may result in wasted kits, so another strategy might be to allow those who don't attend appointments to request kits (or "opt-in"). The opt-in approach could reduce waste and save money, but it might result in fewer people using the self-sampling kits because it creates an additional step and requires additional effort for the participant.[22,444]

One approach tried in Denmark was to use opt-in HPV self-sampling using paper, telephone, webpage, and mobile app methods for communicating with women.[444] Another alternative tested in France for increasing participation in non-attenders was to implement self-sampling alone, without invitation and recall letters.[443]

In Canada, there are mixed opinions among health care providers and policy-makers about whether self-sampling should be implemented for only under-screened populations or for the whole eligible population. Self-sampling may be appealing to all screening candidates because it provides flexibility, but there are concerns about decreased diagnostic performance (while there is some evidence showing similar performance between clinician- and self-sampling for some test using certain sampling techniques, there is a lot of heterogeneity between studies and firm conclusions remain unclear[63]) and missed opportunities for clinicians to engage in discussions with patients about other health issues.[419]

As with invitation and recall letters, there are logistical issues to consider when implementing self-sampling, such as how to best distribute and keep track of self-sample kits.[413] A possible option to consider is the use of a fulfillment house, which is a business specializing in providing services related to mailing.[440] Fulfillment houses are used by some cervical cancer screening programs for the mass mailing of invitation and recall letters. Using a fulfillment house obtained through competitive procurement process can be more efficient and cost-effective than in-house mailing.[440]

Mobile or integrated screening

Mobile screening centres have been launched as a way to facilitate participation in cancer screening. In Ontario, a 45-foot-long bus called the Screen for Life Coach goes to workplaces and other locations in the community to provide cervical cancer screening as well as breast and colorectal cancer screening and education. Registered nurses perform the sample collection for the cytology test on the bus. Mammograms are also performed on the bus, and participants are given a take-home fecal occult blood test for the colorectal cancer screen. Time on the bus is 20 minutes per person. Screen for Life Coaches operate in the Hamilton area[7,448] and in Northwestern Ontario.[426,449]

Mobile services could also be a possible way of reaching under-screened populations. Authors of a study on the barriers to cervical screening among sex workers in Vancouver report that contact with outreach services that provide cytology tests (e.g., street nurses, mobile outreach) increased the odds of testing by 35%.[450]

Another group of study authors suggest integrating cervical and breast cancer screening services. In this service delivery model, cervical cancer screening performed by a trained health care provider could be offered in breast cancer screening sites with active scheduling of appointments.[451]

On-site colposcopy services

Having on-site colposcopy services has been seen to facilitate adherence.[452] Colposcopy follow-up after abnormal screening results is an important component of cancer screening programs, but non-adherence, defined as failure to attend the recommended colposcopy, is common. In 2009, a sexual health clinic in downtown Toronto, Ontario, established an on-site diagnostic colposcopy service that also includes patient counselling by telephone and individualized supports. The authors reported that this model of care reduced colposcopy non-adherence by two thirds.[452]

Health Care Provider Barriers and Facilitators

Successful implementation of a new screening strategy would require acceptance and participation by health care providers. Several barriers and facilitators were identified in the literature and through consultations.

Difficulty adapting to a change in practice

Guidelines that recommend reducing interventions can be difficult for clinicians and the public to understand and accept.[415,453,454] One paper states that, although providers are quick to adopt new tests, they are slow to adopt longer screening intervals. The authors of this paper speculate this resistance could be the result of pre-graduate training, disincentives due to loss of reimbursements with longer intervals, and a lack of well-organized information systems to track screening history and ensure patient recall.[403] In one survey, physicians expressed concern that women would not come for annual exams if cervical cancer screening was not offered and concern that extended intervals would lead to inadequate screening.[454] A longer screening interval reduces the number of opportunities for clinician-patient interaction and provides fewer opportunities to screen for other STIs and to discuss contraception options or other sexual health concerns.[419] Clinicians may be resistant to this potential change in the clinician-patient relationship and they may find it difficult to adapt their practices to actively schedule sexual health wellness appointments.

Authors of the VASCAR study in Montreal reported that the learning curve for some healthcare workers when adopting HPV-based primary screening was longer than expected.[397] Despite providing diagrams, oral presentations at Grand Rounds, and written recommendations for risk management after test results, there were 3,414 protocol violations reported in this study (involving 11.7% of the 23,739 women who were screened). Most protocol violations took place in the first year, and the most common protocol violation was a conventional cytology test being conducted at the initial screening visit instead of the recommended HPV test (9.3% of those who were screened).[397,398]

Lack of time and resources

A survey of primary care physicians in British Columbia asked about cervical, breast, colorectal, prostate and other cancer screening and identified several barriers including physician time constraints, lack of financial compensation to discuss screening, and having patients with multiple health concerns.[455] An Ontario study found that some doctors may not offer cervical cancer screening to women with intellectual and developmental disabilities because of the extra time required to provide education and because of a false perception that these women are not sexually active.[456] The authors of the survey in British Columbia concluded that the study highlights the need for more physician education on screening programs, referral criteria, follow-up process, and screening guidelines.[455]

One strategy attempted in Ontario was to provide financial bonuses for physicians. However, the cervical screening rate did not change significantly from year to year before or after the incentives were introduced. The lead author stated that governments around the world are experimenting with paying doctors extra to improve the quality of care but there's little evidence that this strategy works.[457]

In terms of HPV-based screening, clinicians in the UK have acknowledged a lack of confidence in explaining HPV infection and sexual transmission.[458] Conversations about HPV were described as "awkward", "a can of worms", and "a minefield." These clinicians acknowledged a need for more education in the science relating to HPV and cancer and for training in communicating sensitive information to patients.[458]

Health care provider characteristics

Certain health care provider characteristics, such as gender or being trained outside of Canada, may influence cervical cancer screening practices.

Some studies report that female providers have patients with higher screening participation rates.[451,459] It is speculated that the female physician approach to care delivery is different because they may have a stronger orientation to preventive care and adherence to guidelines,[454,459] and female physicians may take on a lighter workload so that they can spend more time with individual patients.[459] Female physicians also report feeling more comfortable with performing cervical cancer screening than male physicians.[455] Patient preferences may also factor in to this point.[198,204,460] and this is described in more detail in the Patients' Perspectives and Experiences section of this report.

One study in the United States found that practitioners in group practices were more likely to follow both vaccination and screening guidelines than those in solo practices.[454] The authors speculate that perhaps the reason for this discrepancy is that physicians in group settings have better access to new information and sharing of knowledge among colleagues, and that financial pressures may also influence practice differently in solo and group practices.[454]

In another study, physicians who attended medical schools in the Caribbean, Latin America, the Middle East, North Africa, South Asia, and Western Europe were less likely than those trained in Canada to screen their patients for cervical cancer.[461] The lead author says this finding may reflect differences in what is emphasized in medical school curriculums around the world. The author recommends that physician characteristics should be considered when designing physician-targeted interventions for cancer screening.[461]

Clinician education about cervical screening in general

Education tailored to health care providers and their specific needs can help address gaps in training and knowledge, and can help optimize cervical cancer screening practices, regardless of the screening technology being used.[462] Many organizations are already involved in providing education and resources; for example, Cancer Care Ontario offers continuing medical education modules and develops a suite of tools for primary care providers and other specialist audiences to facilitate knowledge transfer and increase screening according to guidelines. Their tools are disseminated to providers primary though their professional organizations (e.g., the Ontario Medical Association, the Nurse Practitioners' Association of Ontario) and include clinical guidelines summaries, decision support tools, handouts, and e-bulletins.[463]

Clinician education and training specific to HPV-based screening

Education and professional development opportunities could be made available for clinicians to encourage acceptance and participation in a new screening strategy.[2,432,453] It has been recommended that, to enhance engagement of primary care providers, it would be helpful to identify the gaps in HPV knowledge. This could be achieved through a baseline survey of practitioners.[401] Practitioners should be aware of HPV and the role it plays in cervical cancer, the disease etiology, and that this is an area of evolving knowledge.[401] If there is a change to HPV-based screening, practitioners will need to know how to manage HPV positive results, abnormal cytology triage results, and how to counsel patients and their partners.[2,401,455]

One study found that knowledge translation workshops can be an effective approach for communicating evidence on HPV-based screening to colposcopists.[453] Several organizations across Canada, including CADTH, have the capacity to provide these kinds of knowledge translation opportunities.

In England, where HPV-based screening is being implemented, e-learning formats are in development for sample takers. Similar e-learning tools are being developed for colposcopy staff to explain new clinical management pathways. The e-learning format was selected because of the number of staff and locations needing to be reached (Janet Rimmer: personal communication, 2017 August).

"Multi-media education for clinicians is best. Young doctors might prefer e-platforms while older doctors might prefer a phone number they can call." (Dr. Marc Steben: personal communication, 2017 December).

Because primary care practitioners play a central role in explaining and recommending screening to patients, education for them will in turn improve education for their patients.[391,433,462] Having communication materials prepared for clinicians that they can share with their patients could save clinicians time in explaining changes to screening. In the UK, clinicians mentioned that it would be particularly useful to have a written handout to give to patients.[458] A group of UK researchers developed and field-tested HPV consultation guides including information handouts for patients diagnosed with HPV-related cancer.[458]

Clinicians might not be prepared for certain questions, so providing Q&A tools can help facilitate conversations with patients (Laurie Smith: personal communication, 2017 September). In addition to explaining HPV testing for primary cervical cancer screening, clinicians will need to be able to explain the meaning of positive results and the steps required for follow-up.[2,401,405] Patients who learn they are HPV positive may feel anxiety, shame, or anger, and clinicians should be prepared to explain the prevalence of HPV in the population and stress that having HPV is no reason for shame. Those who are HPV-positive may have questions about whether to tell their sexual partner, if HPV

can be treated, and how to avoid re-infection.[433] The full list of questions received from patients during the FOCAL trial, including responses, is available in the FAQ section of the BC Cancer Agency website.[464]

Recently, the International Centre for Infectious Diseases (ICID) produced a booklet[438] for health care providers suggesting ways in which to counsel patients about HPV testing and test results. It includes sections on HPV testing for cervical cancer screening, HPV transmission, and vaccination.

"For clinician education to be effective, we need something very structured. We need not only counselling tools but also a dissemination and education strategy." (Dr. Marc Steben: personal communication, 2017 December)

In many Canadian communities, sample collection for cervical cancer screening is performed by nurses and community education and promotion is provided by other health care professionals. Therefore, training and education would need to be offered to a range of health care practitioners including physicians, nurses, and community health workers.[405]

Access to experts

Access to experts in the field of HPV-based cervical screening who can answer clinician's questions regarding HPV testing and cervical cancer may be a facilitator to implementation.[401,453]

The French National Agency for Accreditation and Evaluation in Healthcare (ANAES) recommends that a cancer screening programme should include coordination between clinicians (general practitioners, specialists, nurses, pharmacists), and that their job is to encourage screening candidates, technicians, and operators.[406]

Databases and IT solutions for health care providers

User-friendly databases can facilitate clinician participation in new cervical cancer screening pathways because they can make it easier for clinicians to keep track of patients and results.

An example of a large electronic database already in place is the Screening Activity Report (SAR) for physicians, developed by Cancer Care Ontario. It was evaluated in 2014 and a modest association was found between using the SAR and increases in screening participation (cervical screening using the Pap cytology test as well as breast and colorectal cancer screening).[426] The SAR lets physicians know which of their patients have been screened, which ones are overdue for screening, and which ones need follow-up after abnormal test results. It also enables them to compare their performance with others within their regions and the province.[463] Cancer Care Ontario is working to integrate the SAR with other eHealth platforms, such as electronic medical records.[426] Although the SAR is not specific to HPV-based screening (currently it is being used for cytology-based screening), it serves as an example of a facilitator that helps clinicians participation in screening.

Clinical practice guidelines

Clinical practice guidelines can also be a facilitator for health care providers.

"Given the improved sensitivity with HPV testing, an extended screening interval will occur for routine screening. Cervical screening by a clinician is often an opportunity for the clinician to review other medical issues with patients. As a result, clear guidelines on HPV primary testing and follow-up, as well as recommendations for other STI testing, can support clinicians in decision-making and can counteract the potential loss of opportunity to screen for other STIs and ensure women still attend for visits with their providers for other medical issues as needed." (Laurie Smith: personal communication, 2017 September).

Geographical, Socioeconomic, and Sociocultural Issues

There are several implementation issues related to geographical, socioeconomic, and sociocultural perspectives. The Patient Preferences and Experiences section of this report covers these topics in more detail but, briefly, some barriers and facilitators are outlined below.

Socioeconomic status

Low income and low socioeconomic status have been shown to be a potential barrier to cancer screening. It has been speculated that lack of access to transportation, childcare, or the inability to take time off work are factors to low screening participation in those with lower socioeconomic status.[198,403,428,446,451,465,466] Cervical cancer screening participation has also been found to decrease with advancing age.[451,467]

Ethnicity and cultural barriers

Participation in screening may vary by ethnic or cultural group. For example, screening participation has been found to be low among Canadians from Muslim-majority countries,[462,468,469] and beliefs about cancer and the lack of culturally safe or appropriate programs and services have been found to be barriers for Indigenous Peoples.[198,255,460] Some of the varying screening rates have been reported in the Clinical section of this report and some of the reasons that individuals who belong to those groups have given for not participating in screening have been outlined in the Patient Experiences section of this report.

Systemic barriers

Systemic barriers to screening include restrictions such as remote geographical location, shortage of health care providers, high staff turnover, and lack of tracking systems for follow-up.[460,470] For example, Muslim immigrants in the Greater Toronto Area have reported difficulties accessing female physicians, language barriers, long wait times, and lack of transportation.[431]

In summary, while barriers related to socioeconomic status, ethnicity, culture, and the health care system are not unique to HPV screening, they are important to note with respect to implementing a new or different screening program.

Culturally appropriate educational materials

Culturally appropriate education materials have the potential to be facilitators to participation in screening programs.[217,430,460,466,468] Creating culturally appropriate education and programming could be done by being intentional and responsive to a community's cultural beliefs regarding cancer and its prevention and treatment.[431,460,471] It has been suggested that health-care providers establish trusting relationships with their patients and be willing to learn about the culture in which they practice.[198] For example, for First Nations communities, it has been suggested that developing health education materials that respectfully depict female bodies, sexuality, and health behavior through a First Nations lens may be appropriate.[255] Further, First Nations women have also emphasized the need for more culturally sensitive education addressed to community members of all genders, starting at school.[217] Again, these are not unique to HPV screening, but may facilitate the implementation of an HPV screening program.

Creative and practical solutions to systemic barriers

Overcoming systemic barriers is often more difficult. Each community must assess its own needs and resources to design creative solutions. One solution that has been proposed by the National Aboriginal Health Organization is that a community health centre could arrange for a health care provider to visit them in conjunction with nearby communities.[460] Additional resources, including more health care staff and more transportation options, could also help address systemic barriers.

HPV self-sampling

As mentioned previously, HPV self-sampling has the potential to overcome many systemic barriers, improving access to people in rural and remote communities and to people from socioeconomically disadvantaged groups.[22,204,217,391,442,446,447] Self-sampling could also overcome cultural barriers, because when conducted at home it can provide a culturally or religiously safe procedure.[22,442,446,472,473]

Summary of Results

In summary, there are several barriers and facilitators that are common to both cytology-based screening and HPV-based screening, and there are also those that are specific to HPV-based screening. Introducing a change to the screening strategy could be an opportunity to address some of the current barriers and to improve cervical cancer screening programs.[405]

Table 32: Barriers and Facilitators to Implementation

Barriers	**Barriers Common to Both Cytology- and HPV-based screening**	**Barriers Specific to HPV-based Screening**
	• Cultural barriers (e.g., patient beliefs, fear, lack of knowledge, modesty) • Systemic barriers (e.g., travel, lack of access) • Doctors are busy — lack of time for procedure and patient communication • Limited number of female doctors • No centralized registry/lack of good IT systems	• Difficult to make a large system change • Lab reconfiguration may be needed – many logistics to consider and will take time • Lab human resourcing issues (loss of jobs for cytologists, difficulty maintaining skills in the laboratory workforce) • Concerns about risk of overdiagnosis and overtreatment • Concerns about increase in colposcopy referrals • Stigma of testing for an STI • Screening participation drop-off due to longer screening interval and later start age
Facilitators	**Facilitators Common to Both Cytology- and HPV-based Screening**	**Facilitators Specific to HPV-based Screening**
	• Organized screening programs • Clinician education • Patient & community education • Culturally appropriate education tools • A centralized registry and good IT systems • Recruitment and recall letters (reminders of appointments) • Mobile and integrated screening	• Plans and funding in place • Step-wise rollout • Triage system and appropriate screening intervals • Patient & community education • Clinician and laboratory personnel education • Retraining and career transition • Self-sampling • Vaccinated cohort growing

Conclusion

The key implementation issue that emerged is that a switch to HPV-based screening would be a big operational and culture shift for clinicians, patients, and laboratories. If a switch is made good planning, funding, and coordination will be needed to make sure implementation runs smoothly. One of the main challenges is acceptance of the new screening strategy by patients and clinicians, and preventing a drop in screening participation rates. The other main challenge is the major change required to laboratory configuration, workflow, and human resourcing. There are several facilitators that can help with overcoming these barriers; for example: education, step-wise rollout, organized screening programs, good IT systems, self-sampling.

Many of the barriers and facilitators identified are not specific to HPV-based screening, but are common to cytology-based screening as well. Therefore, many of challenges that patients and providers face are not new, and there are already solutions in place or being developed for cytology-based screening that could be applied to HPV-based screening.

Nonetheless, a change to HPV-based screening would be a significant culture shift. It is important to keep in mind the magnitude of the system change and the level of organization that would be required to ensure all components are in place and functioning well. If a decision is made to adopt HPV testing for primary cervical cancer screening, implementation will need to be carefully planned, and sufficient time and resources will need to be allotted to ensure structures and supports are in place — at the patient, clinician, laboratory, and system level.

4893

Discussion

Acceptance of/participation in screening

For those who are eligible, the acceptance of and participation in any screening program is not a 'given'. Many barriers and facilitators to screening participation are common to both cytology-based and HPV-based strategies. Some of the facilitators currently being used to increase acceptance of and participation in programmatic screening could be applied to HPV-based approaches to screening (e.g., mailing appointment invitation and recall letters). There was overall limited evidence from this review indicating differential participation rates to screening between approaches and, as such, the economic model assumed no difference in participation rates between screening approaches. However, the clinical review does signal potential opportunities to develop new ways of encouraging participation in screening, such as new IT systems, better connectivity and communication, and offering the option of self-sampling if an HPV-based strategy is adopted. Additionally, with self-sampling for HPV testing potentially able to achieve similar accuracy to clinician-collected samples (depending on the test type)[63] this may further increase the acceptance of and participation in screening programs for some eligible individuals, particularly those who have never participated in screening.[442] It is important to note that at this time, the evidence regarding the comparative accuracy of self- versus clinician-sampling is heterogeneous and self-sampling seems to be less sensitive and specific than cytology at the threshold of ASCUS or more severe dysplasia.[63]

Eligible individuals consider the relevance and value of screening to them prior to participating – an understanding of the etiology and the risk factors for both cervical cancer and HPV could be important to patients when answering the question 'should I go for screening.' There can be stress and anxiety related to the testing itself and to a possible detection of a precancerous lesion. Both the testing itself and the presence of HPV can bring feelings of embarrassment, shame, and vulnerability to some – an HPV diagnosis is also daunting despite how common the virus is.

For participants undergoing screening, screening is a big deal. The patient perspectives review identified that programs that reduce the frequency of screening may be received positively by those who are eligible for screening. Frequency of screening was a variable evaluated in the economic evaluation, specifically for the screening approach involving primary HPV with cytology triage. By reducing the frequency of screening from every 3 years to every 5 years, the incremental costs were found to be lower as fewer programmatic screening tests would be performed while expected utilities remained comparable. Overall lifetime risk of developing cervical cancer was predicted to increase from 0.31 (for screening starting at the age of 25) or 0.34 (for screening starting at the age of 30) to 0.39; this equates to one additional missed cancer case for every 1,250 to 2,000 individuals.
The economic model incorporated current screening participation rates and the model was not sensitive if rates achieved target levels of 80% as set by the Canadian Task Force on Preventative Health Care.[1]

Choice is important for those who undergo screening. Population-based screening programs increasingly proceed on a model of "informed choice" where the goal of the program is to encourage participants to make choices that are consistent with their own priorities and values. This may raise or lower uptake of screening.

The perspectives of clinicians and the laboratory sector are also important to acceptance and participation in a new screening program. The potential for a reduced cytology workload and, therefore, job losses for cytologists, is a concern related to implementing HPV-based primary screening. However, some of the changes to the cytology workforce are already happening, and the transition may not be as abrupt as feared.

Special populations

Whether the program is cytology or HPV based, the population eligible for cervical cancer screening is diverse. Communication and education materials that appeal to, are accessible to, and meet the specific needs of the diverse screening population would likely be beneficial. Language, cultural, socioeconomic, geographic, and other barriers all exist with respect to any cancer screening program and are therefore relevant to an HPV-based screening program.

Not all eligible populations speak English or French and literacy rates differ. Based on the findings in the Implementation Issues review, it may be beneficial to develop a wide range of communication and education materials that are culturally appropriate and that address the specific needs of certain populations. The eligible population for cervical cancer screening also differs in terms of socioeconomic characteristics and geographical location. Special implementation programs or additional resources may be necessary to reach particular groups.

Regardless of testing medium, those who are historically underscreened may benefit from tailored, patient-centred screening strategies as well as outreach about those strategies. As HPV-based screening allows for the self-collection of samples, an HPV-based approach may increase participation for those who are either less comfortable with or have difficulty accessing clinicians for sampling.[419,442] Acceptance and attitudes toward self-sampling have been found to be positive both among the general screening population[63] and among those who normally have not participated in screening.[442] For transgender individuals, any type of cervical cancer screening may be associated with emotional distress due to gender dissonance[474] and for those who are undergoing androgen therapy, the interpretation of Pap cytology tests can be more challenging.[475] HPV-based screening strategies that include self-sampling have the potential to ameliorate screening in that population.

As with any strategy, an HPV-based screening strategy that includes self-sampling would not reach all underserved or underscreened populations. Those who are not comfortable with STI testing may still be hesitant to undergo HPV testing regardless of who takes the sample and the option of purchasing a self-sampling kit would not address socio-economic based barriers. While there is some evidence that HPV-based tests using certain self-sampling tests and tecniques have been found to have similar test accuracy as clinician-sampled tests [63] and may improve screening uptake in certain populations,[442] it is not guaranteed to improve screening uptake.

The clinical review highlighted early evidence on how self-sampling may increase participation to screening in underscreened population.[476] The potential economic value of introducing self-sampling was not further explored in the economic evaluation given it was unclear how self-sampling may differ from conventional approaches of physician-collected samples. In particular, variables important to consider include how the cost of screening and how the rates of participation may differ from a self-sampling approach compared to a physician-collected approach. A scenario analyses that evaluated the impact if patients do not return to their missed screen did find that more intensive screening approaches (i.e., increasing the frequency) and switching from primary HPV with cytology triage to primary cytology with HPV triage may be a cost-effective strategy in such instances.

High rate of positive tests

Concerns have been raised about the potential high rate of HPV-positive tests and how that will affect referrals to colposcopy, patient wait times, and the strain of increased demand on clinics and laboratories. If the increased sensitivity of HPV-based screening results in increased rates of cryotherapy, LEEP/LLETZ, or CKC with no reduction in cervical cancer mortality, this increased treatment rate may constitute overdiagnosis-driven overtreatment. As noted in the ethics analysis, the avoidance of unneeded radiation, chemotherapy, surgery and their consequences, as a result of overtreatment, is also important. This concern was corroborated in the economic evaluation as, keeping both the frequency and targeted age range identical, a higher lifetime average rate of colposcopy was noted in screening approaches that involved primary HPV with cytology triage compared to strategies based on cytology. However, when varying the frequency of screening, the analysis suggests that referral rates for colposcopy may not increase but could in fact reduce over a patient's lifetime especially if the frequency of screening was reduced for primary HPV with cytology triage to every five years with minimal impact on expected QALYs or in overall risks of developing cervical cancer.

Similar concerns have also been raised about high rates of diagnosis of the HPV infection itself, where no treatment or prevention (apart from abstinence) is possible. Patient harm can arise in the form of psychological distress and practical uncertainty when learning of a positive HPV status. As discussed in the Patients' Perspectives and Experiences section of this report, those who were aware of the relationship between HPV and cervical cancer tended to overestimate the causal relationship and equate a diagnosis of HPV with an inevitable diagnosis of cancer and the strong possibility of death from that cancer. This can cause undue fear and worry. Patients who have a positive diagnosis of high-risk oncogenic HPV face decisions about future sexual activity and partner notification with little clinical and public health guidance. Bodily harm can occur from unwarranted colposcopies and cervical treatments (with potential for iatrogenic harms to future pregnancy outcomes). It has been documented that harms to future pregnancies are a possible adverse event associated with the excision of CIN lesions.[39] The use of cold knife conization was associated with higher rates of cesarean section, low birth weight, pre-term birth, and perinatal mortality.[39] This technique of CIN lesion excision was more common before the introduction of LEEP, but is still sometimes used in practice. The results of a Norwegian cohort study demonstrated that individuals who underwent excisional CIN treatment before pregnancy were more likely to experience pre-term birth than those who had not

undergone excisional treatment before their pregnancies.[39] A systematic review that examined the impact of CIN treatment on fertility and early pregnancy found that there was no significant difference in fertility rates among those who had been treated for CIN and those who had not.[39] The authors did find an association between CIN treatment and ectopic pregnancy, late second term miscarriage, and elective termination of the pregnancy, though they determined the quality of the supporting evidence to be of low to very low quality.[39] Of note, the economic model was found to be sensitive if a one-year disutility was incorporated into patients at the time of receiving abnormal screening results. Despite appling small disutilities (> - 0.001) at the time of follow-up management, the sensitivity analysis found that primary cytology with HPV triage was associated with the highest expected QALYs and was economically attractive as this strategy resulted in the fewest number of repeat visits.

A potential for a higher rate of positive tests may also affect clinicians. From an increased number of call-backs to the potential for delivering unsettling news more often, a switch to HPV-based cervical cancer screening may require additional time and effort on the part of Canadian clinicians. The patient perspectives and experiences section discussed the importance of the patient-health care provider relationship and found that clear communication from the health care provider that emphasizes the importance of cervical cancer screening is likely to improve participation in a screening program.

As the presence and grade of cervical lesions needs to be confirmed based on colposcopy and biopsy, different programmatic screening strategies were associated with different numbers of patients referred to such procedures. Specifically, HPV-based strategies were associated with slightly higher numbers of colposcopy performed over an individual's lifetime due to its lower specificity and thus, more false-positive results compared to cytology. The burden of false positives can be reduced by lengthening screening intervals. As discussed in the ethics report, such approaches to non-maleficence (to reducing the harms of screening) have been interpreted by some members of the public and by some clinicians as motivated by economics and not by non-maleficence, contributing to over screening and a failure to reap the benefits of improvements in technology.

Screening age and interval

Adopting an appropriate screening age (when to start and when to end screening) and an appropriate interval (how often screening takes place) are important considerations with respect to any cervical cancer screening program particularly if there were to be a change to an HPV-based screening strategy. Less frequent screening may be perceived as a relief by patients who find the screening process uncomfortable, but it may also be perceived as a cut-back to health care services. Several studies document screening participant preferences for a screening modality which was less likely to require return visits for further testing.

Starting age and the frequency of programmatic screening are important factors to the effectiveness of the screening program and its costs. An earlier starting age and shorter interval between screening can lead to a higher number of screening tests during an individual's lifetime. The economic evaluation found that more frequent screening may improve the effectiveness of a screening program, if measured based on lowering one's lifetime risk of cervical cancer, but would also increase the burden and costs for participants, health care providers and governments. From a clinical perspective, as screening frequency increases, more cases of cervical cancer were averted as more pre-cancerous lesions were detected but this also resulted in more unnecessary colposcopies due to false positive screening results. The trend in terms of optimal start age to begin programmatic screening was less clear. Although a lower start age resulted in slightly more numbers of programmatic screening tests, it was not always clear whether this would translate to clinical benefits in terms of reducing the impact for repeat testing or averting cervical cancer. It is therefore important to consider the optimal length to screening given the trade-off between overscreening that may lead to unnecessary and costly procedures and the intended value of screening in preventing cervical cancer.

HPV vaccination

The introduction of the HPV vaccination is expected to reduce the incidence of HPV infection and, therefore, the incidence of CIN lesions and cervical cancer.[439] In 2013, the uptake of the first dose of HPV vaccine in Canada ranged from 47% in the Northwest Territories to 92.3% in Newfoundland and Labrador.[1] The Cancer Risk Management Model has projected a large reduction in the prevalence of HPV 16 and 18 if an overall vaccination rate

of 70% is achieved.[1] Ogilvie et al.[477] examined the rates of CIN in 15 to 22 year olds screened for cervical cancer in British Columbia before and after the introduction of the HPV vaccination program. Overall, there was a reduction in the rates of CIN2 and CIN2+ after the introduction of the vaccine.[477] The difference in the adjusted incidence rate ratio of CIN2+ decreased significantly after vaccination for participants between 15 and 17 years of age.[477] Vaccine uptake was less than 70% in the population of this study.[477]

While vaccination is expected to reduce HPV infection and the incidence of cancer, there is some evidence that increased vaccination rates may decrease the performance of cytology-based screening programs.[478] First predicted in modelling studies,[479,480] evidence from a population-based cohort study in Scotland[478] suggests despite test sensitivity and specificity remain constant, as disease prevalence decreases, so does the relevance of a population-based screening program. As vaccination rates increase and further cohorts of the vaccinated population enter screening age, this is an important consideration for screening programs.

However, as the association between disease prevalence and cytology test performance is not well understood, the economic evaluation assumed that the performance of cytology remained identical regardless of an individual's vaccination status. Rather, in the model, vaccination reduced the rate of acquiring an HPV infection and thereby, it was observed to lower the incidence of cervical cancer by nearly a half. Although the strategies on the efficiency frontier differed, the overall interpretation of the findings remained similar as primary HPV with cytology triage (every five years from ages 25 to 69) was found to be the cheapest strategy and was further the most likely cost-effective strategy below a willingness-to-pay threshold of $100,000 per QALY.

Disinvestment

Disinvestment is the elimination or reduction in use of a health technology (drug or device) or clinical intervention. Disinvestment may occur in response to new information that a technology or intervention is no longer as safe, clinically effective, or cost-effective as first thought, or that another technology would work better and provide more benefits in its place.

The concept of disinvestment can be applied to this implementation issue. If the HPV test is recommended as the primary test for cervical cancer screening, there would likely be disinvestment in the form of reduced volume of cytology testing. This was in fact observed in the economic analysis as the average number of cytologies performed were lower in screening strategies that involved either primary HPV screening or primary cytology with HPV triage (Table 28). Laboratories would be affected by this disinvestment decision, resulting in fewer cytotechnologist and cytopathologist positions needed to interpret results. However, some cytology staff would still be required for triage testing, validation, and quality control. Non-gynecologic cytology testing would continue to be needed and cytology staff would be needed for these tasks.

There could be a reduction in the number of laboratories if a centralized laboratory structure is adopted, or a reduction in the scope of work that smaller laboratories undertake.

There would also be disinvestment in the frequency and volume of screening. Resource use associated with sample collection would decrease if screening begins at a later age and if the screening interval is increased, because sample collection would occur less frequently.

Shortening the duration of screening and lengthening the interval of screening has proven to be controversial in many cancer screening programs. Such disinvestment has been recommended on the basis of a realization that screening is not an unmitigated benefit: with reductions in disease-specific mortality come burdens and harms of false positives, false negatives (which can lead to missed diagnoses of symptomatic presentation), and overdiagnosis. Some degree of "disinvestment" has been recommended in several jurisdictions for several cancer screening programs on the basis of non-maleficence. Such disinvestment may, however, be perceived as motivated by economic considerations even where this is not the case. Even where a change in policy achieves a population-level reduction of harms, this may come about by distributing unavoidable harms (of false positives and false negatives) differently. The anticipated concern with HPV-based screening is that this technology may improve screening outcomes for the population as a whole while worsening the performance of screening for participants in their 20s—this is why the onset of HPV-based screening is typically later, at age 30.

Generalizability of Findings

Limited information was identified regarding transgender, Indigenous, and older individuals who are eligible for screening as well as those who have never participated in cervical cancer screening. Particularly with respect to the effectiveness of the various tests, it is unclear whether or not the results generalize to those who are transgender and eligible for cervical cancer screening. The patient perspectives review identified that that transgender individuals who are eligible for cervical cancer screening often find the process emotionally difficult. The model of care for screening and subsequent medical follow-up may not be culturally appropriate for all, including for Indigenous people, however there was some clinical evidence that did include those who self-identified as First Nations People.

The economic evaluation was informed by Canadian data where possible. Although some data on the natural history of cervical cancer and incidence rate of HPV were based on data from the US, these inputs were expected to be widely generalizable to a Canadian setting given the similarities in risk profiles between these two countries. Where possible, sensitivity analyses were run with alternative data sources to understand the potential variability of the model's results. Furthermore, the economic results are, to the most part, founded on the described screening algorithms in terms of management and follow-up. However, variations to the clinical management of screening test results and the clinical practice pathways for colposcopy may result in different findings on cost-effectiveness of the screening strategies. This may need to be explored further in cases where significant differences exist.

The Canadian healthcare system is not homogenous. As healthcare is a provincial responsibility, the context for descision-making and implementation of programs is heterogeneous. While the implementation review sought to identify and gather information from stakeholders throuought the country, the various barriers and facilitators are not relevant to all jurisdictions.

Study Limitations

The body of literature identified in the review lacks data with respect to long term outcomes – particularly with respect to cancer death; the time frame for cancer outcomes, particularly in the context of screening, is not amenable to a clinical trial therefore, cancer outcomes and cancer death were not observed. The clinical literature was further limited based on the fact that the majority of the identified information was relevant HC2 tests.

The economic model had a number of limitations. Firstly, there was considerable uncertainty with respect to the longitudinal nature of HPV infection. Several simplifying assumptions had to be made in support of the model. Furthermore, unknown factors may contribute to an individual's risk of disease progression although the true relationship has not been well document. Therefore, the economic model could not capture how individual heterogeneity may impact one's risk of disease progression. For instance, increased sexual activity did not translate to an increased risk of HPV infection beyond impacting the age of onset of sexual activity and therefore, the duration of risk exposure to an HPV infection. Issues of adherence were modelled where possible to reflect real-world data. Although screening participation rate was age-specific, it was assumed identical in all strategies as there still uncertainty to whether participation rates in screening may differ between an HPV-based versus a cytology-based screening program. Adherence is further only one of the factors that may impact the outcome cervical cancer screening. Another important variation is how screening tests are used and interpreted. This may depend on clinical presentation and patient history. A microsimulation model was selected as the modelling approach in order to capture the recommendations on how screening tests should be interpreted although this remains a simplification as deviations from recommended clinical guidance would not be captured.

With respect to the patient experiences review, we have previously described the limitations of syntheses of qualitative research.[481] Qualitative research provides theoretical and contextual insights into the experiences of limited numbers of people in specific settings. Qualitative research findings are not intended to generalize directly to populations, although meta-synthesis across a number of qualitative studies builds an increasingly robust

understanding that is more likely to be transferable. While qualitative insights are robust and often enlightening for understanding experiences and planning services in other settings, the findings of the studies reviewed here—and of this synthesis—do not strictly generalize to the Canadian (or any specific) population. The findings are limited to the conditions included in the body of literature synthesized (i.e., cervical cancer screening). This evidence must be interpreted and applied carefully, in light of expertise and the experiences of the relevant community.

Our review did not provide the opportunity to collect primary data, or query participants about issues which may be important to their preferences and perspectives. Accordingly, our findings are limited to the research questions and data collection conducted by other authors. Absence of a particular topic or theme (e.g. overdiagnosis in cervical cancer screening) should not be interpreted to mean that issue is not important to women, or that it is not relevant to their experiences or perspectives. Rather, the issue should be considered unexplored. This is particularly important for issues that may be new or quickly evolving, such as HPV screening after HPV vaccination. HPV vaccination has been available at a population level in many Canadian jurisdictions for several years. Women vaccinated through this program will soon be eligible for cervical cancer screening. We did not find any empirical qualitative literature which discussed women's preferences and beliefs about HPV testing after HPV vaccination. This will be an important area to explore in future research.

There is limited existing ethical and legal analysis of the research questions in the specific context of HPV as a primary test for cervical cancer screening and in the context of cervical cancer screening in general. Hence this report blends the results of the systematic review with novel ethical analysis.

The PPE review focused on barriers and facilitators to uptake, which did not necessarily capture comprehensively three clusters of literature that we noted in the ethics review: research into information needs and patient preferences for screening modality; experiences of abnormal test results,[314] and preferences for the management of these.[316] We did not systematically review this literature but drew on it in the discussions of harms and information needs.

While important lessons can be learned from other countries, it is important to consider that Canada has differences in terms of geography, population distribution, political systems, and delivery of health care, so not all identified approaches to screening, testing, and the implementation of those may be relevant to the Canadian context. For example, while other countries adopting HPV-based screening have centralized their laboratory system, it is not clear if this is an appropriate strategy in Canada. Not all stakeholder groups in Canada are represented. Many individuals and organizations who we contacted did not reply or declined the invitation to participate in a consultation, so not all perspectives are included.

Directions for Future Research

Authors of one study[407] speculate that in 20 to 30 years, nearly all individuals entering screening age will be vaccinated and lesion prevalence will be so low that this will affect the overall efficiency of any cervical cancer screening program, irrespective of technology.[407] It may also render an HPV-based approach the logical approach for targeted screening. However, these authors may not have considered certain populations in Canada, including those who will never receive vaccination. Cervical cancer screening will likely need to be reassessed with consideration of population needs, including populations who tend to be at risk for healthcare inequities, and a re-examination of cost-effectiveness. Perhaps other targeted strategies may become more appropriate.

Additional high quality studies regarding the diagnostic test accuracy and utility of HPV tests other than the HC2 test would decrease the uncertainty regarding the accuracy and utility of those tests. Longitudinal studies that extend to periods long enough to measure cancer outcomes would also reduce uncertainty and be useful in validating the economic model's predictions. Rigorous trials examining self-sampling strategies may also reduce the remaining uncertainty regarding any differences between the diagnostic accuracy of self-sampled versus clinician sampled tests. If a meaningful difference exists in diagnostic accuracy between self-samples and clinician-obtained samples, incorporation into an economic evaluation may be suitable to characterize the tradeoff between clinical outcomes and differing costs.

Conclusions and Implications for Decision or Policy Making

Cervical cancer screening aims reduce the risk of disease and associated mortality by detecting and treating cancer precursors prior to progression to cervical cancer. Currently, the majority of those who undergo cervical cancer screening in Canada undergo screening through cytology testing, however the type of cytology and the approach to screening age and interval varies. A change to an HPV-based screening approach would represent a change for all jurisdictions and stakeholders throughout the screening process.

With respect to the clinical efficacy of HPV tests versus cytology testing (with and without triage), at the HPV threshold of 1pg/mL or 1 RLU, HC2 was found to be more sensitive and less specific than cytology at the threshold of ASCUS for the detection of CIN2+ and CIN3+. Multiplexed genotyping, Aptima, Cobas, and Confidence were also found to demonstrate higher sensitivity and lower specificity than either LBC or conventional cytology.

Acceptance of screening is important to any screening program. HPV testing allows for self-sampling, whereas cytology does not. In this review, the option of self-sampling was found to increase testing participation in most of those who were considered as non-attenders for cervical cancer screening – though this may not hold true for First Nations People. It remains unclear as to which strategy for the delivery of self-sampling kits would result in increased participation rates.

With respect to colposcopy referral, the higher sensitivity of HPV testing results in higher rates of referral to colposcopy when compared with cytology, particularly among those who are younger than 35. Harms and clinical utility were not well-reported in the studies included in the review.

Four HPV triage strategies (primary HPV testing with cytology triage, primary HPV testing followed by triage with partial genotyping for HPV 16/18, primary HPV testing followed by triage with sequential partial genotyping for HPV 16/18 followed by cytology to further triage those positive for HPV 16/18, primary HPV testing followed by co-testing triage [partial genotyping for HPV 16/18 and cytology triage]) were examined to determine both baseline and longitudinal DTA of the various HPV testing strategies. With respect to baseline DTA, there seemed to be a trade-off between the sensitivities and specificities of the four strategies. Due to study heterogeneity and insufficient numbers of primary studies in the triage strategies, there were no meta-analyses conducted for the triage strategies. With respect to longitudinal DTA, the sensitivity and specificity of the primary HPV testing followed by cytology remained high after one to four years of follow-up. The longitudinal DTAs of the other three triage strategies of interest were compared to baseline DTA. Primary HPV testing followed by co-testing with genotyping and cytology seemed to have higher referral rates to colposcopy , compared to primary HPV testing followed by either cytology alone, genotyping alone, or sequential genotyping and cytology.

Incorporating the clinical review's findings (HPV test is more sensitivite but less specific than cytology) switching the primary test from cytology to HPV testing and increasing the screening frequency could improve the effectiveness and decrease the cost of cervical cancer screening in Canada with limited harm in terms of higher risk of developing cervical cancer. Regardless of the population age or vaccination status, the model found that HPV tests with cytology triage, every five years, from the ages of 25 to 69 was the least costly and would be the mostly likely cost-effective strategy under a willingness-to-pay threshold of $100,000 per QALY.

Some of the strongest patient preferences would not be affected by a change in screening modality from cytology to HPV. For example, both require a cervical cell sample, and therefore the potential for embarrassment, pain, and logistical inconvenience of that procedure is unchanged. There is a reasonable body of literature on self-sampling strategies for HPV testing which indicate that it may be widely, but not universally accepted. The opportunity to choose self-sampling may encourage participation from those who would otherwise find the barriers of having a clinician take cervical cells to be a disincentive to screening participation. The importance of the relationship between

patient and health care provider will also continue to be important. Sensitive, clear communication from the health care provider that emphasizes the importance of cervical cancer screening is likely to improve participation.

Screening involves balancing the benefits of disease detection (beneficence) with harms and burdens of screening attendance, false positives, and overdiagnosis (non-maleficence). The clinical review provides evidence for how this balance will or may shift. The ethics review provides context and content for understanding the nature of these harms and benefits and the ethical values that involved in weighing them. There is no common agreement on the line between an acceptable and an unacceptable balance of harms and benefits in screening. The balance of those harms and benefits depends on patients and providers following guidelines intended to de-intensify screening (start later and extend intervals) and manage the intensity of treatment. There appears to be mixed, and largely speculative, views about the effects on equity of HPV as a primary screen. Some underscreened groups may be especially concerned about the possibility that HPV as a primary cervical cancer screening test will generate a positive STI test result for 3 to 4 out of 10 participants over a relevant time frame, and this may lower uptake; some groups may benefit from self-sampling as an outreach strategy targeted to those who experience barriers to clinical sampling.

The key implementation issue that emerged was that a switch to HPV-based screening would be a big operational and culture shift for clinicians, patients, and laboratories. If a switch occurs, good planning, funding, and coordination will be needed to make sure implementation runs smoothly. One of the main challenges is acceptance of the new screening strategy by patients and clinicians, and preventing a drop in screening participation rates. A different screening interval is a shift for all those involved. The other main challenge is the major change required to laboratory configuration, workflow, and human resourcing. There are several facilitators that can help with overcoming these barriers; for example: education, step-wise rollout, organized screening programs, good IT systems, and offering self-sampling. Many of the barriers and facilitators identified are not specific to HPV-based screening, but are common to cytology-based screening as well. Therefore, many of challenges that patients and providers face are not new, and there are already solutions in place or being developed for cytology-based screening that could be applied to HPV-based screening as well.

Vaccination for HPV and the rates of vaccination are an important consideration with respect to any future policy decision regarding cervical cancer screening programs. Although a switch to HPV-based screening has the potential to be disruptive and potentially not cost-effective in the short term, as highly vaccinated cohorts continue to enter the age for screening the performance of cytology-based screening programs will likely decrease, potentially rendering them ineffective.

Recent guidance from the AHRQ and the US Preventative Services Taskforce recommends different screening approaches for different age groups.[482] In addition to recommending a cytology based approach for younger cohorts and HPV based approaches for older cohorts, three and five year intervals are also recommended, depending on the screening approach.These recommendations are based on similar clinical evidence as the current review, though they do not take into consideration the economic consequences within the Canadian context or healthcare system. Regardless, similar strategies the may be appropriate, depending on willingness to pay.

Appendix 1: Literature Search Strategy

Clinical Database Search

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials January 2017 EBM Reviews - Cochrane Database of Systematic Reviews 2005 to Present EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016 Embase 1974 to Present Ovid MEDLINE 1946 to Present Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 24, 2017
Alerts:	Monthly search updates until project completion.
Study Types:	No filters used.
Limits:	Language limit: English- and French-language Date limit: 2002 - present Conference abstracts excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase, Cochrane, DARE)
.dm	Device manufacturer (Embase)
.dv	Device trade name (Embase)
/di	Diagnosis subheading (MEDLINE, Embase)
/ip	Isolation & purification subheading (MEDLINE)
/ge	Genetics subheading (MEDLINE)
ppez	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials
dare	Ovid database code; Database of Abstracts of Reviews of Effects
coch	Ovid database code; Cochrane Database of Systematic Reviews

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
1	Human Papillomavirus DNA Tests/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
2	DNA Probes, HPV/
3	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,kf,kw.
4	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
5	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
6	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf,kw.
7	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf,kw.
8	Papillomavirus Infections/di
9	or/1-8
10	Papillomaviridae/ip, ge or exp Alphapapillomavirus/ip, ge
11	Papillomavirus Infections/
12	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,kf,kw.
13	or/10-12
14	Molecular Diagnostic Techniques/
15	Nucleic Acid Amplification Techniques/
16	exp *Polymerase Chain Reaction/
17	DNA Methylation/
18	Genotyping Techniques/
19	exp Nucleic Acid Hybridization/
20	exp Nucleic Acid Probes/
21	(polymerase chain reaction or PCR or methylation or genotyping or hybridization or probe*).ti,kf,kw.
22	(molecular adj2 (screen* or diagnos*)).ti,ab,kf,kw.
23	or/14-22
24	13 and 23
25	(GenoArray or Geno-Array or Cobas or Aptima or Linear Array or LinearArray or RealTime or Hybrid Capture or HybridCapture or HC2 or HC 2 or HCII or HC II or Xpert or Amplicor or Inno-LiPa or InnoLiPa or PreTect or Pre-Tect or Euro-Array or EuroArray or OncoTect or Onco-Tect or OncoE6 or Quantivirus or Cervical Sampler or CervicalSampler or Delphi Screener or DelphiScreener or PapType or Anyplex or SoloPap or Solo-Pap or Onclarity).ti,ab,kf,kw.
26	(Digene or Roche or Hologic or Abbott or Quigen or Arbor Vita or Breakspear or DAAN Gene or DiaCarta or Fujirebio or Genera Biosystems or IncellDx or Seegene or Trovagene).ti,ab,kf,kw.
27	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kf,kw,hw.
28	(25 or 26) and 27
29	(Cervista or CINtec or CIN-tec or HPV28 or HPV-28 or PapilloCheck or Papillo-Check or careHPV).ti,ab,kf,kw.
30	28 or 29
31	Cervical Intraepithelial Neoplasia/
32	Uterine Cervical Neoplasms/
33	Uterine Cervical Dysplasia/
34	Atypical Squamous Cells of the Cervix/
35	Cervix Uteri/
36	Vaginal Smears/
37	(cervical or cervix or cervixes or cervico*).ti,kf,kw.
38	((cervical or cervix or cervixes or cervico*) adj5 (precancer* or cancer* or neoplas* or dysplas* or

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
	dyskaryos* or tumor* or tumour* or malignanc* or carcinoma* or adenocarcinoma* or lesion* or squamous or small cell or large cell)).ti,ab,kf,kw.
39	(atypical glandular cell* or AGC or AGUS).ti,ab,kf,kw.
40	(CIN or CINII* or CIN2* or CINIII* or CIN3* or SIL or HSIL or LSIL or ASCUS or AS-CUS).ti,ab,kf,kw.
41	((pap or papanicolaou or vagina* or cervical or cervix or cervixes or cervico*) adj3 (smear* or test* or swab* or scrap*)).ti,ab,kf,kw.
42	or/31-41
43	Mass Screening/
44	"Direct-To-Consumer Screening and Testing"/
45	Early Detection of Cancer/
46	Triage/
47	(screen* or triage* or triaging or reflex).ti,ab,kf,kw.
48	(detect* or test* or diagnos* or identify* or identifi* or predict*).ti,kf,kw.
49	or/43-48
50	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (screen* or triage* or triaging or reflex)).ti,kf,kw.
51	((HPV* or hrHPV*) adj3 (screen* or triage* or triaging or reflex)).ab.
52	((Papillomavirus* or Papilloma Virus*) adj5 (screen* or triage* or triaging or reflex)).ab.
53	or/50-52
54	(9 or 24) and 42 and 49
55	30 and 49
56	42 and 53
57	or/54-56
58	"Sensitivity and Specificity"/
59	"Limit of Detection"/
60	ROC Curve/
61	Diagnostic Errors/
62	False Negative Reactions/
63	False Positive Reactions/
64	"Predictive Value of Tests"/
65	diagnostic accuracy/
66	receiver operating characteristic/
67	exp diagnostic error/
68	predictive value/
69	diagnostic value/
70	diagnostic test accuracy study/
71	"Diagnostic Uses of Chemicals"/
72	(Sensitivity or specificity).ti,ab,kw,kf.
73	(false adj2 (positive* or negative*)).ti,ab,kw,kf.
74	((positive* or negative*) adj2 (predictive or likelihood)).ti,ab,kw,kf.
75	(predictive valu* or validit*).ti,ab,kw,kf.
76	(receiver adj2 operating).ti,ab,kw,kf.
77	(ROC or AUROC* or SROC or HSROC).ti,ab,kw,kf.
78	((under or over) adj2 curve*).ti,ab,kw,kf.
79	(detect* adj2 (abilit* or rate*)).ti,ab,kw,kf.

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
80	((gold* or reference*) adj2 standard*).ti,ab,kw,kf.
81	((test or diagnos*) adj2 (perform* or accura* or value* or "use" or useful or usefulness or utilit* or effica* or compar* or evaluat*)).ti,ab,kw,kf.
82	or/58-80
83	(9 or 24) and 42 and 82
84	(30 or 53) and 82
85	83 or 84
86	57 or 85
87	86 use ppez
88	86 use cctr
89	9 or 24 or 30 or 53
90	89 use dare
91	89 use coch
92	Human papillomavirus DNA test/
93	exp nucleic acid probe/ and (HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kw,hw.
94	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,kw.
95	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
96	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
97	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kw.
98	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kw.
99	papillomavirus infection/di
100	or/92-99
101	Papillomaviridae/
102	exp Alphapapillomavirus/
103	papillomavirus infection/
104	Wart virus/
105	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,kw.
106	or/101-105
107	molecular diagnosis/
108	exp *polymerase chain reaction/
109	DNA Methylation/
110	Genotyping Technique/
111	nucleic acid hybridization/
112	exp nucleic acid probe/
113	nucleic acid amplification/
114	(polymerase chain reaction or PCR or methylation or genotyping or hybridization or probe*).ti,kw.
115	(molecular adj2 (screen* or diagnos*)).ti,ab,kw.
116	or/107-115
117	106 and 116
118	(GenoArray or Geno-Array or Cobas or Aptima or Linear Array or LinearArray or RealTime or Hybrid Capture or HybridCapture or HC2 or HC 2 or HCII or HC II or Xpert or Amplicor or Inno-LiPa or InnoLiPa or PreTect or Pre-Tect or Euro-Array or EuroArray or OncoTect or Onco-Tect or OncoE6 or

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
	Quantivirus or Cervical Sampler or CervicalSampler or Delphi Screener or DelphiScreener or PapType or Anyplex or SoloPap or Solo-Pap or Onclarity).ti,ab,kw,dv,hw.
119	(Digene or Roche or Hologic or Abbott or Quigen or Arbor Vita or Breakspear or DAAN Gene or DiaCarta or Fujirebio or Genera Biosystems or IncellDx or Seegene or Trovagene).ti,ab,kw,dm.
120	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kw,hw.
121	(118 or 119) and 120
122	(Cervista or CINtec or CIN-tec or HPV28 or HPV-28 or PapilloCheck or Papillo-Check or careHPV).ti,ab,kw,dv,hw.
123	121 or 122
124	uterine cervix disease/
125	uterine cervix dysplasia/
126	squamous intraepithelial lesion of the cervix/
127	uterine cervix tumor/
128	uterine cervix cancer/
129	uterine cervix carcinoma/
130	uterine cervix carcinoma in situ/
131	uterine cervix cytology/
132	exp uterine cervix/
133	vagina smear/
134	(cervical or cervix or cervixes or cervico*).ti,kw.
135	((cervical or cervix or cervixes or cervico*) adj5 (precancer* or cancer* or neoplas* or dysplas* or dyskaryos* or tumor* or tumour* or malignanc* or carcinoma* or adenocarcinoma* or lesion* or squamous or small cell or large cell)).ti,ab,kw.
136	(atypical glandular cell* or AGC or AGUS).ti,ab,kw.
137	(CIN or CINII* or CIN2* or CINIII* or CIN3* or SIL or HSIL or LSIL or ASCUS or AS-CUS).ti,ab,kw.
138	((pap or papanicolaou or vagina* or cervical or cervix or cervixes or cervico*) adj3 (smear* or test* or swab* or scrap*)).ti,ab,kw.
139	or/124-138
140	screening/
141	mass screening/
142	cancer screening/
143	screening test/
144	DNA screening/
145	early cancer diagnosis/
146	(screen* or triage* or triaging or reflex).ti,ab,kw.
147	(detect* or test* or diagnos* or identify* or identifi* or predict*).ti,kw.
148	or/140-147
149	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (screen* or triage* or triaging or reflex)).ti,kw.
150	((HPV* or hrHPV*) adj3 (screen* or triage* or triaging or reflex)).ab
151	((Papillomavirus* or Papilloma Virus*) adj5 (screen* or triage* or triaging or reflex)).ab
152	or/149-151
153	(100 or 117) and 139 and 148
154	123 and 148
155	139 and 152
156	153 or 154 or 155

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
157	(100 or 117) and 139 and 82
158	123 and 82
159	152 and 82
160	157 or 158 or 159
161	156 or 160
162	161 use oemezd
163	162 not conference abstract.pt.
164	87 or 88 or 90 or 91 or 163
165	limit 164 to (english or french) [Limit not valid in CDSR,DARE; records were retained]
166	limit 165 to yr="2002 -Current" [Limit not valid in DARE; records were retained]
167	limit 166 to yr="2002 - 2010" [Limit not valid in DARE; records were retained]
168	remove duplicates from 167
169	166
170	limit 169 to yr="2011 - 2014" [Limit not valid in DARE; records were retained]
171	remove duplicates from 170
172	169
173	limit 172 to yr="2015 -Current" [Limit not valid in DARE; records were retained]
174	remove duplicates from 173
175	168 or 171 or 174

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, and limits used as per MEDLINE search, with appropriate syntax used.

Patient Perspectives and Experience Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE 1946 to Present Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations PsycINFO 1967 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	HPV testing search: January 20, 2017 Cervical cancer screening search: February 6, 2017
Alerts:	Monthly search updates until project completion.
Study Types:	Qualitative literature
Limits:	Language limit: English- and French-language Conference abstracts excluded HPV testing search: No date limits Cervical cancer screening search: 2002-Present

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
$	A truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.mp	Multi-purpose; searches several fields at once including Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields
.af	All fields
.tw	Textword; searches all of the fields in a database which contain text words and which are appropriate for a subject search
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)

SYNTAX GUIDE	
.id	Key concepts (PsycINFO)
.pt	Publication type
.dm	Device manufacturer (Embase)
.dv	Device trade name (Embase)
/di	Diagnosis subheading (MEDLINE, Embase)
/ip	Isolation & purification subheading (MEDLINE)
/ge	Genetics subheading (MEDLINE)
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
psyb	Ovid database code; PsycINFO 1967 to present

5305

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
Search #1: HPV Testing	
1	Human Papillomavirus DNA Tests/
2	DNA Probes, HPV/
3	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,kf.
4	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
5	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
6	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf.
7	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf.
8	Papillomavirus Infections/di
9	or/1-8

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
10	Papillomaviridae/ip, ge or exp Alphapapillomavirus/ip, ge
11	Papillomavirus Infections/
12	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,kf.
13	or/10-12
14	Molecular Diagnostic Techniques/
15	Nucleic Acid Amplification Techniques/
16	exp *Polymerase Chain Reaction/
17	DNA Methylation/
18	Genotyping Techniques/
19	exp Nucleic Acid Hybridization/
20	exp Nucleic Acid Probes/
21	(polymerase chain reaction or PCR or methylation or genotyping or hybridization or probe*).ti,kf.
22	(molecular adj2 (screen* or diagnos*)).ti,ab,kf.
23	or/14-22
24	13 and 23
25	(GenoArray or Geno-Array or Cobas or Aptima or Linear Array or LinearArray or RealTime or Hybrid Capture or HybridCapture or HC2 or HC 2 or HCII or HC II or Xpert or Amplicor or Inno-LiPa or InnoLiPa or PreTect or Pre-Tect or Euro-Array or EuroArray or OncoTect or Onco-Tect or OncoE6 or Quantivirus or Cervical Sampler or CervicalSampler or Delphi Screener or DelphiScreener or PapType or Anyplex or SoloPap or Solo-Pap or Onclarity).ti,ab,kf.
26	(Digene or Roche or Hologic or Abbott or Quigen or Arbor Vita or Breakspear or DAAN Gene or DiaCarta or Fujirebio or Genera Biosystems or IncellDx or Seegene or Trovagene).ti,ab,kf.
27	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kf,hw.
28	(25 or 26) and 27
29	(Cervista or CINtec or CIN-tec or HPV28 or HPV-28 or PapilloCheck or Papillo-Check or careHPV).ti,ab,kf.
30	28 or 29
31	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ti,kf.
32	((HPV* or hrHPV*) adj3 (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ab.
33	((Papillomavirus* or Papilloma Virus*) adj5 (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ab.
34	or/31-33
35	9 or 24 or 30 or 34
36	35 use ppez
37	Human papillomavirus DNA test/
38	exp nucleic acid probe/ and (HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kw,hw.
39	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,kw.
40	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
41	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
42	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kw.
43	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kw.

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
44	papillomavirus infection/di
45	or/37-44
46	Papillomaviridae/
47	exp Alphapapillomavirus/
48	papillomavirus infection/
49	wart virus/
50	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,kw.
51	or/46-50
52	molecular diagnosis/
53	exp *polymerase chain reaction/
54	DNA Methylation/
55	Genotyping Technique/
56	nucleic acid hybridization/
57	exp nucleic acid probe/
58	nucleic acid amplification/
59	(polymerase chain reaction or PCR or methylation or genotyping or hybridization or probe*).ti,kw.
60	(molecular adj2 (screen* or diagnos*)).ti,ab,kw.
61	or/52-60
62	51 and 61
63	(GenoArray or Geno-Array or Cobas or Aptima or Linear Array or LinearArray or RealTime or Hybrid Capture or HybridCapture or HC2 or HC 2 or HCII or HC II or Xpert or Amplicor or Inno-LiPa or InnoLiPa or PreTect or Pre-Tect or Euro-Array or EuroArray or OncoTect or Onco-Tect or OncoE6 or Quantivirus or Cervical Sampler or CervicalSampler or Delphi Screener or DelphiScreener or PapType or Anyplex or SoloPap or Solo-Pap or Onclarity).ti,ab,kw,dv,hw.
64	(Digene or Roche or Hologic or Abbott or Quigen or Arbor Vita or Breakspear or DAAN Gene or DiaCarta or Fujirebio or Genera Biosystems or IncellDx or Seegene or Trovagene).ti,ab,kw,dm.
65	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kw,hw.
66	(63 or 64) and 65
67	(Cervista or CINtec or CIN-tec or HPV28 or HPV-28 or PapilloCheck or Papillo-Check or careHPV).ti,ab,kw,dv,hw.
68	66 or 67
69	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ti,kw.
70	((HPV* or hrHPV*) adj3 (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ab.
71	((Papillomavirus* or Papilloma Virus*) adj5 (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ab.
72	or/69-71
73	45 or 62 or 66 or 72
74	73 use oemezd
75	Human Papillomavirus/
76	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,id.
77	or/75-76
78	exp Nucleic Acids/ or Cancer Screening/ or Diagnosis/ or Genotypes/
79	(screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*).ti,ab,id.
80	(polymerase chain reaction or PCR or methylation or genotyping or hybridization or probe*).ti,ab,id.

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
81	(GenoArray or Geno-Array or Cobas or Aptima or Linear Array or LinearArray or RealTime or Hybrid Capture or HybridCapture or HC2 or HC 2 or HCII or HC II or Xpert or Amplicor or Inno-LiPa or InnoLiPa or PreTect or Pre-Tect or Euro-Array or EuroArray or OncoTect or Onco-Tect or OncoE6 or Quantivirus or Cervical Sampler or CervicalSampler or Delphi Screener or DelphiScreener or PapType or Anyplex or SoloPap or Solo-Pap or Onclarity).ti,ab,id.
82	(Digene or Roche or Hologic or Abbott or Quigen or Arbor Vita or Breakspear or DAAN Gene or DiaCarta or Fujirebio or Genera Biosystems or IncellDx or Seegene or Trovagene).ti,ab,id.
83	or/78-82
84	77 and 83
85	(Cervista or CINtec or CIN-tec or HPV28 or HPV-28 or PapilloCheck or Papillo-Check or careHPV).ti,ab,id.
86	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,id.
87	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
88	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
89	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,id.
90	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,id.
91	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) adj3 diagnos*).ti,ab,id.
92	or/85-91
93	84 or 92
94	93 use psyb
Qualitative Filter	
95	Qualitative Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or Narration/ or Nursing Methodology Research/
96	95 use ppez
97	qualitative research/ or qualitative analysis/ or exp interview/ or nursing methodology research/ or narrative/ or storytelling/
98	97 use oemezd
99	Qualitative research/ or Interviews/ or Storytelling/
100	99 use psyb
101	interview$.mp.
102	(theme$ or thematic).mp.
103	qualitative.af.
104	questionnaire$.mp.
105	ethnological research.mp.
106	ethnograph$.mp.
107	ethnonursing.af.
108	phenomenol$.af.
109	(grounded adj (theor$ or study or studies or research or analys?s)).af.
110	(life stor$ or women* stor$).mp.
111	(emic or etic or hermeneutic$ or heuristic$ or semiotic$).af. or (data adj1 saturat$).tw. or participant observ$.tw.
112	(social construct$ or postmodern$ or post-structural$ or post structural$ or poststructural$ or post modern$ or post-modern$ or feminis$).mp.
113	(action research or cooperative inquir$ or co operative inquir$ or co-operative inquir$).mp.

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
114	(humanistic or existential or experiential or paradigm$).mp.
115	(field adj (study or studies or research)).tw.
116	human science.tw.
117	biographical method.tw.
118	theoretical sampl$.af.
119	((purpos$ adj4 sampl$) or (focus adj group$)).af.
120	(account or accounts or unstructured or open-ended or open ended or text$ or narrative$).mp.
121	(life world or life-world or conversation analys?s or personal experience$ or theoretical saturation).mp.
122	((lived or life) adj experience$).mp.
123	cluster sampl$.mp.
124	observational method$.af.
125	content analysis.af.
126	(constant adj (comparative or comparison)).af.
127	((discourse$ or discurs$) adj3 analys?s).tw.
128	narrative analys?s.af.
129	heidegger$.tw.
130	colaizzi$.tw.
131	spiegelberg$.tw.
132	(van adj manen$).tw.
133	(van adj kaam$).tw.
134	(merleau adj ponty$).tw.
135	husserl$.tw.
136	foucault$.tw.
137	(corbin$ adj2 strauss$).tw.
138	glaser$.tw.
139	or/96,98,100-138
140	36 or 74 or 94
141	139 and 140
142	141 not conference abstract.pt.
143	limit 142 to (english or french)
144	remove duplicates from 143 **[Results for Search #1: HPV Testing]**
Search #2: Cervical Cancer Screening	
145	Mass Screening/
146	"Direct-To-Consumer Screening and Testing"/
147	Early Detection of Cancer/
148	(screen* or triage* or triaging or smear* or test*).ti,kf.
149	or/145-148
150	Cervical Intraepithelial Neoplasia/
151	Uterine Cervical Neoplasms/
152	Uterine Cervical Dysplasia/
153	Atypical Squamous Cells of the Cervix/
154	Vaginal Smears/
155	Papanicolaou Test/

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
156	(cervical or cervix or cervixes or cervico* or pap or papanicolaou or vagina*).ti,kf.
157	or/150-156
158	149 and 157
159	((pap or papanicolaou or cervical or cervix or cervixes or cervico*) adj5 (screen* or triage* or triaging or smear* or test*)).ab.
160	158 or 159
161	160 use ppez
162	uterine cervix disease/
163	uterine cervix dysplasia/
164	squamous intraepithelial lesion of the cervix/
165	uterine cervix tumor/
166	uterine cervix carcinoma/
167	uterine cervix carcinoma in situ/
168	uterine cervix cytology/
169	exp uterine cervix/
170	vagina smear/
171	Papanicolaou test/
172	(cervical or cervix or cervixes or cervico* or pap or papanicolaou or vagina*).ti,kw.
173	or/162-172
174	screening/
175	mass screening/
176	cancer screening/
177	screening test/
178	DNA screening/
179	early cancer diagnosis/
180	(screen* or triage* or triaging or smear* or test*).ti,kf.
181	or/174-180
182	173 and 181
183	((pap or papanicolaou or cervical or cervix or cervixes or cervico*) adj5 (screen* or triage* or triaging or smear* or test*)).ab.
184	182 or 183
185	184 use oemezd
186	((cervical or cervix or cervixes or cervico* or pap or papanicolaou or vagina*) and (screen* or triage* or triaging or smear* or test*)).ti,id.
187	((pap or papanicolaou or cervical or cervix or cervixes or cervico*) adj5 (screen* or triage* or triaging or smear* or test*)).ab.
188	186 or 187
189	188 use psyb
190	161 or 185 or 189
191	139 and 190
192	191 not 141
193	192 not conference abstract.pt.

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
194	limit 193 to (english or french)
195	limit 194 to yr="2002 -Current"
196	remove duplicates from 195 **[duplicates removed from search #1]**

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Same keywords, and limits used as per MEDLINE search. Syntax adjusted for EBSCO platform. MEDLINE records excluded.
Scopus	Same keywords and limits used as per MEDLINE search, with appropriate syntax used. Limited to subject areas: Social Sciences, Multidisciplinary, Psychology, Arts & Humanities.

Ethics Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE 1946 to Present Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations PsycINFO 1967 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	HPV testing search: February 9, 2017 Cervical cancer screening search: March 3, 2017
Alerts:	Monthly search updates until project completion.
Study Types:	No study design filters used.
Limits:	Language limit: English- and French-language
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
SYNTAX GUIDE	
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.id	Key concepts (PsycINFO)
.fs	Floating sub-heading
.jw	Journal word
ppez	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
psyb	PsycINFO database code; PsycINFO 1967 to February Week 1 2017

5309

MULTI-DATABASE STRATEGY	
#	**Ethics Database Search Strategy**
Search #1: HPV Testing	
1	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ti,kf.
2	((HPV* or hrHPV*) adj3 (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ab.
3	((Papillomavirus* or Papilloma Virus*) adj5 (screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*)).ab.
4	Human Papillomavirus DNA Tests/
5	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,kf.
6	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
7	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
8	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf.
9	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf.
10	or/1-9
11	10 use ppez
12	Human Papillomavirus/
13	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,id.
14	or/12-13
15	exp Nucleic Acids/ or Cancer Screening/ or Diagnosis/ or Genotypes/
16	(screen* or triage* or triaging or reflex or self-sampl* or selfsampl* or self-collect* or selfcollect*).ti,ab,id.
17	or/15-16
18	14 and 17
19	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,id.
20	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
21	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
22	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,id.
23	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,id.
24	or/18-23
25	24 use psyb
26	11 or 25
Ethics, Legal, Psychosocial Filter	
27	exp Ethics/
28	exp Privacy/
29	exp Jurisprudence/
30	exp Morals/
31	Paternalism/
32	exp Prejudice/
33	Social Values/
34	Social Norms/

MULTI-DATABASE STRATEGY	
#	**Ethics Database Search Strategy**
35	Stereotyping/
36	Social Stigma/
37	exp Geography, Medical/
38	Medically Underserved Area/
39	Health Services Accessibility/
40	Health Equity/
41	Healthcare Disparities/
42	Medical Overuse/
43	exp Disclosure/
44	exp Human Rights/
45	Coercion/
46	exp Mandatory Programs/
47	exp Social Problems/
48	"Legislation & Jurisprudence".fs.
49	ethics.fs.
50	or/27-49 use ppez
51	exp ethics/
52	exp "law (government)"/
53	privacy/
54	exp social influences/
55	morality/
56	or/51-55
57	56 use psyb
58	((healthcare or health care or nonclinical or community based or public health or preventive care) adj (access or deliver* or distribution* or system*)).ti,kf,id.
59	(ethic or ethics or ethical or moral or morals or bioethic*).ti,ab,hw,kf,jw,id.
60	(legal* or liabilit* or litigation* or constitutional or justice or law or laws or jurisprudence or complicit*).ti,ab,hw,kf,jw,id.
61	(lawsuit* or lawyer* or lawmaker*).ti,ab,kf,id.
62	human right*.ti,ab,kf,id.
63	civil right*.ti,ab,kf,id.
64	(prejudice* or stigma or stigmas or stigmatization or stigmatize or stigmatise or stigmatisation or stereotyp*).ti,ab,kf,id.
65	(inequalit* or equalit* or inequit* or equit* or disparit* or fair or fairness or unfair or unfairness).ti,ab,kf,id.
66	(distributive justice or precautionary principle or solidarity).ti,ab,kf,id.
67	((care or treatment) adj2 (duty or obligat*)).ti,ab,kf,id.
68	(social* adj (responsib* or obligat* or justice)).ti,ab,kf,id.
69	(psychological or psychosocial or socioeconomic or socio-economic or psychosexual).ti,kf,id.
70	((social or psychological or psychosocial or socioeconomic or socio-economic or psychosexual) adj2 (impact* or burden*)).ti,ab,kf,id.
71	(communitarian* or beneficence or nonmaleficence or maleficence or accountability).ti,ab,kf,id.
72	(harm or harms or harming or harmful).ti,ab,kf,id.
73	(privacy or confidential*).ti,ab,kf,id.
74	((informed or presumed or shared) adj2 (consent or choice or decision making)).ti,ab,kf,id.
75	(coercion or persuasion or information provision).ti,ab,kf,id.

MULTI-DATABASE STRATEGY	
#	**Ethics Database Search Strategy**
76	((conflict or financial or industry) adj3 interest*).ti,ab,kf,id.
77	(industry adj3 (funding or involvement or sponsor*)).ti,ab,kf,id.
78	autonomy.ti,ab,hw,kf,id.
79	transparency.ti,ab,kf,id.
80	(overdiagnos* or over-diagnos* or underscreen* or under-screen* or overtreat* or over-treat*).ti,ab,kf,id.
81	underserved.ti,ab,kf,id.
82	or/50,57-81
83	26 and 82
84	limit 83 to (english or french)
85	remove duplicates from 84 **[Results for Search #1: HPV Testing]**
Search #2: Cervical Cancer Screening	
86	Cervical Intraepithelial Neoplasia/
87	Uterine Cervical Neoplasms/
88	Uterine Cervical Dysplasia/
89	Atypical Squamous Cells of the Cervix/
90	Vaginal Smears/
91	Papanicolaou Test/
92	(cervical or cervix or cervixes or cervico* or pap or papanicolaou or vagina*).ti,kf.
93	or/86-92
94	Mass Screening/
95	"Direct-To-Consumer Screening and Testing"/
96	Early Detection of Cancer/
97	Triage/
98	(screen* or triage* or triaging or smear* or test* or cytology).ti,kf.
99	or/94-98
100	93 and 99
101	((pap or papanicolaou or cervical or cervix or cervixes or cervico*) adj3 (screen* or triage* or triaging or smear* or test* or cytology)).ab.
102	100 or 101
103	102 use ppez
104	((cervical or cervix or cervixes or cervico* or pap or papanicolaou or vagina*) and (screen* or triage* or triaging or smear* or test* or cytology)).ti,id.
105	((pap or papanicolaou or cervical or cervix or cervixes or cervico*) adj3 (screen* or triage* or triaging or smear* or test* or cytology)).ab.
106	104 or 105
107	106 use psyb
108	103 or 107
109	82 and 108
110	limit 109 to (english or french)
111	remove duplicates from 110 **[Results for Search #2: Cervical Cancer Screening]**

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Same keywords, and limits used as per MEDLINE search. Syntax adjusted for EBSCO platform. MEDLINE records excluded.

5322

Implementation Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE 1946 to Present Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations Embase 1974 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 2017
Alerts:	Monthly search updates until project completion.
Study Types:	No study design filters used.
Limits:	Language limit: English- and French-language Date limit: 2002 - Present Conference abstracts excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword field (Embase)
/di	Diagnosis subheading (MEDLINE, Embase)
.jn	Journal name
.jw	Journal word (MEDLINE)
.jx	Journal word (Embase)
.pt	Publication type
ppez	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
1	Human Papillomavirus DNA Tests/
2	DNA Probes, HPV/
3	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,kf,kw.
4	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
5	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
	amplification)).ab.
6	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf,kw.
7	((((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kf,kw.
8	Papillomavirus Infections/di
9	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (screen* or triage* or triaging or reflex)).ti,kf,kw.
10	((HPV* or hrHPV*) adj3 (screen* or triage* or triaging or reflex)).ab.
11	((Papillomavirus* or Papilloma Virus*) adj5 (screen* or triage* or triaging or reflex)).ab.
12	Cervical Intraepithelial Neoplasia/
13	Uterine Cervical Neoplasms/
14	Uterine Cervical Dysplasia/
15	Atypical Squamous Cells of the Cervix/
16	Cervix Uteri/
17	Vaginal Smears/
18	Papanicolaou Test/
19	(cervical or cervix or cervixes or cervico* or pap or papanicolaou).ti,kf,kw.
20	((cervical or cervix or cervixes or cervico*) adj3 (precancer* or cancer* or neoplas* or dysplas* or dyskaryos* or tumor* or tumour* or malignanc* or carcinoma* or adenocarcinoma* or lesion* or squamous or small cell or large cell)).ti,ab,kf,kw.
21	(atypical glandular cell* or AGC or AGUS).ti,ab,kf,kw.
22	(CIN or CINII* or CIN2* or CINIII* or CIN3* or SIL or HSIL or LSIL or ASCUS or AS-CUS).ti,ab,kf,kw.
23	or/12-22
24	Mass Screening/
25	"Direct-To-Consumer Screening and Testing"/
26	Early Detection of Cancer/
27	Triage/
28	(screen* or triage* or triaging or reflex).ti,ab,kf,kw.
29	(detect* or test* or diagnos* or identify* or identifi* or predict* or cytology).ti,kf,kw.
30	or/24-29
31	23 and 30
32	((pap or papanicolaou or cervical or cervix or cervixes or cervico*) adj2 (screen* or triage* or triaging or smear* or test* or cytology)).ab.
33	or/1-11,31-32
34	Policy/ or Delivery of Health Care/ or Health Policy/ or Health Services Accessibility/
35	(implementation or implementer* or barrier* or facilitat* or enabler*).ti,ab,kf.
36	implementation science.jn.
37	(adopt* or sustainability or accept* or access* or appropriat* or feasibility or uptake).ti,ab,kf.
38	(training or trained or train or travel* or cultur* or socio* or social* or society or determinants or education* or communication or participation or wait time*).ti,ab,kf.
39	(geography or geographic or transportation or reimbursement or staff or staffing or workforce or workflow* or equipment or incentive*).ti,ab,kf.
40	(physician* adj2 (knowledge or perspective*)).ti,ab,kf.
41	Decision Support Techniques/ or (decision rule* or decision support or decision aid* or decision analys?s or decision model*).ti,ab,kf.

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
42	(policy or policies or health services or health care services or healthcare services).ti,ab,kf.
43	Laboratory Personnel/ or Laboratories/
44	(laboratory assistant* or laboratory scientist* or laboratory technician* or laboratory professional* or cytologist*).ti,ab,kf.
45	(referral* adj2 rate*).ti,ab,kf.
46	(screening adj2 rate*).ti,ab,kf.
47	(self-test* or self-sampl* or home-test*).ti,ab,kf.
48	(physician* adj2 visit*).ti,ab,kf.
49	or/34-48
50	33 and 49
51	50 use ppez
52	Human papillomavirus DNA test/
53	exp nucleic acid probe/ and (HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kw,hw.
54	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (test* or assay* or genotyping or typing or detection or amplification)).ti,kw.
55	((HPV* or hrHPV*) adj3 (test* or assay* or genotyping or typing or detection or amplification)).ab.
56	((Papillomavirus* or Papilloma Virus*) adj5 (test* or assay* or genotyping or typing or detection or amplification)).ab.
57	(((HPV* or hrHPV*) adj3 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kw.
58	(((Papillomavirus* or Papilloma Virus*) adj5 (deoxyribonucleic or ribonucleic or nucleic or DNA or RNA or mRNA)) and (test* or assay* or genotyping or typing or detection or amplification)).ti,ab,kw.
59	papillomavirus infection/di
60	((HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*) and (screen* or triage* or triaging or reflex)).ti,kw.
61	((HPV* or hrHPV*) adj3 (screen* or triage* or triaging or reflex)).ab.
62	((Papillomavirus* or Papilloma Virus*) adj5 (screen* or triage* or triaging or reflex)).ab.
63	uterine cervix disease/
64	uterine cervix dysplasia/
65	squamous intraepithelial lesion of the cervix/
66	uterine cervix tumor/
67	uterine cervix cancer/
68	uterine cervix carcinoma/
69	uterine cervix cytology/
70	exp uterine cervix/
71	vagina smear/
72	Papanicolaou test/
73	(cervical or cervix or cervixes or cervico* or pap or papanicolaou).ti,kw.
74	((cervical or cervix or cervixes or cervico*) adj5 (precancer* or cancer* or neoplas* or dysplas* or dyskaryos* or tumor* or tumour* or malignanc* or carcinoma* or adenocarcinoma* or lesion* or squamous or small cell or large cell)).ti,ab,kw.
75	(atypical glandular cell* or AGC or AGUS).ti,ab,kw.
76	(CIN or CINII* or CIN2* or CINIII* or CIN3* or SIL or HSIL or LSIL or ASCUS or AS-CUS).ti,ab,kw.
77	or/63-76
78	screening/
79	mass screening/

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
80	cancer screening/
81	screening test/
82	DNA screening/
83	early cancer diagnosis/
84	(screen* or triage* or triaging or reflex).ti,ab,kw.
85	(detect* or test* or diagnos* or identify* or identifi* or predict* or cytology).ti,kw.
86	or/78-85
87	77 and 86
88	((pap or papanicolaou or cervical or cervix or cervixes or cervico*) adj2 (screen* or triage* or triaging or smear* or test* or cytology)).ab.
89	or/52-62,87-88
90	health care policy/ or policy/ or health care delivery/
91	(implementation or implementer* or barrier* or facilitat* or enabler*).ti,ab,kw.
92	(adopt* or sustainability or accept* or access* or appropriat* or feasibility or uptake).ti,ab,kw.
93	(training or trained or train or travel* or cultur* or socio* or social* or society or determinants or education* or communication or participation or wait time*).ti,ab,kw.
94	(geography or geographic or transportation or reimbursement or staff or staffing or workforce or workflow* or equipment or incentive*).ti,ab,kw.
95	(physician* adj2 (knowledge or perspective*)).ti,ab,kw.
96	(policy or policies or health services or health care services or healthcare services).ti,ab,kw.
97	Decision Making/ or (decision rule* or decision support or decision aid* or decision analys?s or decision model*).ti,ab,kw.
98	laboratory personnel/ or laboratory/
99	(laboratory assistant* or laboratory scientist* or laboratory technician* or laboratory professional* or cytologist*).ti,ab,kw.
100	(referral* adj2 rate*).ti,ab,kw.
101	(screening adj2 rate*).ti,ab,kw.
102	(self-test* or self-sampl* or home-test*).ti,ab,kw.
103	(physician* adj2 visit*).ti,ab,kw.
104	or/90-100
105	89 and 104
106	89 use oemezd
107	51 or 106
108	exp Canada/
109	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).ti,ab,kf,kw,hw.
110	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).jw,jx.
111	or/108-110
112	107 and 111
113	112 not conference abstract.pt.
114	limit 113 to yr="2002 -Current"
115	limit 114 to (english or french)

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
116	remove duplicates from 115

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Same keywords and limits used as per MEDLINE search. Syntax adjusted for EBSCO platform. MEDLINE records excluded.

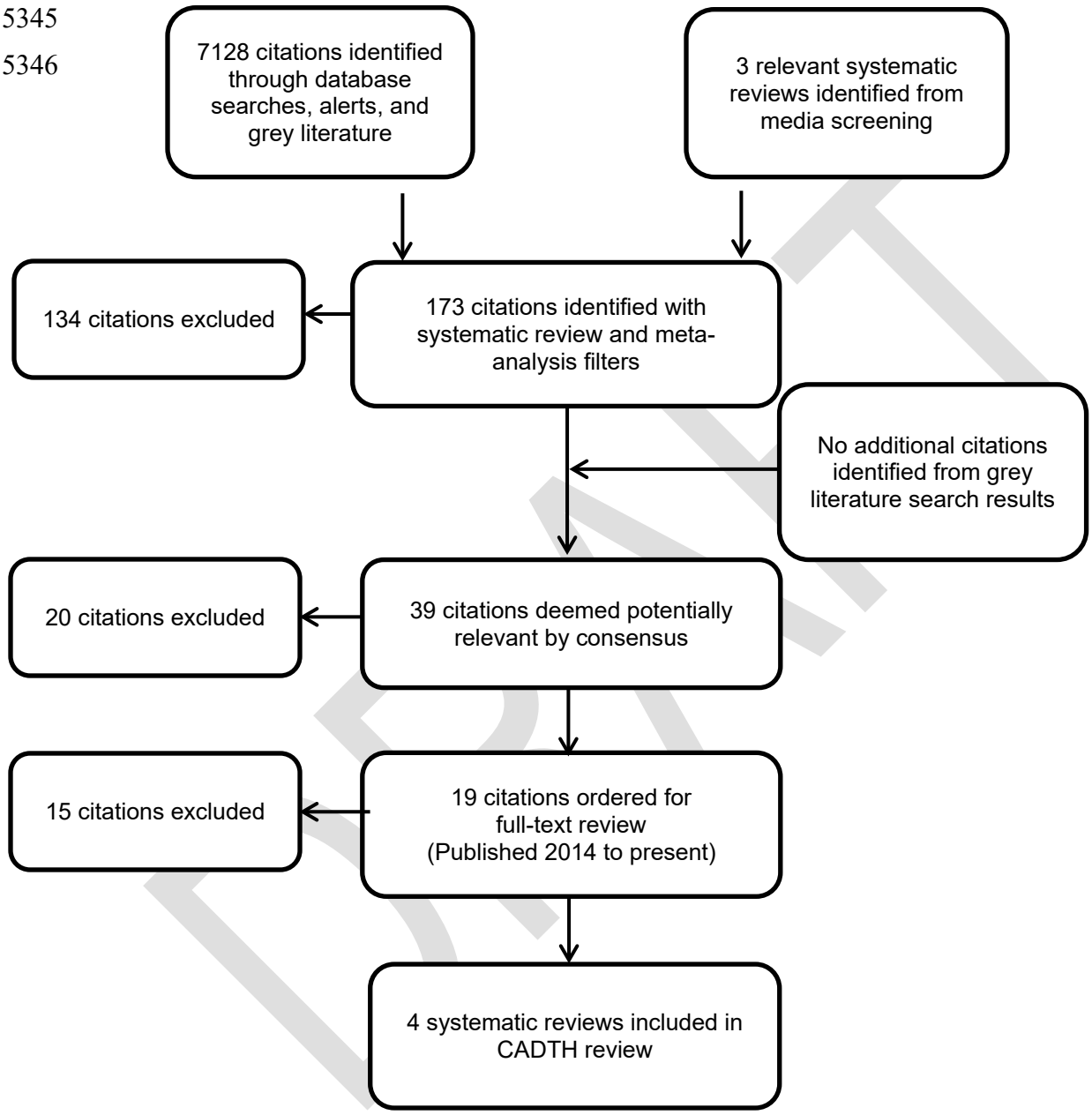
Grey Literature

Dates for Search:	February/March, 2017
Keywords:	Included terms for HPV testing and cervical cancer screening.
Limits:	Publication years 2002-present English or French language only

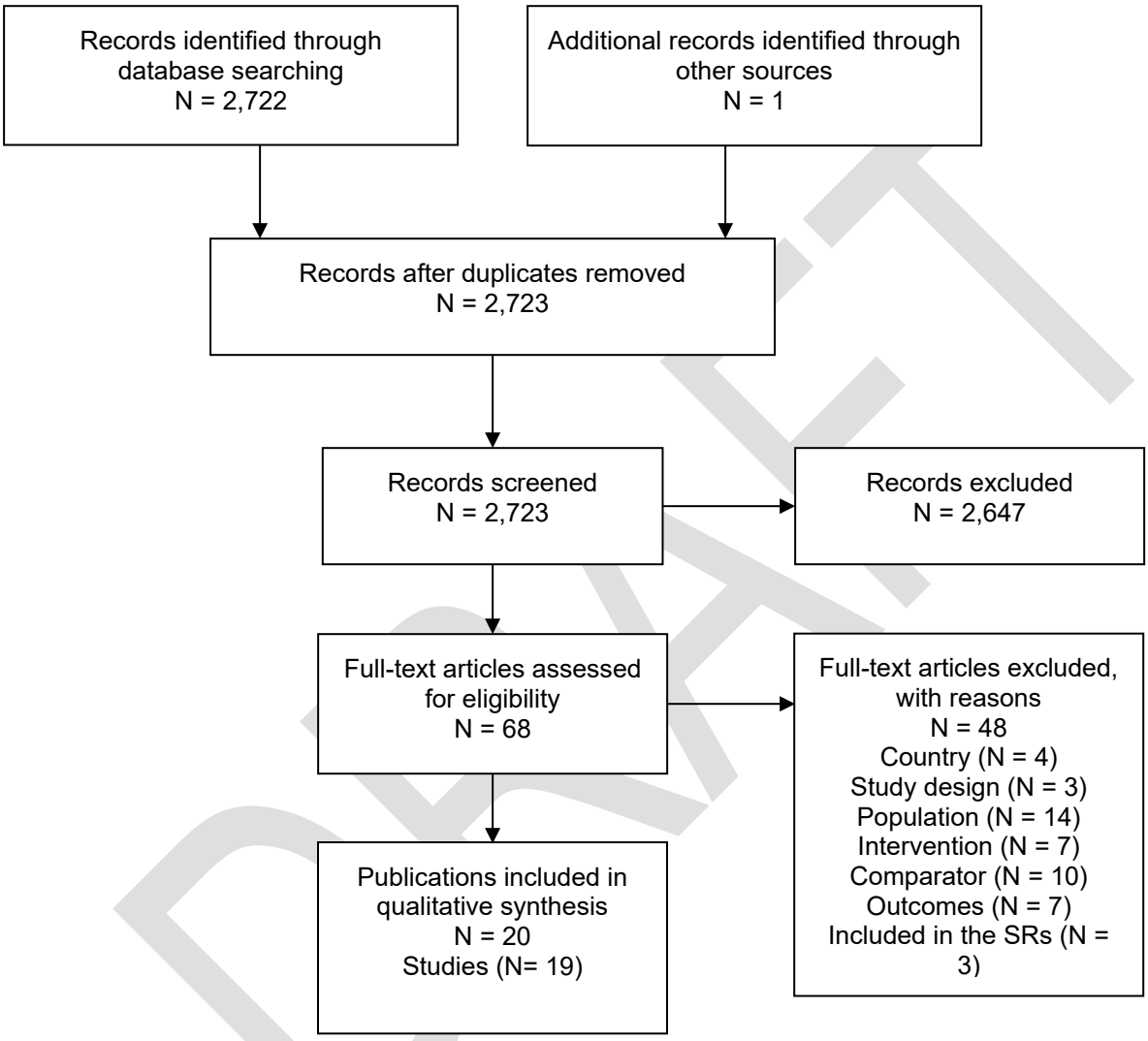
Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/resources/finding-evidence/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Clinical Trials (ongoing)
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 2: Study Selection Flow Diagram — SRs, HTAs, and Meta-Analyses



Appendix 3: PRISMA – Primary Studies Published After SRs (2015 to present)



Appendix 4: List of Excluded Primary Studies

Table 33: List of excluded primary studies that were published since 2015.

Excluded for being included in Melnikow 2018[39]
Ogilvie G, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical hpv testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: The hpv focal randomized clinical trial. *JAMA.* 2018;320(1):43-52.
Ogilvie GS, Krajden M, van Niekerk D, Smith LW, Cook D, Ceballos K, et al. HPV for cervical cancer screening (HPV FOCAL): complete round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer. *International Journal of Cancer.* 2017;140(2):440-448.
Canfell K, Caruana M, Gebski V, rlington-Brown J, Heley S, Brotherton J, et al. Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial. *PLoS Medicine.* 2017;14(9):e1002388.
Excluded for countries of origin
Wong EL, Cheung AW, Huang F, Chor JS. Can Human Papillomavirus DNA Self-sampling be an Acceptable and Reliable Option for Cervical Cancer Screening in Female Sex Workers?. Cancer Nurs. 2017;, 2017 Jan 20():.
Wong EL, Chan PK, Chor JS, Cheung AW, Huang F, Wong SY. Evaluation of the Impact of Human Papillomavirus DNA Self-sampling on the Uptake of Cervical Cancer Screening. Cancer Nurs. 2016;39(1):E1.
Gao K, Eurasian M, Zhang J, Wei Y, Zheng Q, Ye H, Li L. Can Genomic Amplification of Human Telomerase Gene and C-MYC in Liquid-Based Cytological Specimens Be Used as a Method for Opportunistic Cervical Cancer Screening?. Gynecol Obstet Invest. 2015;80(3):153.
Liu L, Chen YM, Zhang QY, Li CZ. Roles of high-risk human papilloma virus (HR-HPV) E6/E7mRNA in triaging HPV16/18 cases. Clin Exp Obstet Gynecol. 2017;44(5):740.
Excluded for study design
Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test. Obstet Gynecol Surv. 2015;70(5):321.
Excluded for populations
Sewali B, Okuyemi KS, Askhir A, Belinson J, Vogel RI, Joseph A, Ghebre RG. Cervical cancer screening with clinic-based Pap test versus home HPV test among Somali immigrant women in Minnesota: a pilot randomized controlled trial. Cancer Med. 2015;4(4):620.
Gustinucci D, Giorgi RossiP, Cesarini E, Broccolini M, Bulletti S, Carlani A, D'Angelo V, D'Amico MR, Di DatoE, Galeazzi P, Malaspina M, Martinelli N, Spita N, Tintori B, Giaimo MD, Passamonti B. Use of Cytology, E6/E7 mRNA, and p16INK4a-Ki-67 to Define the Management of Human Papillomavirus (HPV)-Positive Women in Cervical Cancer Screening. Am J Clin Pathol. 2016;145(1):35.
Tewari D, Novak-Weekley S, Hong C, Aslam S, Behrens CM. Performance of the cobas HPV Test for the Triage of Atypical Squamous Cells of Undetermined Significance Cytology in Cervical Specimens Collected in SurePath. Am J Clin Pathol. 2017;():.
Zhou H, Mody RR, Luna E, Armylagos D, Xu J, Schwartz MR, Mody DR, Ge Y. Clinical performance of the Food and Drug Administration-Approved high-risk HPV test for the detection of high-grade cervicovaginal lesions. Cancer cytopathol.. 2016;124(5):317.
Heard I, Cuschieri K, Geraets DT, Quint W, Arbyn M. Clinical and analytical performance of the PapilloCheck HPV-Screening assay using the VALGENT framework. J Clin Virol. 2016;81:6-11, 2016 Aug():.
Cuzick J, Myers O, Lee J-H, Shi Y, Gage JC, Hunt WC, Robertson M, Wheeler CM. Outcomes in women with cytology showing atypical squamous cells of undetermined significance with vs without human papillomavirus testing. JAMA oncology. 2017;3(10):1327.
Comes MD, Oncins R, Clemente E, Aragon MA, Cortes A, Valles V, Guardia L, Millanes P. Prevalence of human papillomavirus and genotype distribution in women undergoing cervical cancer screening in the area of Barbastro, Spain. Revista Espanola de Patologia. 2016;49(4):208.

Dijkstra MG, van ZummerenM, Rozendaal L, Van Kemenade FJ, Helmerhorst TJ, Snijders PJ, Meijer CJ, Berkhof J. Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. BMJ. 2016;355:i4924, 2016 Oct 04():.
Leinonen MK, Schee K, Jonassen CM, Lie AK, Nystrand CF, Rangberg A, Furre IE, Johansson MJ, Trope A, Sjoborg KD, Castle PE, Nygard M. Safety and acceptability of human papillomavirus testing of self-collected specimens: A methodologic study of the impact of collection devices and HPV assays on sensitivity for cervical cancer and high-grade lesions. J Clin Virol. 2018;99-100()(pp 22-30), 2018. Date of Publication: February 2018.):22.
Bhatia R, Serrano I, Wennington H, Graham C, Cubie H, Boland E, Fu G, Cuschieri K. An evaluation of a novel single tube method for extended genotyping of Human Papillomavirus. J Clin Microbiol. 2017;():.
Igidbashian S, Boveri S, Bottari F, Vidal UrbinatiA, Preti E, Casadio C, Landoni F, Sideri M, Sandri MT. Prevalence and Risk Factors of Human Papillomavirus Infection in 18-Year-Old Women: Baseline Report of a Prospective Study on Human Papillomavirus Vaccine. J. 2017;low. genit. tract dis.. 21(1):4.
Isidean SD, Mayrand MH, Ramanakumar AV, Rodrigues I, Ferenczy A, Ratnam S, Coutlee F, Franco EL. COMPARISON OF TRIAGE STRATEGIES FOR HPV POSITIVE WOMEN: CANADIAN CERVICAL CANCER SCREENING TRIAL RESULTS. Cancer Epidemiol Biomarkers Prevent. 2017;, 2017 Jan 17():.
Excluded for interventions
Flannelly GM, Mooney MT, Greehy GM, Keogh EB, McNally SA, Fitzpatrick PE. Establishment of a national cervical screening programme in Ireland, CervicalCheck: the first 6 years. Eur J Cancer Prev. 2016;, 2016 Nov 07():.
Tracht J, Wrenn A, Eltoum IE. Primary HPV testing verification: A retrospective ad-hoc analysis of screening algorithms on women doubly tested for cytology and HPV. Diagn Cytopathol. 2017;():.
MacLaughlin KL, Kessler ME, Komandur ElayavilliR, Hickey BC, Scheitel MR, Wagholikar KB, Liu H, Kremers WK, Chaudhry R. Impact of Patient Reminders on Papanicolaou Test Completion for High-Risk Patients Identified by a Clinical Decision Support System. . 2018;():.
Silver MI, Schiffman M, Fetterman B, Poitras NE, Gage JC, Wentzensen N, Lorey T, Kinney WK, Castle PE. The population impact of human papillomavirus/cytology cervical cotesting at 3-year intervals: Reduced cervical cancer risk and decreased yield of precancer per screen. Cancer. 2016;122(23):3682.
Del MistroA, Frayle H, Ferro A, Fantin G, Altobelli E, Giorgi RossiP. Efficacy of self-sampling in promoting participation to cervical cancer screening also in subsequent round. Prev Med Rep. 2017;5:166-168, 2017 Mar():.
Excluded for comparators
Lim AW, Hollingworth A, Kalwij S, Curran G, Sasieni P. Offering self-sampling to cervical screening non-attenders in primary care. J Med Screen. 2017;24(1):43.
Passamonti B, Gustinucci D, Giorgi RossiP, Cesarini E, Bulletti S, Carlani A, Martinelli N, Broccolini M, D'Angelo V, D'Amico MR, Di DatoE, Galeazzi P, Malaspina M, Spita N, Tintori B, Giaimo MD. Cervical human papilloma virus (HPV) DNA primary screening test: Results of a population-based screening programme in central Italy. J Med Screen. 2016;, 2016 Sep 10():.
Passamonti B, Gustinucci D, Giorgi RossiP, Cesarini E, Bulletti S, Carlani A, Martinelli N, Broccolini M, D'Angelo V, D'Amico MR, Di DatoE, Galeazzi P, Malaspina M, Spita N, Tintori B, Giaimo MD. Cervical human papilloma virus (HPV) DNA primary screening test: Results of a population-based screening programme in central Italy. J Med Screen. 2017;24(3):153.
Ejegod D, Bottari F, Pedersen H, Sandri MT, Bonde J. The BD Onclarity HPV Assay on Samples Collected in SurePath Medium Meets the International Guidelines for Human Papillomavirus Test Requirements for Cervical Screening. J Clin Microbiol. 2016;54(9):2267.
Cuzick J, Cuschieri K, Denton K, Hopkins M, Thorat MA, Wright C, Cubie H, Moore C, Kleeman M, Austin J, shdown-Barr L, Hunt K, Cadman L. Performance of the Xpert HPV assay in women attending for cervical screening. Papillomavirus Research. 2015;1()(pp 32-37), 2015. Date of Publication: December 01, 2015.):32.
Monsonego J, Cox JT, Behrens C, Sandri M, Franco EL, Yap PS, Huh W. Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: data from the ATHENA trial. Gynecol Oncol. 2015;137(1):47.
Lam JUH, Elfstrom KM, Ejegod DM, Pedersen H, Rygaard C, Rebolj M, Lynge E, Juul KE, Kjaer SK, Dillner J, Bonde J. High-grade cervical intraepithelial neoplasia in human papillomavirus self-sampling of screening non-attenders. Br J Cancer. 2017;():.

Zorzi M, Frayle H, Rizzi M, Fedato C, Rugge M, Penon MG, Bertazzo A, Callegaro S, Campagnolo M, Ortu F, Del MistroA, Veneto HPV-screening Working Group. A 3-year interval is too short for re-screening HPV negative women: a population-based cohort study. BJOG. 2017;, 2017 Jan 24():.
Uijterwaal MH, Polman NJ, Van Kemenade FJ, Van Den HaselkampS, Witte BI, Rijkaart D, Berkhof J, Snijders PJ, Meijer CJ. Five-Year Cervical (Pre)Cancer Risk of Women Screened by HPV and Cytology Testing. Cancer Prev Res (Phila Pa). 2015;8(6):502.
Excluded for outcomes
Coldman AJ, Gondara L, Smith LW, van NiekerkD, Ceballos K, Krajden M, Cook D, Quinlan DJ, Lee M, Stuart GC, Peacock S, Martin RE, Gentile L, Franco EL, Ogilvie GS. Disease detection and resource use in the safety and control arms of the HPV FOCAL cervical cancer screening trial. Br J Cancer. 2016;115(12):1487.
Cook DA, Mei W, Smith LW, van Niekerk DJ, Ceballos K, Franco EL, Coldman AJ, Ogilvie GS, Krajden M. Comparison of the Roche cobas 4800 and Digene Hybrid Capture 2 HPV tests for primary cervical cancer screening in the HPV FOCAL trial. BMC Cancer [electronic resource]. 2015;15:968, 2015 Dec 16():.
Stanczuk G, Baxter G, Currie H, Lawrence J, Cuschieri K, Wilson A, Arbyn M. Clinical validation of hrHPV testing on vaginal and urine self-samples in primary cervical screening (cross-sectional results from the Papillomavirus Dumfries and Galloway-PaVDaG study). BMJ Open. 2016;6(4):e010660, 2016.
Rebolj M, Bonde J, Preisler S, Ejegod D, Rygaard C, Lynge E. Human Papillomavirus Assays and Cytology in Primary Cervical Screening of Women Aged 30 Years and Above. . 2016;11(1):e0147326, 2016.
Castle PE, Aslam S, Behrens C. Cervical Precancer and Cancer Risk by Human Papillomavirus Status and Cytologic Interpretation: Implications for Risk-Based Management. Cancer Epidemiol Biomarkers Prevent. 2016;25(12):1595.
Isidean SD, Mayrand MH, Ramanakumar AV, Gilbert L, Reid SL, Rodrigues I, Ferenczy A, Ratnam S, Coutlee F, Franco EL, CCCaST Study Group. Human papillomavirus testing versus cytology in primary cervical cancer screening: End-of-study and extended follow-up results from the Canadian cervical cancer screening trial. Int J Cancer. 2016;139(11):2456.

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Appendix 5: Summary of Assessment of Existing Systematic Reviews

Table 34: Summary of Existing Systematic Reviews

	CADTH	Melnikow[a] (2018)[39]	HIQA (2017)[6]	Cochrane (2017)[38]	Verdoodt (2015)[22]
Objective	To address the policy questions: "Should HPV testing replace Pap cytology in Canadian jurisdictions as the primary screening tool for cervical cancer? If yes, what criteria, including appropriate screening interval and age to start and stop screening, should guide HPV-based cervical screening programs in Canada?"	"To systematically review the benefits and harms of screening for cervical cancer using HR-HPV testing as the screening strategy (with or without cytology)." (online supplement)	"This HTA was carried out to assess the impact of changing from a policy of using liquid-based cytology (LBC) as the primary screening test to a policy of using HPV testing as a primary screening test. The sequence of screening tests including options for triage were assessed along with alternative screening intervals and age bands, including both for HPV-vaccinated and unvaccinated cohorts."	"To determine the diagnostic accuracy of HPV testing for detecting histologically confirmed cervical intraepithelial neoplasias (CIN) of grade 2 or worse (CIN 2+), including adenocarcinoma in situ, in women participating in primary cervical cancer screening; and how it compares to the accuracy of cytological testing (liquid-based and conventional) at various thresholds."	"A systematic review and meta-analysis were performed to evaluate the participation after an invitation including a self-sampling device (self-sampling arm) versus an invitation to have a sample taken by a health professional (control arm), sent to under-screened women."
Population	≥21 years or age of screening initiation in the region	≥21 years of age	Not specified • Current screening program includes women aged 25 to 60	Not specified • Women aged between 20 and 70 years old were included in primary studies	• Irregularly or never-screened women, or women who did not respond to one or more invitations for conventional screening for cervical cancer • Women aged between 25

	CADTH	Melnikow[a] (2018)[39]	HIQA (2017)[6]	Cochrane (2017)[38]	Verdoodt (2015)[22]
					and 69 were included in primary studies
HPV tests	All commercially available HPV tests	Any HR-HPV test	Any HR-HPV test • DTA analysis limited to HC2 • Triage analysis included any HR-HPV test	Any HPV tests	Self-administered HPV tests
Comparators	Cytology (LBC or conventional) or other HPV tests with or without triage	Any cervical cancer screening test including cytology-based or other HR-HPV screening strategies.	Gold standard application of colposcopy and or biopsy on at least all cytology- and HPV-positive samples	Cytology	Clinician-administered HPV tests
Outcomes	• DTA • Harms • Acceptance of screening • Referral to colposcopy • Morbidity/mortality • Quality of life	• Mortality (all-cause or cervical cancer) • Invasive cervical cancer incidence • Early detection of disease (CIN3+) • Rates of false-positive and false-negative screening • Colposcopy and biopsy rates • Quality of life • Other harms.	• DTA (HC2 VS cytology) ○ Cross-sectional ○ Longitudinal • Referral to colposcopy	DTA (HPV tests VS cytology)	Acceptance of screening
Setting	• Canada • United States • Australia • New Zealand • United Kingdom • countries in the European Economic Area	Countries categorized as “very high” or equivalent on the 2014 Human Development Index	Studies conducted in “industrialised” countries • Canada • United States • United Kingdom • Germany • France • Western and eastern Europe • Italy • Norway • Switzerland • Taiwan • Chile • Japan • Russia	Inclusion was not limited by country • Sensitivity analysis undertaken and determined country did not impact results	• Netherlands • Sweden • France • Sweden • UK • Italy • Argentina • Mexico • Finland

	CADTH	Melnikow[a] (2018)[39]	HIQA (2017)[6]	Cochrane (2017)[38]	Verdoodt (2015)[22]
Search timeframe	2002 to present	Jan 2011 to Feb 15, 2017; surveillance through May 25, 2018	• Search for Q1 (DTA of HC2) to Jan 2016 ○ Update of two previous SRs from 2007 and 2015 • Search for Q2 (DTA of triage strategies) to April 2016	1992 to November 2015	Up to February 2015
Number of primary studies included in systematic review	NA	14 for harms, referral to colposcopy, or morbidity/mortality • Excluded low quality studies from analysis • 8 RCTs • 5 cohort studies • 1 individual participant data meta-analysis	• 23 in HC2 DTA analysis • 15 in the triage DTA analysis	40 for DTA analyses • 27 for HC2 • 10 for PCR primers • 4 for Aptima • 2 for Cobas • 5 for other HPV tests	16 for acceptance of screening tests
Study designs	RCT, Cohort	RCT, cohort	RCT, NRS	NRS	RCT
Meta-analysis?	NA	Qualitative synthesis due to heterogeneity	Yes	Yes	Yes
Quality appraisal tools used	NA	• Newcastle-Ottawa • USPSTF criteria	QUADAS-2	QUADAS	Cochrane RoB
Major named studies included	NA	• NTCC-I and II (New Technology in Cervical Cancer) in Italy • HPV FOCAL (HPV for cervical cancer screening) in Canada • Compass in Australia • FINNISH, a cervical cancer screening trial in Finland and called Public health Trial Finland in the HIQA review • SWEDESCREEN, a cervical cancer screening trial in Sweden • ARTISTIC (A	• NTCC • ARTISTIC • POBASCAM • SWEDESCREEN in Sweden • Public Health Trial Finland, called FINNISH in the AHRQ review • ATHENA (Addressing the Need for Advanced HPV Diagnostics) in the US • PROHTECT-3 (PRotection by Offering HPV TEsting on self-sampled Cervico-vaginal specimens Trial-3) in the Netherlands	• ATHENA • SHENCCAST (Shenzhen Cervical Cancer Screening Trials) I in China	NR

	CADTH	Melnikow[a] (2018)[39]	HIQA (2017)[6]	Cochrane (2017)[38]	Verdoodt (2015)[22]
		Randomized Trial In Screening To Improve Cytology) in the UK • POBASCAM (population-based screening study Amsterdam) in the Netherlands • WOLPHSCREEN (Wolfsburg primary HPV screening project) in Germany	• VUSA-Screen ((Vrije Universiteit Medical Centre-Saltro) in the Netherlands		

DTA = diagnostic test accuracy; HC2 = hybrid capture 2; HPV = human papillomavirus; LBC = liquid-based cytology; MA = meta-analysis; NA = not applicable; NR = not reported; NRS = non-randomized study; RCT = randomized controlled trial; RoB = risk of bias; SR = systematic review; UK = United Kingdom; USA = United States of America

[a]The original review was based on data published in 2011 and some methodological information was used[257]. An updated version was published on August 21, 2018[39] and the data has been incorporated into this report.

Table 35: The primary studies included in the Cochrane Review and the Research Question 1 in the HIQA review

Author year	HIQA review	Cochrane review	Both
Agorastos 2005		X	
Belinson 2003		X	
Belinson 2010		X	
Bigras 2005	X	X	X
Cardenas-Turanzas 2008	X	X	X
Chao 2008	X		
Clavel 2001	X	X	X
Coste 2003	X		
Cuzick 2003	X	X	X
Cuzick 2008	X		
Cuzick 2013	X		
de Cremoux 2003		X	
Depuydt 2011		X	
Ferreccio 2013	X	X	X
Gravitt 2010		X	
Hovland 2010		X	
Iftner 2015	X	X	X
Ikenberg 2013	X		
Iue 2006	X		
Kitchener 2014	X		
Kulasingam 2002		X	
Labani 2014		X	
Li 2009		X	
Luyten 2009	X		
Mahmud 2012		X	
McAdam 2010		X	
Monsonego 2011	X	X	X
Moy 2010		X	
Nieves 2013		X	
Nygard 2014	X		
Pan 2003		X	
Paraskevaidis 2001		X	
Petry 2003	X	X	X
Qiao 2008		X	
Ratnam 2000	X		
Ronco 2006a	X		
Ronco 2006b	X	X	X
Salmeron 2003		X	
Sankaranarayanan 2004		X	
Sarian 2005		X	
Schneider 2000		X	
Shipitsyna 2011	X	X	X
Syrjanen 2002	X	X	X
Szarewski 2007	X		
Wu 2010		X	
Total	23	33	11

Table 36: The primary studies included in the Cochrane Review and the Research Question 2 in the HIQA review

Author year	HIQA review	Cochrane review	Both
Agorastos 2005		**X**	
Belinson 2003		X	
Belinson 2010		X	
Cardenas-Turanzas 2008		X	
Carozzi 2013	X		
Carozzi 2008	X		
Castle 2011	X	X	X
Clavel 2001		X	
Cuzick 2003		X	
de Cremoux 2003		X	
Depuydt 2011		X	
Dijkstra 2014	X		
Ferreccio 2013		X	
Gravitt 2010		X	
Hovland 2010		X	
Iftner 2015		X	
Kitchener 2009	X		
Kitchener 2014	X		
Kulasingam 2002		X	
Labani 2014		X	
Leinen 2013	X		
Li 2009		X	
Mahmud 2012		X	
McAdam 2010		X	
Monsonego 2011		X	
Moy 2010		X	
Naucler 2009	X	X	X
Nieves 2013		X	
Pan 2003		X	
Paraskevaidis 2001		X	
Petry 2003		X	
Qiao 2008		X	
Rijkaart 2012	X		
Ronco 2006a	X		
Ronco 2006b	X	X	X
Salmeron 2003		X	
Sankaranarayanan 2004		X	
Sarian 2005		X	
Schneider 2000		X	
Shipitsyna 2011		X	
Syrjanen 2002		X	
Verhoef 2015	X		
Wright 2016	X		
Wright 2015	X		
Wu 2010		X	
Total	14	34	3

Table 37: Summary of Relevance Assessments of Existing SRs and HTAs

	CADTH	Melnikow (2018)[39]	HIQA (2017)[6]	Cochrane (2017)[38]	Verdoodt (2015)[22]
Population	≥21 years or age of screening initiation in the region	Relevant	Relevant	Relevant	Relevant
Interventions	HR-HPV tests	Relevant	Relevant	Relevant	Relevant
Comparators	Cytology (LBC or conventional) or other HPV tests with or without triage	Relevant	Relevant	Relevant	Relevant
Outcomes	DTA Harms Acceptance of screening Referral to colposcopy Morbidity/mortality Quality of life	Partially relevant: assessed some but not all outcomes of interest	Partially relevant: assessed some but not all outcomes of interest	Partially relevant: assessed some but not all outcomes of interest	Partially relevant: assessed some but not all outcomes of interest
Country	Canada United States Australia New Zealand United Kingdom European Economic Area	Relevant	Relevant	Relevant	Relevant
Confidence on the results based on AMSTAR 2 tool	NA	Moderate confidence for two identified weaknesses	Moderate confidence for three identified weaknesses	Moderate confidence for two identified weaknesses	Moderate confidence for four identified weaknesses
Decisions for the inclusion of existing systematic reviews in the CADTH review	NA	To be used to assess: • Harms • Referral to colposcopy • Morbidity/mortality • Quality of life	To be used to assess: • HC2 VS cytology • DTA • Any HR-HPV testing with triage • Cross-sectional and longitudinal DTA • Referral to colposcopy	To be used to assess: • DTA	To be used to assess: • Acceptance of screening

DTA = diagnostic test accuracy; LBC = liquid-based cytology; HC2 = Hybrid Capture 2; HR-HPV = high-risk human papillomavirus

5377 Table 38: Summary of Excluded Systematic Reviews

Author	Topic	PICO	Reason for exclusion from the inclusion of reviews
Kaiser Permanente Research Affiliates Evidence-based Practice Center (2017)[20]	Effectiveness and harms	NA	Updated in Melnikow 2018[39]
Ceilleachair (2017)[483]	QoL	Outcomes	The population was not limited to a general screening population. The specific HPV tests used in the studies were not mentioned. Cytology was not mentioned as a comparator. The outcomes of the review did not fit with the CADTH PICO.
Nelson (2017)[484]	Acceptance of self-testing	Outcomes	There were no proportions of acceptance presented. The results were about the acceptability considered by participants.
Jentschke (2017)[485]	Published in Danish	NA	Not published in English
Jentschke (2016)[486]	Methodological differences between meta-analyses on cervical cancer screening	Study design: SR of SRs - only searched Medline	Only one database was searched to identify SRs for assessment. The authors assessed the quality of the included reviews and provided a brief summary of the overall conclusions without any formal analysis. The authors determined that there were significant differences between reviews in regards to the primary studies they included, the analysis methods that were utilized, and the recommendations that were developed based on the results.[486] Despite the differences in included studies and approaches taken, the results of these reviews generally indicated that HPV testing for cervical cancer screening was better when compared with cytology-based screening
Santesso (2016)[487]	DTA	Study design	The publication was a summary of a guideline and not a publication of the systematic review that supported the guideline.
Haedicke (2016)[488]	DTA of Aptima	Study design	The publication was a review article examining the DTA of a specific HPV test.
de Thurah (2017)[489]	Agreement between HPV tests	Intervention	The reference standard, colposcopy, was not applied.
Mustafa (2016)[490]	DTA - HPV, VIA, cytology and colposcopy	NA	The eligible primary studies were included in more recent SRs.
Li (2016)[491]	DTA of co-testing vs cytology	Intervention	The review did not examine the DTA of HPV testing alone, only in combination with cytology (co-testing).
Nelson (2016)	Acceptability of self-testing	NA	This publication was a duplicate publication of Nelson (2017)[484] (e-publication ahead of print).
Yin (2014)[492]	DTA of HC2	Comparator	This review did not include a comparator group and therefore did not address the research questions in terms of comparing HPV testing to other testing methods or pathways.
Bouchard-	DTA of co-testing vs cytology	NA	The studies included in the analysis were also in the more recent HIQA HTA report.

Author	Topic	PICO	Reason for exclusion from the inclusion of reviews
Fortier (2014)[493]			
Pileggi (2014)[494]	Specificity of HPV testing vs cytology	Outcomes	The results reported did not align with the outcomes of interest.
Giorgi Rossi (2014)[495]	Socio-economic inequalities	Outcomes	The results reported did not align with the outcomes of interest.

CADTH = Canadian Agency for Drugs and Technologies in Health; DTA = diagnostic test accuracy; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; HPV = human papillomavirus; HTA = health technology assessment; PICO = population, intervention, comparator, and outcome; QoL = quality of life; SR = systematic review; VIA = visual inspection with acetic acid

Appendix 6: Strengths and Limitations of Systematic Reviews using the AMSTAR 2 checklist

Table 39: AMSTAR 2 Checklist

AMSTAR 2 Item[34]	Melnikow (2018)[39]	HIQA (2017)[6]	Cochrane (2017)[38]	Verdoodt (2015)[22]
Did the research questions and inclusion criteria for the review include the components of PICO?	⊕[a]	⊕	⊕	⊕
*Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	⊕	X	⊕	X
Did the review authors explain their selection of the study designs for inclusion in the review?	⊕[a]	⊕	⊕	⊕
*Did the review authors use a comprehensive literature search strategy?	⊕	⊕	⊕	⊕
Did the review authors perform study selection in duplicate?	⊕	⊕	⊕	?
Did the review authors perform data extraction in duplicate?	⊕	⊕	⊕	⊕
*Did the review authors provide a list of excluded studies and justify the exclusions?	⊕[a]	⊕	⊕	X
Did the review authors describe the included studies in adequate detail?	⊕[a]	⊕	⊕	⊕
*Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	⊕	⊕	⊕	⊕
Did the review authors report on the sources of funding for the studies included in the review?	X	X	X	X
*If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	⊕	⊕	⊕
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	X	X	X
*Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	⊕	X	X	X
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	⊕	X	⊕	⊕
*If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A	X	X	X
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	⊕	⊕	⊕	⊕

Legend: ⊕ = Yes, X = No; ? = Unclear, N/A = not applicable, RoB = risk of bias, * = AMSTAR 2 critical domains, AMSTAR = A MeaSurement Tool to Assess systematic Reviews.

[a] Available in the supplemental materials[496]

5389

Appendix 7: Characteristics of Included Primary Studies

Table 40: Characteristics of Primary Studies Published after Systematic Reviews

First Author, Year Trial Name	Country, Clinical Setting, Study Design	Study Population (n)	Index Test	Comparator Test	Screening Pathway and Interval	Outcomes of Interest
Randomized Controlled Trials						
Lamin, 2017[40]	Sweden • Established and routinely running organised, large-scale population-based screening programme	Women aged 56 to 60 years invited to their last cervical cancer screening appointment (n = 14,763)	HPV test (Cobas) with cytology triage of HPV positive patients	Cytology with HPV triage (Cobas) of low-grade cytological abnormalities • Abnormal = ASCUS +)	• Cytology testing • HPV testing with cytology triage Routine screening interval • 5 years after age 51	• Acceptance of screening • Referral to colposcopy
Cook, 2016[41] **HPV FOCAL Trial, subset of the Intervention Arm**	Canada • Subanalysis of HPV FOCAL Trial	Women aged 25 to 65 years randomized after 2010, HC2 positive and LBC negative at baseline and rescreened after 12 months (n = 3,473)	Clinician-collected HPV test (Aptima)	Clinician-collected HPV test (HC2)	Subset of HPV testing in Ogilvie, 2017[28]	• DTA • Referral to colposcopy
Enerly, 2016[42]	Norway • Norwegian cervical cancer screening program	Women aged 25 to 69 years who did not regularly attend the national cervical cancer screening program (due for a second reminder, at least four years since last screening) (n = 3393)	Self-collected HPV test (CLART and HC2) at home	Clinician-collected LBC test	• Cytology testing ○ No triage or colposcopy specified • HPV testing with cytology triage ○ No colposcopy specified Routine screening interval • 3 years	Acceptance of screening
Racey, 2016[43]	Canada • Cervical cancer screening by	Women aged 30 to 70 years who were overdue for	Self-collected HPV test at home	• Reminder letter for Pap test • Standard of	• Cytology • Self-collected HPV	Acceptance of screening/compliance

Table 40: Characteristics of Primary Studies Published after Systematic Reviews

First Author, Year Trial Name	Country, Clinical Setting, Study Design	Study Population (n)	Index Test	Comparator Test	Screening Pathway and Interval	Outcomes of Interest
	family health team in Ontario	cervical cancer screening, at least three years since last screening (n = 818)		care opportunistic screening	Routine screening interval • every 2 to 3 years	
Sultana, 2016[44] iPap Trial	Australia • Established routine cervical cancer screening program	Women aged 30 to 69 years who were under- or never-screened for cervical cancer, not screened in the past five years (n = 16,320)	Self-collected HPV test (Cobas)	Clinician-collected Pap test • Abnormal = not mentioned	• Cytology • HPV self-collected sample ○ HPV 16/18+ to colposcopy Routine screening interval • receive reminders every 27 months after last negative test	Acceptance of screening
Williams, 2016[45]	United States • Patients recruited from medically underserved and low-income neighborhoods	Women aged 21 years or greater who lived in identified areas or were previous participants of the screening program and were due for a screening test (n = 120)	Self-collected HPV test with tampons (Cobas)	Clinic administered Pap test, HPV test, and pelvic exam	• HPV self-collected sample followed by invite to cytology, clinician-collected HPV test and pelvic exam Routine screening interval • Cytology = 3 years • HPV = 5 years	Acceptance of screening/compliance
Zehbe, 2016[46]	Canada • Cervical cancer screening in First Nations communities in Northwest	Women aged 25 to 69 years living in 11 First Nations communities eligible for cervical	Self-collected HPV test	Clinician-collected Pap test • Abnormal not defined	• Cytology ○ per Ontario screening program • HPV self-collected	Acceptance of screening

Table 40: Characteristics of Primary Studies Published after Systematic Reviews

First Author, Year Trial Name	Country, Clinical Setting, Study Design	Study Population (n)	Index Test	Comparator Test	Screening Pathway and Interval	Outcomes of Interest
	Ontario	cancer screening (randomized by community) (n = 834)			sample ○ cytology triage for high-risk positive sample Routine screening interval • 3 years	
Cadman, 2015[47]	United Kingdom • Newcastle upon Tyne	Women aged 25 to 65 years who had failed to attend cervical cancer screening after at least two invitations, at least 46 weeks since initial invitation (n = 6000)	Self-collected HPV test (HC2)	Physician-collected cytology test • Abnormal not defined	• Two groups were sent up to two reminders for screening within 46 weeks	Acceptance of screening
Rossi, 2015[48]	Italy • Organized screening program	Women aged 30 to 64 years non-responding to screening invitation three months ago (n = 14,041)	• Self-collected HPV test (HC2) at home • Self-collected HPV test in pharmacy	• Pap test at clinic ○ Abnormal = ASCUS+ • Physician-collected HPV test (HC2) at clinic	• HPV with cytology triage ○ ≥ASCUS to colposcopy OR ○ HPV+ straight to colposcopy and cytology Routine screening interval • Cytology = 3 years • HPV = 5 years	Acceptance of screening
Cotesting studies						
Jin, 2016[21]	United States • Primary cervical cancer	Women aged 30 years and older undergoing	Clinician-collected HPV test (HC2)	Cytology from co-testing • Abnormal = ASCUS+	• Cytology ○ Negative to routine screening	DTA

Table 40: Characteristics of Primary Studies Published after Systematic Reviews

First Author, Year Trial Name	Country, Clinical Setting, Study Design	Study Population (n)	Index Test	Comparator Test	Screening Pathway and Interval	Outcomes of Interest
	• screening in an integrated health system • Retrospective cohort	cervical cancer screening with HPV test and cytology co-testing (n = 99,549)			○ ASCUS to HPV triage with HPV+ to colposcopy ○ ≥ASC-H to colposcopy • HPV with cytology triage • Co-testing ○ >ASCUS or =ASCUS and HPV+ to colposcopy Routine screening interval • 3 years	
Wright, 2015[58] **ATHENA Study**	United States • Routine cervical cancer screening • Prospective cohort study • Cotesting study	Women aged 25 years and older attending routine cervical cancer screening with HPV test and cytology co-testing (n = 41,955)	Clinician-collected HPV test (Cobas)	LBC • Abnormal = ASCUS+	• Co-testing ○ All those with abnormal cytology and HPV+ and a subset of those with negative results went to colposcopy Routine screening interval • not specified • 3 year follow-up within the study	DTA
Non-Randomized Studies						
Chatzistamatiou, 2017[49] **PIPAVIR study**	Greece and Germany • Routine cervical cancer screening in primary care • Prospective cohort study	Women aged 30 to 60 visiting primary care clinics for cervical cancer screening (n = 1723)	Clinician-collected HPV test (Multiplexed Genotyping)	LBC • Abnormal = ASCUS+	• Co-testing ○ Negative on both tests returns to routine screening ○ HPV+, cytology positive or HPV and cytology	• DTA • Referral to colposcopy

Table 40: Characteristics of Primary Studies Published after Systematic Reviews

First Author, Year Trial Name	Country, Clinical Setting, Study Design	Study Population (n)	Index Test	Comparator Test	Screening Pathway and Interval	Outcomes of Interest
					positive referred to colposcopy Routine screening interval • not reported	
Granados, 2017[50]	Spain • Opportunistic screening program	Women aged 25 to 65 visiting primary care physicians for cervical cancer screening (n = 5063)	HPV co-testing (Aptima and Pap test)	Analysis of Pap results only Abnormal = ASCUS+	• Co-testing ○ ASCUS+ reviewed by cytotechnologist ○ Cytology HSIL directly to colposcopy ○ HPV+ offered colposcopy Routine screening interval not specified	• Acceptance of screening • Referral to colposcopy
Kocsis, 2017[51] **TRACE trial**	Hungary • Outpatient clinic-based cervical cancer screening • Prospective multi-centre cohort study	Women aged 18 to 65 years presenting for cervical cancer screening (n = 6,761)	HPV test (CONFIDENCE assay)	• HPV test (Cobas andFull Spectrum HPV test) • LBC ○ Abnormal = ASCUS+	• Cross-sectional cotesting	DTA
Altobelli, 2016[52]	Italy • Comparing organized and spontaneous cervical cancer screening	Women aged 25 to 64 years undergoing cervical cancer screening after invitation or attending spontaneously (n = 38,348)	HPV test (HC2)	Conventional cytology • Abnormal = ASCUS	• Cytology ○ Negative returns to routine screening ○ • HPV test with cytology triage ○ Cytology positive on triage to colposcopy	Acceptance of screening

Table 40: Characteristics of Primary Studies Published after Systematic Reviews

First Author, Year Trial Name	Country, Clinical Setting, Study Design	Study Population (n)	Index Test	Comparator Test	Screening Pathway and Interval	Outcomes of Interest
					Routine screening interval = 3 years	
Ilangovan, 2016[53]	United States • "Safety net clinics" for uninsured and low income patients	Haitian and Latina women aged 30 to 65 years with no Pap smear in the past 3 years (n = 180)	Self-collected HPV test (Aptima and Cervista Invader)	Clinician-collected Pap test • Abnormal not specified	• HPV+ were referred to clinicians for further follow-up Routine screening interval not specified	Acceptance of screening
Agorastos, 2015[54] **HERMES Study**	Greece • Established cervical cancer screening program • Ongoing prospective observational study	Women aged 25 to 55 years attending routine cervical cancer screening with co-testing (n = 4,009)	HPV test (Cobas)	LBC • Abnormal = ASCUS+	• Co-testing ○ Negative on both tests returns to usual screening ○ Positive on cytology and / or HPV to colposcopy Routine screening interval = 3 years	DTA
Chiappetta, 2015[55]	Italy • Assessment of a new cervical cancer screening program	Women aged 25 to 64 due for routine cervical cancer screening (n = 25,210)	HPV test (HC2) with LBC triage • women aged 35 to 64 • HPV positive = ≥1 RLU	Cytology test • only women aged 25 to 34	• Cytology ○ Negative to routine screening ○ ASCUS to HPV triage ○ LSIL+ to colposcopy • HPV test ○ Negative to routine screening ○ Positive to cytology triage Routine screening interval = 3 years	• Acceptance of screening • Referral to colposcopy
Iftner, 2015[56]	Germany	Women aged	HPV test	LBC	• Co-testing	DTA

Table 40: Characteristics of Primary Studies Published after Systematic Reviews

First Author, Year Trial Name	Country, Clinical Setting, Study Design	Study Population (n)	Index Test	Comparator Test	Screening Pathway and Interval	Outcomes of Interest
	• Established cervical cancer screening program • Prospective observational study	30 to 60 years undergoing routine cervical cancer screening with co-testing (n = 10,040)	(Aptima and HC2)	Abnormal = ASCUS+	○ All negative tests return to routine screening ○ Some participants from the single and double positive groups went to colposcopy Routine screening interval not specified.	
Pasquale, 2015[57]	Italy • Established screening program switching from Pap testing to HPV testing for cervical cancer screening	Women aged 25 to 64 years eligible for a new round of cervical cancer screening within an established screening program (n = 18,728)	Co-testing (HC2 and cytology) • HC2 Positive = ≥1 RLU	Midwife-collected cytology test • Abnormal = ASCUS+	• HPV and cytology positive to colposcopy Routine screening interval = 3 years	Acceptance of screening

ASC-H = atypical squamous cells – cannot exclude HSIL; ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; DTA = diagnostic test accuracy; HC2 = Hybrid Capture 2; FOCAL = FOr CervicAL cancer; HIQA = Health Information and Quality Authority; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; HTA = health technology assessment; LBC = liquid-based cytology; LSIL = low grade squamous intraepithelial lesion; NPV = negative predictive value; PICO = population, intervention, comparator, and outcome; PIPAVIR = Detection of persistent infections by human papillomaviruses; PPV = positive predictive value; QoL = quality of life; RLU = relative light unit; SR = systematic review; TRACE = Triage and Risk Assessment of Cervical Precancer by Epigenetic Biomarker; VIA = visual inspection with acetic acid

Appendix 8: Critical Appraisal of Primary Studies

Table 41: QUADAS-2 risk of bias and applicability assessment for included primary studies

		Wright (2015) [58]	Kocsis (2017) [51]	Cook (2017) [41]	Jin (2016) [21]	Iftner (2015) [56]	Chatzistamatiou (2017) [49]	Agorastos (2015) [54]
Risk of Bais	Patient Selection	Unclear	No	No	Unclear	No	No	No
	Screening Test (HPV Test)	No	No	No	Yes	No	No	No
	Supplemental test (Cytology triage)	No	No	No	Unclear	No	No	No
	Comparator index test (HPV or cytology)	No	NA	No	NA	NA	NA	NA
	Diagnostic Test (Colposcopy)	Yes	Yes	No	Yes	Yes	Yes	Yes
	Flow and Timing	No	No	Yes	Yes	No	No	No
Applicability concerns	Patient Selection	No	No	No	Unclear	No	No	No
	Screening Test (HPV Test)	No	No	No	Unclear	No	No	No
	Supplemental test (Cytology triage)	No	No	No	Unclear	No	No	No
	Comparator index test (HPV or cytology)	No	NA	No	NA	NA	NA	NA
	Diagnostic Test (Colposcopy)	No	No	No	No	No	No	No

Table 42: Newcastle-Ottawa risk of bias assessment for included primary non-randomized studies

First Author, Year	Altobelli (2016)[52]	Ilangovan (2016)[53]	Chiappetta (2015)[55]	Pasquale (2015)[57]	Chatzistamatiou (2017)[49]	Granados (2017)[50]
Representative-ness of the exposed cohort	Yes	Yes	Yes	Yes	Yes	Yes
Selection of the non-exposed cohort	Yes	Yes	Yes	Yes	Yes	Yes
Ascertainment of exposure	Yes	Yes	Yes	Yes	Yes	Yes
Outcome not present at start of study	No	Yes	No	No	Yes	No
Comparability of cohorts on the basis of the design or analysis	Yes	Yes	Yes	Yes	Yes	Yes
Assessment of outcome	Yes	Yes	Yes	Yes	Yes	Yes

5403

Table 43: Cochrane Risk of Bias assessment for included randomized controlled trials

	Selection Bias	Performance Bias		Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
First Author, year	Risk of Bias in Sequence Generation is:	Risk of Bias in Allocation Concealment is:	Risk of Bias in binding of participants and personnel is:	Risk of Bias in binding of outcomes assessors is:	Risk of bias from missing outcome data	Risk of Bias from Selective Outcome Reporting	Risk of bias from other biases	
Racey (2016)[43]	Low	Low	Low	Unclear	Low	Low	Low	Good
Williams (2016)[45]	Unclear	High	High	High	Low	Low	Low	Poor
Cook (2017)[41]	Unclear	High	Unclear	Unclear	Low	Low	Unclear	Poor
Zehbe (2016)[46]	Low	Low	High	High	Low	Low	Low	Poor
Sultana (2016)[44]	Low	High	High	High	Low	Low	Low	Poor
Enerly (2016)[42]	Low	High	High	High	Low	Low	Low	Poor
Rossi [48]	Low	High	High	High	Low	Low	Low	Poor
Cadman (2015)[47]	Low	Low	High	High	Low	Low	Low	Poor
Lamin (2017)[40]	Unclear	High	High	High	Low	Low	Low	Poor

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5406 # Appendix 9: Detailed Outcome Data – Clinical Review Question 1

Table 44: Sensitivity and Specificity of Cytology

Test	CIN2+					CIN3+				
	Sensitivity (%)		Specificity (%)		Number of studies	Sensitivity (%)		Specificity (%)		Number of studies
	Range	Pooled (95% CI)	Range	Pooled (95% CI)		Range	Pooled (95% CI)	Range	Pooled (95% CI)	
Systematic Reviews										
Cochrane (2017)[38]										
Conventional (ASCUS+)	43 to 96	65.9 (54.9 to 75.3)	86 to 98	96.3 (94.7 to 97.4)	16	39 to 85	70.3 (57.9 to 80.3)	85 to 98	96.7 (94.6 to 98.0)	9
LBC (ASCUS+)	52 to 94	75.5 (66.6 to 82.7)	73 to 97	91.9 (90.1 to 90.5)	15	52 to 98	76.0 (64.7 to 84.5)	73 to 97	91.2 (90.1 to 90.5)	13
Conventional (LSIL+)	18 to 89	62.8 (46.8 to 76.5)	92 to 100	97.7 (96.1 to 98.7)	9	64 to 80	74.4 (67.8 to 80.1)	95 to 98	96.9 (94.9 to 98.1)	5
LBC (LSIL+)	42 to 87	70.3 (59.7 to 79.1)	90 to 98	96.2 (94.6 to 97.4)	10	48 to 93	71.9 (61.2 to 76)	92 to 98	96.1 (93.5 to 97.6)	5
HIQA (2017)[6]										
Conventional	34 to 85	70.5 (58.2 to 80.7)	62 to 99	95.8 (92.8 to 97.6)	14	39 to 100	71.9 (53.6 to 85.7)	78 to 99	96.3 (92.1 to 98.2)	9
LBC	49 to 100	83.7 (62.2 to 94.8)	78 to 98	92.9 (83.5 to 97.2)	8	53 to 100	85.0 (53.2 to 96.9)	78 to 98	92.6 (75.5 to 98.2)	6
Combined	34 to 100	75.0 (64.1 to 83.3)	62 to 99	95.0 (92.2 to 96.8)	20	39 to 100	78.0 (63.5 to 88.4)	78 to 99	95.1 (91.6 to 97.3)	15

Study (Year) (n)	CIN2+		CIN3+	
	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]
Primary Studies Published After Cochrane[38] and HIQA[6] (Only LBC Used)				
ASCUS+				
Chatzistamatiou (2017)[49] (n = 1,723)	50.0 (31.48 to 68.51)	94.49 (93.38 to 95.59)	NR	NR
Jin (2016)[21]	NR	NR	90.7 (86.4 to 93.8)	97.6 (97.5 to 97.7)

Table 44: Sensitivity and Specificity of Cytology

(n = 99,549)				
Agorastos (2015)[54] (n = 3,993)	53.7 (37.4 to 69.3)	96.8 (96.2 to 97.4)	64.3 (35.1 to 87.2)	96.5 (95.9 to 97.1)
Wright (2015)[58] (n = 40,901)	40.6 (36.1 to 45.1)	97.3 (97.1 to 97.5)	47.8 (41.6 to 54.1)	97.1 (96.9 to 97.2)
LSIL+				
Chatzistamatiou (201,7)[49] (n = 1,723)	50.0 (31.48 to 68.51)	97.30 (96.52 to 98.09)	NR	NR
Agorastos (2015)[54] (n = 3,993)	41.5 (26.3 to 57.9)NR	98.8 (98.4 to 99.1)	57.1 (28.9 to 82.3)NR	98.6 (98.2 to 98.9)
>ASCUS				
Iftner (2015)[56] (n=9,451)	39.5 (29.4 to 49.5)	98.4 (98.1 to 98.7)	49.8 (34.7 to 64.9)	NR

ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HIQA = Health Information and Quality Authority; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion; NR = not reported; + = or more advanced pathological findings (?).

Table 45: Sensitivity and Specificity of Hybrid Capture 2

Systematic Reviews										
Test Cut-off Value	**CIN2+**					**CIN3+**				
	Sensitivity (%)		Specificity (%)		Number of studies	Sensitivity (%)		Specificity (%)		Number of studies
	Range	Pooled (95% CI)	Range	Pooled (95% CI)		Range	Pooled (95% CI)	Range	Pooled (95% CI)	
Cochrane (2017)[38]										
1pg/mL[a]	61 to 100	92.6 (89.6 to 95.3)	64 to 95	89.3 (87 to 91.2)	25	81 to 100	96.5 (94 to 97.9)	69 to 95	89.2 (86.7 to 91.3)	19
2 pg/mL	96 both	NP	94 and 95	NP	2	95 and 96	NP	94 and 95	NP	2
HIQA (2017)[6]										
1pg/mL	69 to 100	95.2 (92.5 to	43 to 100	88.2 (82.9 to	20	95 to 100	98.2 (96.7 to	15.9 to 100	87.6 (78.7 to	15

Table 45: Sensitivity and Specificity of Hybrid Capture 2

		97.1)		92.0)			99.1)		93.2)	
Primary Studies Published After Cochrane[38] and HIQA[6] (HC2 only)										
Study (year) (n)	**CIN2+**				**CIN3+**					
	Sensitivity (95% CI)		Specificity (95% CI)		Sensitivity (95% CI)		Specificity (95% CI)			
1 pg/mL										
Cook (2017)[41] (n = 3473)	100[b]		93.0[b]		100[b]		92.1[b]			
Iftner (2015)[56] (n = 9451)	93.2 (87.1 to 99.2)		94.9 (94.1 to 95.7)		100 (91.8 to 100)		NR			
Cut-off Value Not Specified										
Jin (2016)[21] (n = 99,549)	NR		NR		94.1 (90.3 to 96.5)		98.1 (98.1 to 98.2)			

CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; mL = millilitre; NP = not pooled; NR = not reported; pg = picogram

[a] The pooled sensitivity and specificity of HC2 are 90.5% (95% CI 86.1% to 93.6%) and 89.4% (95% CI 86.9% to 91.4%) respectively if the statistics from Sankaranarayanan 2004a in the Cochrane review was corrected and the diagnostic test accuracy was pooled based on a bivariate random-effects model from the *mada* package within R environment.

[b] Only relative sensitivities and specificities were reported. The statistics were calculated based on the results in Table 2 in Cook et al. (2017)[41]

Table 46: Sensitivity and Specificity of Other HPV Tests

Systematic Reviews										
Test	**CIN2+**					**CIN3+**				
	Sensitivity		Specificity		Number of studies	Sensitivity		Specificity		Number of studies
	Range (%)	Pooled (95% CI)	Range (%)	Pooled (95% CI)		Range (%)	Pooled (95% CI)	Range (%)	Pooled (95% CI)	
Cochrane (2017)[38]										
PCR (13+ hr types)	75 to 100	NP	85 to 97	NP	6	88 to 100	NP	79 to 94	NP	4
PCR (10-11 hr types)	74 and 89	NP	79 and 95	NP	2	79	NP	95	NP	1

Table 46: Sensitivity and Specificity of Other HPV Tests

Aptima	91 to 100	92.7 (31.7 to 99.7)	91 to 97	93.3 (47.3 to 99.5)	3	93 to 100	96 (72.9 to 99.5)	90 to 96	92.8 (86.2 to 96.3)	4
Cobas	88 to 100	NP	58 to 90	NP	2	92 to 100	NP	57 to 90	NP	2

Primary Studies Published after Cochrane[38]				
Study (year) (n)	**CIN2+**		**CIN3+**	
	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]
HPV (Multiplexed genotyping)				
Chatzistamatiou (2017)[49] (n = 1,723)	100.00 (100.00 to 100.00)	85.49 (83.79 to 87.20)	NR	NR
Aptima				
Cook 2017[41] (n = 3,473)	93.8[a]	97.3[a]	100[a]	96.4[a]
Iftner (2015)[56] (n =9,451)	87.8 (80.2 to 95.5)	96.1 (95.5 to 96.7)	90.9 (81.1 to 100)	NR
Cobas				
Kocsis 2017[51] (n = 3,150)	96.4 (89.8 to 99.3)	79.9 (78.5 to 81.4)	98.5 (91.8 to 99.9)	79.6 (78.1 to 81.4)
Agorastos 2015[54] (n = 3,993)	100.0 (91.4 to 100.0)	90.3 (89.3 to 91.2)	100.0 (76.8 to 100.0)	89.7 (88.7 to 90.6)
Wright (2015)[58] (n = 40,901)	69.1 (63.7 to 74.4)	94.0 (93.8 to 94.3)	76.1 (70.3 to 81.8)	93.5 (93.3 to 93.8)
CONFIDENCE				
Kocsis 2017[51] (n = 3,150)	95.2 (88.1 to 98.7)	77.8 (76.2 to 79.2)	98.5 (91.8 to 99.9)	77.4 (75.9 to 78.9)

CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; hr = high risk; NP = not pooled; NR = not reported; PCR = polymerase chain reaction

[a] Only relative sensitivities and specificities were reported. The statistics were calculated based on the results in Table 2 in Cook et al. (2017).[41]

Table 47: Sensitivity and Specificity of Cytology and HPV Tests (Adjusted for Verification Bias)

Systematic Reviews										
Test	CIN2+					CIN3+				
	Sensitivity (%)		Specificity (%)		Number of studies	Sensitivity (%)		Specificity (%)		Number of studies
	Range	Pooled (95% CI)	Range	Pooled (95% CI)		Range	Pooled (95% CI)	Range	Pooled (95% CI)	
Cochrane (2017)[38]										
CC or LBC (ASCUS+)	34 to 94	72.2 (57.5 to 83.3)	77 to 99	93.6 (88.9 to 96.4)	8	NR	NR	NR	NR	0
HC2 (1 pg/mL)[a]	67 to 97	89.0 (81.1 to 93.9)	64 to 95	88.6 (84.2 to 91.9)	12	NR	NR	NR	NR	0

Primary Studies Published after Cochrane[38]				
Study (year) (n)	CIN2+		CIN3+	
	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]
LBC (ASCUS+)				
Iftner (2015)[56] (n = 9,451)	39.5 (29.4 to 49.5)	98.4 (98.1 to 98.7)	49.8 (34.7 to 64.9)	NR
Wright (2015)[58] (n = 40,901)	40.6 (36.1 to 45.1)	97.3 (97.1 to 97.5)	47.8 (41.6 to 54.1)	97.1 (96.9 to 97.2)
HC2 (1 pg/mL)				
Iftner (2015)[56] (n = 9,451)	93.2 (87.1 to 99.2)	94.9 (94.1 to 95.7)	100 (91.8 to 100)	NR
Aptima				
Iftner (2015)[56] (n = 9,451)	87.8 (80.2 to 95.5)	96.1 (95.5 to 96.7)	90.9 (81.1 to 100)	NR
Cobas				
Wright (2015)[58] (n = 40,901)	69.1 (63.7 to 74.4)	94.0 (93.8 to 94.3)	76.1 (70.3 to 81.8)	93.5 (93.3 to 93.8)

ASCUS = atypical squamous cells of undetermined significance; CC = conventional cytology; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; LBC = liquid-based cytology; NR = not reported

[a] The pooled sensitivity and specificity of HC2 are 87.8% (95% CI 79.8% to 92.9%) and 88.8% (95% CI 84.3% to 92.1%) respectively if the statistics from Sankaranarayanan 2004a in the Cochrane review was corrected and the diagnostic test accuracy was pooled based on a bivariate random-effects model from the *mada* package within R environment.

5424

Table 48: Sensitivity and Specificity of Cytology and HPV Tests (Participants older than 30 Years)

Systematic Reviews										
Test	CIN2+					CIN3+				
	Sensitivity (%)		Specificity (%)		Number of studies	Sensitivity (%)		Specificity (%)		Number of studies
	Range	Pooled (95% CI)	Range	Pooled (95% CI)		Range	Pooled (95% CI)	Range	Pooled (95% CI)	
Cochrane (2017)[38]										
HC2 (1 pg/mL)[a]	67 to 100	93.9 (89.3 to 96.6)	80 to 95	91.3 (88.9 to 93.2)	13	NR	NR	NR	NR	0

Primary Studies Published after Cochrane[38]				
Study (year) (n)	CIN2+		CIN3+	
	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]
HC2 (1 pg/mL)				
Iftner (2015)[56] (n = 9,451)	93.2 (87.1 to 99.2)	94.9 (94.1 to 95.7)	100 (91.8 to 100)	NR
Aptima				
Iftner (2015)[56] (n = 9,451)	87.8 (80.2 to 95.5)	96.1 (95.5 to 96.7)	90.9 (81.1 to 100)	NR
Cobas				
Wright (2015)[58] (n = 40,901)	64.8 (58.4 to 71.1)	95.2 (95.0 to 95.5)	72.3 (65.0 to 79.6)	94.9 (94.6 to 95.1)
LBC (ASCUS+)				
Iftner (2015)[56] (n = 9,451)	39.5 (29.4 to 49.5)	98.4 (98.1 to 98.7)	49.8 (34.7 to 64.9)	NR
Wright (2015)[58] (n = 40,901)	40.3 (34.6 to 46.0)	97.9 (97.7 to 98.0)	48.0 (40.6 to 55.4)	97.7 (97.5 to 97.8)

5425
5426 ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HPV = human
5427 papillomavirus; LBC = liquid-based cytology; NR = not reported
5428 [a] The pooled sensitivity and specificity of HC2 are 87.8% (95% CI 79.8% to 92.9%) and 88.8% (95% CI 84.3% to 92.1%) respectively if the statistics from Sankaranarayanan 2004a in
5429 the Cochrane review was corrected and the diagnostic test accuracy was pooled based on a bivariate random-effects model from the mada package within R environment.

Table 49: Sensitivity and Specificity of Self-HPV Testing

Systematic Reviews					
Strategy	CIN2+				Number of studies
	Sensitivity (%)		Specificity (%)		
	Range	Pooled (95% CI)	Range	Pooled (95% CI)	
Cochrane (2017)[38]					
Self-HPV Test	41 to 97	NP	77 to 98	NP	4

CI = confidence interval; HPV = human papilloma virus; NP = not pooled

Table 50 : Predictive Values of Cervical Cancer Screening Tests

Systematic Reviews[a]				
Test	CIN2+		CIN3+	
	PPV (95% CI)	NPV (95% CI)	PPV (95% CI)	NPV (95% CI)
HIQA (2017)[6]				
HC2	11.8%	99.91%	7.6%	99.98%
Cytology	19.9%	99.57%	14.2%	99.76%

ASCH = atypical squamous cells, cannot rule out high-grade squamous intra-epithelial lesion; ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; HPV = human papillomavirus; NPV = negative predictive value; NR = not reported; PPV = positive predictive value

[a] Assuming prevalence of 1.6%, aged 25 to 60 in Irish settings

Table 51: Participation Rates

Systematic Reviews					
Invitation approach	Absolute Participation			Relative Participation	Number of studies
	Self-Sampling (%)		Control (%)		
	Range	Pooled (95% CI)	Pooled (95% CI)	Pooled [% (95% CI)]	
Verdoot (2015)[22]*, n = 16					
Per-protocol analysis					
Mail-to-all	6.4 to 34.0	20.7 (16.9 to 24.8)	10.3 (6.2 to 15.2)	2.06 (1.44 to 2.96)	13

Table 51: Participation Rates

Opt-in	5.8 to 13.4	9.7 (6.5 to 13.5)	12.2 (10.9 to 13.6)	0.72 (0.53 to 099)	3
Door-to-door	79.8 and 98.2	91.3 (65.8 to 100)	54.1 (0.9 to 100)	2.17 (0.33 to 14.13)	2
Intention-to-treat analysis					
Mail-to-all	10.2 to 39.0	23.6 (20.2 to 27.3)	10.3 (6.2 to 15.2)	2.40 (1.73 to 3.33)	13
Opt-in	8.7 to 22.9	14.0 (8.0 to 21.4)	12.2 (10.9 to 13.6)	0.97 (0.65 to 1.46)	3
Door-to-door	83.0 and 98.2	92.4 (71.3 to 100)	54.1 (0.9 to 100)	2.21 (0.32 to 15.48)	2
Primary Studies Published after Verdoot[22]					
Study (year)	Absolute Participation			Relative Participation	Notes
	Intervention		Control		
	% of total offered (n)		% of total offered (n)	Significance	
Self-Sampling					
Self-sampling HPV vs cytology among non-attenders					
Enerly (2016)[42]	33.4 (267), including 98 attending cytology		23.2 (601)	Participation rate in the HPV self-sampling arm higher	Two RCT arms: self-sampling (HC2 and CLART) versus liquid-based cytology
Cadman (2015)[47]	8 (247)		6 (183)	The rate of responding to the intervention by sampling by themselves or going to clinic significantly higher than that of the control	Two RCT arms: HPV self-sampling versus cytology
Self-sampling HPV vs cytology among women without screening in the past three years					
Ilangovan (2016)[53]	67 (121)		33 (59)	Not tested	Two arms in an observational study: HPV self-sampling versus traditional Pap smear

Table 51: Participation Rates

Rossi (2015)[48]	Self-sampler at home 21.6 (974) Self-sampler at pharmacy 12.0 (540)	Cytology at clinic 11.8 (235) HPV at clinic 12.0 (363)	The rate of self-sampling at home higher than that of test at clinic. The rate of taking self-sampler at pharmacy not significantly different from that of test at clinic	Four RCT arms: cytology test at clinic versus HPV test at clinic versus self-sampling at home versus self-sampling pharmacy
Self-sampling HPV vs cytology among women without screening in the last 30 months				
Racey (2016)[43]	HPV invitation 31.9 (107) Cytology invitation 15.4 (51)	Opportunistic screening/ standard of care 8.6 (13)	Not tested	Three RCT arms: HPV self-sampling (PCR-based HPV test) versus cytology versus control
Self-sampling HPV vs cytology among women without screening in the past five years				
Sultana (2016)[44]	Apparently never-screened 15.8 (1131) Apparently under-screened 7.3 (518)	6.0 (61) 6.4 (65)	*P*<0.001 *P*<0.001	Two RCT arms: HPV self-sampling versus cytology
Self-sampling HPV vs cytology among women without screening in the past one year				
Williams (2016)[45]	80 (48)	56.7 (34)	*P*<0.01	Two RCT arms: tampon self-collection versus clinic-based sampling
Self-sampling HPV vs cytology among women in First Nation communities, including attenders, non-attenders and -pregnant women				
Zehbe (2016)[46]	20.0 (54)	14.3 (35)	Not significantly different	Two RCT arms:self-sampling HPV tests versus cytology, cluster-

Table 51: Participation Rates

				randomized
Physician sampling				
Physician-collected HPV vs cytology for women aged 56 to 60 years eligible for routine screening				
Lamin (2017)[40]	34.7 (7325)	34.4 (7438)	Not tested	Two RCT arms: clinic-based Cobas HPV tests versus LBC
Physician-collected HPV vs cytology for women aged 25 to 64 years attending routine screening				
Altobelli (2016)[52]	40.3 (24206)	38.7 (14142)	Not tested	Two historical cohorts: clinic-based HC2 HPV tests between 2011 and 2013 versus cytology between 2008 and 2010
Pasquale (2015)[57]	67.9 (18728)	64.7 (18233)	The relative frequencies of HPV tests higher than cytology	Two arms in an observational study: Cytology versus HPV tests[a]

CI = confidence interval; HC2 = Hybrid Capture 2; HPV = human papillomavirus; LBC = liquid-based cytology; NP = not pooled; NR = not reported; NS = not specified; PCR = polymerase chain reaction

[a] Historical comparison between cytology (2007 to 2009) and HPV tests (2010 to 2013)

Table 52: Referral to Colposcopy

Systematic Reviews			
Melnikow (2018)[39] (n = 14)			
HPV testing strategy	**% of total screened** (N)	**% of total triaged** (N)	**Studies Included**
RCTs			
All participants, round 1			
hrHPV alone	NR	7.9 (1936)[a]	NTCC Phase II
hrHPV with LBC triage	NR	3.8 (154), 5.7 (544)	2, Compass, HPV FOCAL
LBC with hrHPV triage	NR	3.1 (290)	HPV FOCAL
hrHPV with CC triage	NR	1.2 (796)	FINNISH
Conventional cytology	NR	1.1 (755), 2.8 (679)	2, FINNISH, NTCC Phase II
LBC	NR	2.7 (27), 3.1 (290)	2, Compass, HPV FOCAL
All participants, round 2			
hrHPV and LBC cotesting after round 1 hrHPV with LBC triage	NR	4.9 (469)	HPV FOCAL
hrHPV and LBC cotesting after round 1 LBC triage	NR	7.0 (660)	HPV FOCAL
Women aged 35 years or older, round 1[496]			
hrHPV along	NR	5.8 (1029)	NTCC Phase II
hrHPV with LBC triage	NR	2.6 (80), 3.8 (NR)	2, Compass, HPV FOCAL
LBC with hrHPV triage	NR	2.1 (NR)	HPV FOCAL
hrHPV with CC triage	NR	0.9 (506)	FINNISH
Conventional cytology	NR	1.0(544), 2.5 (435)	2, FINNISH, NTCC Phase II

Table 52: Referral to Colposcopy

LBC	NR	2.2 (17), 2.1 (NR)	2, Compass, HPV FOCAL
Women aged less than 35 years, round 1[496]			
hrHPV along	NR	13.1 (970)	NTCC Phase II
hrHPV with LBC triage	NR	8.5 (76), 19.9 (25 to 29 years); 10.8 (30 to 34)	2, Compass, HPV FOCAL, HPV FOCAL
LBC with hrHPV triage	NR	8.1 (25 to 29 years); 6.2 (30 to 34 years)	HPV FOCAL
hrHPV with CC triage	NR	2.3 (290)	FINNISH
Conventional cytology	NR	1.9 (211), 3.6 (244)	3, FINNISH and NTCC Phase II
LBC	NR	4.7 (10), 8.1 (25 to 29 years), 6.2 (30 to 34 years)	2, Compass, HPV FOCAL, HPV FOCAL
Cohort studies on primary HPV testing, 3-year intervals			
Round 1			
Primary HPV	NR	4.4 (2136)	Zorzi (2017)
Round 2			
Primary HPV	NR	2.2 (472)	Zorzi (2017)
Round 1 & 2			
Primary HPV	NR	5.4 (2608)	Zorzi (2017)
Primary Studies Published after the literature search in Melnikow et al.[39]			
Study (year)	**% of total screened** (N)	**% of total triaged** (N)	**Referral at follow-up**
RCTs			
Aptima			
Cook (2017)[41] **HPV FOCAL, subset of Intervention Arm**	Not available due to study design	NR	NR

Table 52: Referral to Colposcopy

HC2			
Cook (2017)[41] HPV FOCAL, subset of Intervention Arm	5.9 (205)	NR	NR
Cobas HPV test			
Lamin (2017)[40]	0.8 (59)	0.3 (59)	NR
LBC (ASCUS+)			
Lamin (2017)[40]	0.7 (51)	0.2 (51)	NR
Non-randomized studies			
HC2			
Chiappetta (2015)[55]	1.1 (234)[b]	NR	NR
Multiplexed genotyping HPV test			
Chatzistamatiou (2017)[49]	16.3 (280)	NR	NR
Aptima			
Granados (2017)[50]	3.5 (177)	NA	NR
LBC (ASCUS+)			
Chatzistamatiou (2017)[49]	6.4 (110)	NR	NR
Chiappetta (2015)[55]	3.6 (154)[c]	NR	NR
Granados (2017)[50]	2.7 (136)	NA	NR

AHRQ = Agency for Healthcare Research and Quality; ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; FINNISH = a cervical cancer screening trial in Finland or called Public health Trial Finland in the HIQA review[6]; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; HPV = human papillomavirus; HPV FOCAL = HPV testing for Cervical Cancer Screening trial; LBC = liquid-based cytology; mL = millilitre; NA = not applicable; NR = not reported; NTCC = New Technologies for Cervical Cancer; pg = picogram

[a] Higher than cytology or LBC control

[b] Aged 25 to 65 years

[c] Aged 25 to 34 years

Table 53: Harms and Clinical Utility Outcomes

Systematic Reviews					
Outcome	**HPV testing**		**Cytology**		**Number of studies**
	Range (%) or values	Pooled (%)	Range (%) or values	Pooled (%)	
Melnikow (2018)[39]					
CIN3+ detection	0.02 (5)[b], 0.2 (22)[b], 0.3 (195)[a], 0.4 (97), 0.4 (102)[a], 0.7 (67)[a], 0.8 (30)[a], 0.9 (89)[b]	NR	0.09 (23)[b], 0.6 (52)[b], 0.2 (118)[a], 0.1 (33), 0.2 (56)[a], 0.4 (41)[a], 0.1 (1)[a], 1.0 (93)[b]	NR	4, NTCC Phase II round 2, HPV FOCAL round 2, FINNISH, NTCC Phase II round 1, NTCC Phase II cumulative round 1 & 2, HPV FOCAL round 1, Compass, HPV FOCAL cumulative round 1 & 2
False-positive rates	5.1 (421), 6.6 (624), 7.2 (4,462), 7.4 (1,799)	NR	5.2 (413), 2.6 (244), 6.5 (4,239), 3.2 (770)	NR	3, HPV FOCAL round 2, HPV FOCAL round 1, FINNISH, NTCC Phase II
Psychological effects including stress, anxiety and sexual satisfaction	NR	NR	NR	NR	4 primary hrHPV testing RCTs (NTCC Phase II, HPV FOCAL, Compass, and FINNISH)[c]
Invasive cervical cancer incidence	0.02 to 0.09	0.05	0.05 to 0.13	0.08	5, 4 cotesting (NTCC Phase I, SWEDESCREEN, ARTISTIC, and POBASCAM) and 1 primary hrHPV testing (NTCC Phase II) trials meta-analyzed in Ronco et al. (2014)[d]
Biopsy rates	5 to 11	6.9	2 to 11	4.8	5, 4 cotesting (NTCC Phase I, SWEDESCREEN, ARTISTIC, and POBASCAM) and 1 primary hrHPV testing (NTCC Phase II) meta-analyzed in Ronco et al. (2014)[d]
Cervical cancer mortality	NR	NR	NR	NR	8 RCTs (including 4 co-testing studies) and 5 cohort studies
Rates of treatment	NR	NR	NR	NR	8 RCTs (including 4 co-testing studies) and 5 cohort studies
Harms	NR	NR	NR	NR	8 RCTs (including 4 co-testing studies) and 5 cohort studies

AHRQ = Agency for Healthcare Research and Quality, ARTISTIC = A Randomised Trial In Screening To Improve Cytology; ASCUS = atypical squamous cells of undetermined significance; CG = control group; CI = confidence interval; CSQ = Cervical Screening Questionnaire; GHQ = General Health Questionnaire; HC2 = Hybrd Capture 2; hr = high-risk; HPV = human papillomavirus; IG = intervention group; LBC = liquid-based cytology; NR = not reported; SRS = Sexual Rating Scale; STAI = Spielberger's State Trait Anxiety Inventory; ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CG = control group; CI = confidence interval; IG = intervention group; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program

[a]Significantly higher than the control group (conventional cytology or liquid-based cytology)

[b]Significantly lower than the control group (conventional cytology or liquid-based cytology)

[c] Related results reported in two cotesting studies, McCaffery (2004) and ARTISTIC that were not presented here

[d] Different screening strategies and study design adopted by the RCTs. " A total of 176,464 women with 1,214,415 person-years of followup were included with 107 cases of ICC in a median followup period of 6.5 years. After 8 years of followup, cumulative detection of ICC was 46.7 per 100,000 in the hrHPV screened women compared with 93.6 per 100,000 women in the control groups." FINNISH reported related statistics, but was not considered for too few cases reported. FINNISH was called Public health Trial Finland in the HIQA review.[6]

Appendix 10: Characteristics of existing published model-based economic evaluation assessing relevant screening strategies of interest to the review based on comparable health care context (e.g., Canada, USA, Australia, New Zealand and European Economic Area[1])

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
Acetta, 2010 [64]	Italy, TPP	Simulated cohort of 10 million women followed from birth	To evaluate the comparative impact of screening strategies with or without the vaccination of young girls.	Specific screening protocols that were evaluated included (with varying age and screening interval): • No intervention but treatment of symptomatic cervical cancer; • Primary cytology • Primary HPV testing (hybrid capture II); • Primary cytology followed by HPV testing for positive Pap test results (ASCUSþ) • Primary HPV with cytology triage	Patient-level state-transition model	• HPV DNA with Pap triage every five years dominates current screening (Pap test every 3 years) • Same in both vaccinated and unvaccinated women, though a higher sequential ICER in vaccinated women	• Increasing vaccine efficacy alters study results
Balasubramanian, 2010 [65]	US, societal	Cohort of women beginning at age 12 years and followed through age 85 years	To estimate the accuracy and cost-effectiveness of cervical cancer screening strategies based on high-risk HPV DNA testing of self-collected vaginal samples	Screening protocols evaluated include (with tests occurring at different intervals, with vaginal tests self-done, cervical tests in clinic): • No screening was the reference • Primary HPV with cytology triage • Primary HPV • Primary cytology with reflex HPV for ASCUS	Cohort-level state-transition model	• Triennial screening by HPV DNA testing followed by in clinic cytology triage • The other two intervals of time for HPV DNA with cytology triage were on efficiency frontier	• Disutility of no clinician contact from home based strategies made HPV DNA testing at home biennially more costly and less effective

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
				• Primary cytology with repeat cytology for ASCUS • Primary HPV testing			than in clinic PAP or HPV based strategies
Berkhof, 2010 [66]	Netherlands, societal	Simulated cohort of 4 Million dutch women from age 10 to 100 years of age	To study the health and economic effects of human papillomavirus (HPV) DNA testing in cervical screening using a simulation model	Screening protocols evaluated include: • Primary cytology at 5 year intervals from 30-60 years of age • Primary HPV with cytology triage • Co-testing • Primary cytology with HPV triage	Patient-level state-transition model	• HPV testing (5 to 7.5 yearly interval) with cytology triage is likely to be cost effective • 5-yearly cytology with HPV triage also considered cost-effective	• No changes
Bistoletti, 2008 [67]	Sweden, TPP	Simulated cohort of women from age 32 to death (of any cause, including cervical cancer)	To estimate life expectancy and health care cost per woman during the remaining lifetime for 4 screening strategies	The following four strategies evaluated: • Strategy 1: Primary cytology at 3 year intervals from 32 to 50, increased to 5 between age 50 to 60 • Addition of HPV DNA co-testing to strategy 1 as of age 32 • Addition of co-testing at ages 32, 41 and 50 • No screening	Patient-level state-transition model	• Co-testing was most cost-effective	• None performed
Chuck, 2010 [68]	Alberta, TPP	Cohort of women from 12 years of age to 80 years of age	To assess the cost-effectiveness of 21 alternative cervical cancer screening (CCS) strategies.	7 alternatives at 1,2 and 3 year intervals, including the following: • Primary cytology (Pap test) • Primary cytology (Pap test) with HPV triage • Primary cytology	Patient-level state-transition model	• Cytology (PAP) with HPV DNA triage testing for women older than 30 years of age every 3 years (Dominated current – PAP	• None performed

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
				(LBC) with HPV triage • Primary HPV with cytology (LBC) triage • Applying an age restriction of HPV DNA test in scenarios above – only women above 30 years of age		every year) Others on efficiency frontier: • Cytology with HPV triage (for women over 30) every year • Cytology with HPV triage every year (no age restriction)	
Coupe, 2012 [69]	Netherlands, societal	A cohort of Dutch women from age 12 to 100	To assess the influence of broad spectrum vaccines and cross-protection against non-HPV16/18 types on the cost-effectiveness of future screening programs	Scenarios compared include: With HPV 16/18 cross protection (8 scenarios) • Either cytology or HPV DNA as the primary screening method at varying intervals starting at age 30 – with cytology triage With broad spectrum vaccination • Primary HPV testing with cytology triage	Patient-level state-transition model	• HPV DNA screening four times between age 30 and 60 years when considering HPV 16/18 cross-protection • One screen during lifetime was cost-effective in conjunction with a broad spectrum vaccination	• No changes observed

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
de Kok, 2012 [70]	Various European countries, adjusted societal perspective (no productivity losses included)	Unvaccinated women born between 1939 and 1992	To investigate, using a Dutch model, whether and under what variables framed for other European countries screening for human papillomavirus (HPV) is preferred over cytology screening for cervical cancer, and to calculate the preferred number of examinations over a woman's lifetime.	Nine different strategies considered: • Primary cytology and cytology triage • Primary HPV testing and cytology or a combination of cytology and HPV triage • Primary cytology and HPV or combination of HPV and cytology triage	Agent-based model given the website of the model's	• Primary HPV screening was the preferred primary test over the age of 30	• Primary cytology preferred when it was low cost and when HPV prevalence was high and HPV testing costs were high
Diaz, 2010 [71]	Spain, societal	A single birth cohort of girls followed fom age 9 throughout their lifetime	To assess the health and economic impact of adding HPV vaccination to cervical cancer screening	Strategies assessed included: • Screening alone of women over age 25, varying frequency (every 1–5 years) and test and triage (cytology, HPV testing, but no primary HPV testing); • HPV vaccination of 11-year-old girls combined with screening.	Patient-level state-transition model	• Strategies that incorporated HPV testing are more effective and cost-effective than those • with cytology alone • (i.e. 5-year organized cytology with HPV testing as triage from age 30 to 65)	• Vaccine price altered ICER
Georgalis, 2016 [72]	Spain, societal	Cohort of 11-year old girls	To compare the effectiveness and cost-effectiveness	Strategies assessed include: • Vaccination alone	Patient-level state-transition	• All screening along strategies and vaccination	• Range of vaccinatio n uptakes

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
			of different cervical prevention scenarios including current status and new proposed prevention strategies to inform health decision-makers in Spain.	• Screening alone (included cytology starting at 25 years of age or HPV testing at 30 years of age with cytology triage, each with further scenarios with varied time intervals between tests (1-5years)) • Combined vaccination and screening	model	with cytology strategies dominated by vaccination plus HPV testing with cytology triage • Strategies on efficiency frontier are: -vaccination -HPV testing in descending order of yearly intervals	
Ginsberg, 2009 [497]	Global, TPP -region specific estimates	Unclear, groups varied based on socioeconomic status	To compare and evaluate the costs and effectiveness of different screening and prevention strategies relating to cervical cancer in all 14 WHO regions of the world.	Strategies assessed include: • Primary cytology • Primary HPV • VIA (Visual inspection after application of 3-5% acetic acid • PAP tri-annually, then co-testing (annually, 3 and 5 years)	Cohort-level state-transition model	• Results presented in context of including vaccination, and by global region, so difficult to discern most-cost effective	• Results most impacted by vaccine price
Goldhaber-Feibert, 2008 [73]	US, societal	Cohort of 1 million girls followed from age 9 throughout their lifetime, one vaccinated group, another unvaccinated group	To assess the quality-adjusted life years (QALYs), lifetime costs, and incremental cost-effectiveness ratios of screening, vaccination of preadolescent girls, and vaccination combined with screening.	Screening strategies varied by initiation age and interval, and included: • Primary cytology with HPV triage • Primary HPV with cytology triage • Co-testing	Patient-level state-transition model	• For unvaccinated women, triennial cytology with HPV triage at age 21, followed by HPV with cytology triage at age 30, was most cost-effective	• Results were sensitive to lower specificity of HPV DNA testing

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
						• For girls vaccinated before 12, same strategy, but beginning at 25 and switching at 35 with screening every 5 years was deemed most cost-effective	
Goldie, 2004[74]	US, societal	Cohort of sexually naïve women, free of disease; begins at age 13	To conduct a comprehensive cost-effectiveness analysis of cervical cytology screening strategies that incorporate HPV DNA testing in women aged 30 years or more	17 strategies assessed, varying the sequence of tests, consisting of: • No screening • Conventional • Primary cytology (Pap test); • Primary LBC w/ HPV tests triage for ASCUS • Primary HPV tests w/ cytology triage for HPV positive test (as of 30 years of age)	Cohort-level state-transition model	Strategies on efficiency frontier: • No screening was reference • Thereafter, more costly and more effective strategies consisted of conventional PAP or liquid PAP w/ HPV triage	• None performed
Huh, 2015 [75]	US, TPP	Cohort non-hysterectomized women (30years of age) who were asymptomatic for cervical cancer and had participated in cervical screening in a US healthcare setting over a 40-year period	to evaluate the cost effectiveness of cervical cancer primary screening with a HPV-16/18 genotyping test which simultaneously detects 12 other high-risk HPV types.	4 strategies assessed: • Primary cytology with reflex HPV testing for ASCUS • Co-testing • Primary HPV testing with reflex cytology • Primary HPV testing with genotyping and reflex cytology (ASCUS threshold)	Cohort-level state-transition model (over 40 year period)	• HPV with genotyping and reflex cytology dominated the co-testing and HPV with reflex cytology strategies by reducing costs and cancer incidence and improving QALYs, while also being more	• Outcome were most influenced by strategy performance

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
						cost-effective than cytology with reflex HPV	
Kulasingam, 2009 [76]	Canada, TPP	Theoretical cohort of women	To estimate lifetime costs and life expectancy of different screening strategies.	27 strategies with different testing frequencies and starting ages: • Primary cytology • Primary HPV testing • Co-testing • Primary cytology with HPV triage • Primary HPV with cytology triage	Cohort-level state-transition model	Strategies on efficiency frontier include: • HPV DNA at age 25, with PAP triage (5 every years, as well as every 3 years) • HPV DNA at age 18 with PAP triage	• No changes observed
Lew, 2016 [24]	New Zealand, TPP	Two populations of interest: 1. Unvaccinated women (older cohort) 2. Vaccinated cohort, born in 1997()	To identify optimal future screening approaches (based on cost-effectiveness) in NZ in both vaccinated and unvaccinated women.	16 strategies (with varying range of screening, frequency, sequence of tests and management of intermediate risk group), were considered, consisting of: • Primary Cytology with HPV triage (if 30 years of age or older) • Primary HPV tests w/ cytology triage for HPV positive test • Primary HPV tests w/ partial genotyping • Co-testing • Co-testing w/ partial genotyping	Hybrid model: system dynamics for HPV transmission /vaccination and cohort state-transition model	Strategies on efficiency frontier: • All 1° HPV testing were more effective and most were cost saving compared to current practice of cytology alone • Intervention most likely cost effective at λ of 20-50K per life-year saved: 5 yearly 1° HPV test with partial genotyping and cytology triage was most cost effective	• Adherence to screening when initiation at 25 years of age altered results
Mittendorf, 2003 [77]	Germany, TPP	A cohort of German women starting at 20 years of age and followed for 20 years	To evaluate the efficiency of different screening	4 screening strategies were considered: • No screening • Primary cytology	Cohort-level state-transition model	• Reference was no screening. • Testing with any HPV DNA test	• No changes observed

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
		(not **lifetime)**	procedures using the HPV test against the currently used strategy in Germany and against a "do nothing" strategy.	(every 5 years) • Primary HPV test (every 5 years unless positive result) • HPV + cytology co-testing (every 10 years unless positive result)	(20years)	(alone or in combination) is superior to cytology along or no screening	
Naber, 2016 [78]	Netherlands, Societal	20-year-old cohort of 100 million women with life expectancy as observed in the Netherlands, which was not affected by HPV vaccination (neither directly nor through herd immunity).	To quantify the consequences of a switch to primary HPV screening for over-screened women, taking into account its higher sensitivity but lower specificity than cytology.	12 strategies (for both primary HPV DNA and primary cytology): • Varied starting age (20, 25, 30) and screening interval (1,2,3,5) • All incorporated a "cost-effective triage strategy" and the primary screening was followed by triage with the other strategy	Agent-based model	• Reference case was no screening • Frequent screening (or over-screening) harms outweigh life-years gained when going from cytology to HPV DNA as primary test • No cost-effectiveness frontier presented	• No changes, except when background risk of cc mortality increased, more frequent screening and switching to HPV resulted in more QALYS gained for women 30 years of age and screened bienially
Naber, 2016 [79]	Netherlands, Societal	Two populations of 1 million women, : 1. Pre-vaccination 2. Vaccinated	To determine the optimal screening strategy for a pre-vaccination population and for vaccinated women	4 strategies considered: • Primary HPV with reflex cytology triage • Primary cytology with reflex HPV triage • Co-testing	Agent-based model	• Reference was no screening • Primary HPV screening with cytology triage was the optimal strategy for both	• When background risk of cervical cancer is reduced, screening

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
				• Primary cytology with cytology and HPV triage after 6 months and cytology triage after 18 months		populations (8 lifetime screens in pre-vacc. group, 3 lifetime screens in vaccinated group) • Depending on Herd immunity levels, once 50% is reached, reducing screening intensity can then be considered	can be optimized to vaccinated women in unvaccinated women
Popadiuk, 2016[80]	Canada, TPP	Women aged 21 to 65, 70% of whom were assumed to be vaccinated with 100% efficacy	To use the cervical cancer and hpv transmission models of the Cancer Risk Management Model to study the health and economic outcomes of primary cytology compared with HPVtesting	14 screening scenarios with varying screening modalities and intervals • Primary cytology starting at ages 21 or 25 at 3 year intervals • Primary HPV testing starting at age 30 at different intervals (3,5,7.5,10) • Combinations of primary cytology or HPV tests at different intervals starting at age 30 with triage as follow-up for primary HPV protocols	Dynamic event-based micr osimulation (30 years, not lifetime)	Reference case was triennial cytology from age 25 Strategies on the cost-effectiveness frontier were: • HPV DNA testing along at all year intervals • Triennial cytology at age 21 or 25 combined with HPV testing every 3 years at age 30	• Results were sensitive to cost variations in HPV DNA testing
Sherlaw-Johnson, 2004 [81]	UK, TPP	Following women from 15 years of age	To evaluate different options for introducing LBC and HPV testing into the UK cervical cancer	Screening options included the following at 3 and 5 year intervals, both with and without LBC:	Patient-level state-transition model	Strategies on efficiency frontier: • repeat cytology follow-up with LBC (5-year)	• Higher cost of LBC leads to primary Pap test

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
			screening programme	• Primary cytology • Primary cytology with HPV triage • Primary HPV testing as of age 30 with cytology triage (cytology until age 30) • Co-testing as of age 30 (Cytology alone until age 30)		• Cytology with HPV triage with LBC (5-year) • Primary HPV testing with LBC (5-year) • Co-testing (5-year) • Primary HPV testing with LBC (3-year) • Co-testing (3-year)	options being more cost-effective
Sroczynski, 2010[82]	Germany, TPP	Cohort of 15 year old women	To determine -What is the cost-effectiveness (in Euro per LYG) of HPV testing in primary cervical cancer screening in the German health care context? -What is the optimal algorithm for HPV-based cervical cancer screening (i. e., test combination, start and stopping age of screening, screening interval), and which recommendations should be derived for the German health care context?	18 screening strategies assessed differing by screening interval and test combinations: • No screening • Primary cytology (>=20 y-o) at 1,2,3,5 year intervals • Annual primary cytology, followed by HPV testing as of age 30 at 1,2,3,5 year intervals • Biennial primary cytology, then primary HPV DNA at 2, 3, or 5 years • Biennial primary cytology, then combined cytology and HPV as of 30 years of age at intervals of 2, 3, or 5 years • Biennial primary cytology, then	Cohort-level transition-state model	• Reference case was no screening • On the cost-effectiveness frontier were: -cytology every five years -Biennial cytology and hpv -Biennial cytology, then biennial hpv and cytology triage -annual cytology from 20-29 then annual HPV DNA	• Variation in increase in sensitivity of HPV testing influenced ICER results

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
				primary HPV testing as of 30 years of age, in intervals of 2,3 or 5 years, for HPV negative women and PAP triage for HPV positive women			
Sroczynski, 2011 [83]	Germany, TPP	Cohort of 15 year old women	To systematically evaluate the long-term effectiveness and cost-effectiveness of HPV-based primary cervical cancer screening in the German health care context using a decision-analysis approach.	18 screening strategies assessed differing by screening interval and test combinations: • No screening • Primary cytology test (>=20 y-o) at 1,2,3,5 year intervals • Annual primary cytology test, followed by HPV testing as of age 30 at 1,2,3,5 year intervals • Biennial primary cytology, then primary HPV testing at 2, 3, or 5 years • Biennial primary cytology, then combined cytology and HPV as of 30 years of age at intervals of 2, 3, or 5 years • Biennial primary cytology, then primary HPV testing as of 30 years of age, in intervals of 2,3 or 5 years, for HPV negative	Cohort-level transition-state model	Reference case was no screening On the cost-effectiveness frontier were: • Cytology every five years • Cytology every three years • Biennial cytology, HPV every three years • Biennial cytology, then biennial HPV • Biennial cytology, then Biennial HPV and cytology triage every 2 years • Annual cytology from 20-29 then annual HPV DNA Annual cytology dominated by HPV DNA strategies	• Increasing age of initiation lowers costs

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
				women and PAP triage for HPV positive women			
VanRosmalen, 2011	Netherlands, societal	Dutch women without HPV vaccination at risk for cervical cancer	To compare a variety of nationally and internationally recommended HPV and cytology triage schedules	9 strategies were assessed (varying age range of screening and frequency): • Primary cytology w/ cytology triage for borderline mildly abnormal smears • Primary HPV tests w/ combination of cytology and HPV tests triage for HPV positive test • Primary HPV testing w/ cytology triage for HPV positive test • Primary cytology w/ combination of cytology and HPV DNA tests for borderline mildly abnormal smears • Primary cytology w/ HPV tests triage for borderline mildly abnormal smears	Agent-based model given the website of the model's	Strategies on efficiency frontier: • 1° cytology w/ HPV triage was reference • Thereafter, more costly and more effective strategies consisted of 1° HPV screening w/ either cytology triage/ combination of cytology and HPV triage	• Lab costs for HPV tests • Utility loss associated with time spent in triage • Compliance with triage tests • Cervical cancer risk • Discount rates
Vijayaraghavan, 2010 [85]	Quebec, TPP	Cohort of women beginning at age 13	To determine the cost-effectiveness of several cervical cancer screening strategies utilizing conventional cytology and HR-HPV testing	6 strategies were considered, (cytology only prior to age 30): • No screening; Conventional cytology (every 1 to 3 yrs) w/ repeat cytology for ASCUS ; • Primary cytology w/ HPV triage for ASCUS (ever 1-3	Patient-level state-transition model	Strategies on efficiency frontier were those that incorporated HPV as 'only' or triage • Conventional cytology was reference • Thereafter, more costly and more effective	• Compliance & loss-to-follow-up

First Author, Year	Country, perspective	Population	Decision Problem	Interventions assessed[2]	Approach	Findings (most cost-effective strategy)[†]	Uncertainty Analyses (author's conclusions)
				yrs) • Primary HPV test (every 3 yrs) • Primary HPV test w/ cytology triage (every 3 yrs) • Co-screening w/ HPV DNA test and cytology (every 3 yrs)		strategies consisted of 1° HPV tests and HPV-only strategy	
Vijayaraghavan, 2010 [86]	United States, TPP	Hypothetical cohort of 100,000 U.S. women over their lifetimes, starting at age 13 year	To determine the cost-effectiveness of adding HPV-16 and 18 genotype triage to current cervical cancer screening strategies in the United States.	All women underwent biennial Pap until age 30, followed by: • Primary cytology (LBC) every 2 years • Primary cytology (LBC) every 2 years with HPV for equivocal results • Primary HPV test w/ cytology triage for HPV positive tests • Co-testing every 3 years • Co-testing every 3 year with reflex HPV DNA genotyping and intensive follow-ups for HPV types 16/18 • Primary HPV test with HPV genotyping for all positive tests	Patient-level state-transition model	• HPV genotyping with co-screening was the most effective strategy and had an ICER of $33,807 per QALY compared to HPV genotyping for all high-risk HPV-positive women.	• No changes reported

HPV = human papillomavirus; LBC = liquid base cytology

[1] Defined as Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany,Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta,Netherlands, Poland, Portugal, Romania, Slovakia and the UK

[2] Cytology refers to Pap test unless otherwise noted

Appendix 11: Study Characteristics and Critical Appraisal – Patient Experiences

Author, publication year	Country	Methodological and Analytic Approach	Participants	Data collection	Study Objectives
Abdullahi et al. (2009)	UK	Thematic analysis	50 First-generation Somali immigrant women	Interviews; focus groups	To explore barriers to, and ways to improve, uptake of cervical screening among Somali women in Camden, London.
Ackerson (2010)	USA	Constant comparative analysis	24 African-American women	Interviews	To explore personal influencing factors that contribute to Pap smears in African American women who do (routine-use group) and do not (non-routine-use group) obtain routine testing.
Ackerson et al. (2011)	USA	Content analysis	24 African American women	Interviews	Explore inductively African American women's use of Pap smear screening services and consider how well the data did or did not affirm the usefulness of the interaction model of client health behavior (IMCHB).
Ackerson (2012)	USA	Content analysis	15 African-American women	Interviews	To investigate the role of sexual and intimate partner violence in Pap smear avoidance behavior in African American women.
Ackerson et al. (2008)	USA	Qualitative description	7 African-American women with high school education or less and yearly income <$35 000	Interviews	A qualitative study exploring personal influences regarding Pap smears in low-income African American women.
Adegboyega et al. (2016)	USA	Qualitative description	22 sub-Saharan African immigrant women	Focus groups; demographic questionnaires	To understand the factors influencing Pap smears among sub-Saharan African immigrant women.
Agenor et al. (2015)	USA	Thematic analysis	18 black lesbian, bisexual, and queer women	Focus groups	To understand the facilitators of and barriers to cervical cancer screening in black lesbian, bisexual, and queer

					(LBQ) women.
Agenor et al. (2016)	USA	Grounded theory	32 transmasculine men; 17 clinicians	Interviews; focus groups	To understand the low rates of Pap smear use in transmasculine people.
Akhagba (2016)	Poland	Qualitative, not otherwise stated	12 migrant African women	Focus groups	To explore the knowledge and perception of migrant women about cervical cancer and other health-related issues; and to understand participants' knowledge about cervical cancer screening, its benefits and the sociocultural issues that impedes migrant women in the participation of the screening programmes in Poland.
Anaman-Torgbor et al. (2017)	Australia	Thematic analysis	19 African immigrant women	Interviews	To describe barriers and facilitators of cervical screening practices among African immigrant women living in Brisbane, Australia.
Andrasik et al. (2008)	USA	Qualitative, not otherwise stated	35 low-income HIV-positive African-American women	Interviews	To elucidate the perspective of low-income HIV-positive African American women, who have not received cervical cancer screening for five or more years, on the barriers they face in accessing and using reproductive health care.
Andreassen et al. (2017)	Romania	Qualitative, not otherwise stated	144 participants (9 interviews with 7 Roma and 2 non-Roma women; 78 participants in observation; 9 screening specialists in two focus groups; 48 Roma women in five focus groups)	Participant observations; interviews; focus groups	To explore Roma women's (non)participation in cervical cancer screening program from women's own perspective and those of health care providers and policy makers.
Anhang et al. (2004)	USA	Grounded theory and adapted approaches	48 low-income women of various ethnic minorities	Focus groups	To investigate women's questions and concerns about HPV or their attitudes toward HPV testing
Armstrong (2005)	UK	Qualitative, not otherwise stated	Ethnic minority women (sample size not provided)	Interviews	To explore how individual women deal with, and react to, the very general information on cervical cancer risks they receive when invited to attend for cervical screening, and the general 'at risk' position that is suggested to them

					through the official UK discourse on screening.
Armstrong (2007)	UK	Qualitative, not otherwise stated	36 women	Interviews	To explore how individual women interpret, negotiate and make sense of this discourse in the context of their personal circumstances, experiences and characteristics of cervical screening.
Armstrong (2012)	UK	Constant comparative analysis	34 women from diverse ethnic backgrounds	Interviews	To investigate this tension using women's accounts of cervical screening, with a view to informing practice to better meet their needs.
Baker et al. (2012)	USA	Community-based participatory research	44 Hmong women	Focus groups	To explore the barriers and facilitators of cancer screening among women of Hmong origin.
Barata et al. (2008)	Canada	Grounded theory and adapted approaches	44 northern Ontario residents	Focus groups	To explore women's beliefs about collecting their own samples for HPV testing instead of participating in conventional Pap smears.
Bellinger et al. (2015)	USA	Content analysis	28 African-American women	Focus groups	To explore behavior, knowledge, and attitudes as influences on health decisions and preferences for cervical cancer prevention and control among African-American women in South Carolina.
Black et al. (2011)	Canada	Thematic analysis	80 Indigenous women	Focus groups	To evaluate young women's knowledge of CCS and identifying barriers to and facilitators of participation in CCS.
Blake et al. (2015)	USA	Qualitative, not otherwise stated	24 African-American women	Interviews	To understand the cervical cancer experiences of women enrolled in Georgia's Women's Health Medicaid Program (WHMP).
Blomberg et al. (2008)	Sweden	Thematic analysis	86 women	Telephone interviews and fax messages	To explore how women who actively declined participation in the cost-free population-based cervical cancer screening programme (PCCSP) reasoned about their choice.
Blomberg et al. (2011a)	Sweden	Content analysis	138 women	Face to face and online focus group discussions.	To explore issues that 30-year-old women have addressed as encouraging CCS attendance, with

					particular focus on aspects susceptible to intervention.
Blomberg et al. (2011b)	Sweden	Interpretive description	38 women	Focus groups	To explore how 30-year-old women reason about health, ill health, health maintenance, and disease prevention, in relation to cervical cancer, its prevention, and screening.
Brown et al. (2007)	Canada	Grounded theory	20 women	Interviews	To investigate the role of stigma on HPV testing.
Brown et al. (2011)	USA	Thematic content analysis	44 Black women (Haitians, African immigrants, Anglophone Caribbean immigrants, and African-Americans)	Focus groups	A descriptive study of cervical cancer screening knowledge, attitudes, beliefs, and practices among ethnically diverse black women.
Buetow et al. (2007)	New Zealand	Phenomenology	6 Maori women	Interviews	To enhance understanding of how having a cervical smear can lead some women not to keep up-to-date with this test.
Burke et al. (2004)	USA	Thematic content analysis	53 first-generation Vietnamese immigrant women	Interviews; focus groups	To identify cultural factors influencing Pap testing knowledge, including barriers and facilitators to testing; and to develop culturally appropriate intervention materials to increase knowledge about risk factors for cervical cancer and to increase Pap smear rates.
Byrd et al. (2007)	USA	Qualitative, not otherwise stated	84 Hispanic women	Focus groups	To better understand the barriers and facilitators for Pap smears for Hispanic women.
Chang et al. (2013)	Canada	Content analysis	13 first-generation Chinese immigrant women	Focus groups	To delineate the mechanisms underlying low Pap smear rates amongst Chinese women living in North America.
Cohen et al. (2016)	USA	Framework analysis	24 medically underserved women in Appalachia	Interviews	To investigate how patient uncertainty concerning cervical cancer screening guidelines is appraised and managed through communication with healthcare providers.
Curmi et al. (2014)	Australia	Thematic analysis	9 Lesbian women	Interviews	To explore the attitudes and practices that lesbians have towards cervical cancer screening and aims to identify why such disparities occur.

Curmi et al. (2016)	Australia	Thematic analysis	9 Lesbian women	Interviews	To provide deeper insights into the experiences of lesbian women in accessing cervical cancer screening and to inform strategies to increase the uptake of these services for this group of women.
Donnelly (2006)	Canada	Qualitative, not otherwise stated	15 Vietnamese women; 6 clinicians	Interviews	To explore the participation of Vietnamese-Canadian women in screening for breast and cervical cancer; the appropriateness of current cancer-prevention services for Vietnamese women; and the influence of social, cultural, political, historical, and economic factors, shaped by race, gender, and class, on the screening practices of Vietnamese-Canadian women.
Donnelly et al. (2009)	Canada	Qualitative, not otherwise stated	15 Vietnamese women; 6 clinicians	Interviews	To investigate the influence of socioeconomic factors on Vietnamese Canadian women's breast and cervical cancer screening behaviors.
Fernandez et al. (2009)	USA	Ethnography	30 Hispanic women; 11 Hispanic men	Focus groups	To explore the level of HPV knowledge, attitudes, and cultural beliefs among Hispanic men and women on the Texas Mexico border.
Fletcher et al. (2014)	USA	Qualitative description with content analysis	33 Low-income, HIV-positive women	Focus groups	To describe the barriers and facilitators related to cervical cancer screening in a sample of HIV-infected women seeking care at an integrated HIV clinic in Houston, Texas.
Flores et al. (2011)	USA	Case study	1 first-generation Mexican immigrant woman	Interview	To explore an older Mexican American woman's decision-making process to engage in cervical cancer screening.
Freeman et al (2018)	England	Framework analysis	38 women over 50 years old	Interviews; focus groups	To assess the acceptability of non speculum HPV testing for cervical screening in older women.
Friedman et al. (2012)	USA	Grounded theory	51 obese women	Interviews; focus groups	To explore obese women's barriers to Pap smears and mammograms.
Gele et al. (2017)	Norway	Qualitative, not otherwise stated	18 Pakistani women; 17 Somali women	Focus groups	To obtain better insight into perceived barriers and challenges to cervical cancer screening among Somali and Pakistani women in the Oslo region.

Ghebre et al. (2015)	USA	Thematic Analysis	23 Somali immigrant women	Interviews	To examine the barriers to and facilitators of cervical cancer screening among Somali immigrant women in Minnesota.
Goldman et al. (2004)	USA	Qualitative, not otherwise stated	74 Dominican and Puerto Rican women; 73 Dominican and Puerto Rican men	Interviews	This study explored perceptions of cancer, risk, and screening among Dominicans and Puerto Ricans in Rhode Island.
Grandahl et al. (2012)	Sweden	Content analysis	50 Immigrant	Focus groups	To explore immigrant women's experiences and views on the prevention of cervical cancer, screening, HPV vaccination and condom use
Gregg et al. (2011a)	USA	Thematic analysis	28 Mexican immigrant women; 23 Mexican immigrant men	Interviews	To investigate beliefs about the Pap smear among Mexican immigrants.
Gregg et al. (2011b)	USA	Thematic analysis	31 Vietnamese women	Interviews	To understand the beliefs of Vietnamese-American women regarding the Pap smear.
Guilfoyle et al. (2007)	USA	Content analysis	98 low-income African-American and Hispanic older women	Focus groups	To investigate how low-income, African American and Hispanic older women make decisions about cervical cancer screening.
Hanlon & Payne (2018)	New Zealand	Qualitative, not otherwise stated	11 women living with a physical impairment	Interviews	To identify experiences of women with physical impairments and their uptake of cervical cancer screening services in New Zealand.
Head et al. (2017)	USA	Thematic analysis	30 African-American women	Interviews	To evaluate patient understanding of HPV testing along with Pap smears.
Howard et al. (2009)	Canada	Grounded theory	77 low socioeconomic status and immigrant women (Cantonese, Arab, Afghan, Somali, and Central American)	Focus groups	To understand the perceptions of lower SES and immigrant women regarding self-sampling for HPV.
Hulme et al. (2016)	Canada	Grounded theory	37 South Asian and Chinese immigrant women	Interviews; focus groups	To better understand how Chinese and South Asian immigrants conceive of breast and cervical cancer screening.
Johnson et al. (2016)	USA	Content analysis	226 Lesbian and bisexual women and transgender men; (226 surveys; 20 in depth interviews)	Interviews; online questionnaire	To examine cervical cancer screening behaviors of LBQ women and transgender men using American Cancer Society guidelines as the standards for comparison and to determine factors that influence

					participation in cervical cancer screening.
Katz et al. (2016)	USA	Qualitative, not otherwise stated	15 women from a rural area; 28 clinicians	Focus groups	To understand the perceived acceptability of mailed HPV self-tests low among Appalachian Ohio women.
Kim et al. (2004)	USA	Qualitative, not otherwise stated	16 Korean women	Focus groups	To describe the perceptions about cervical cancer and factors related to cervical cancer screening among Korean American women.
Kim et al. (2016)	USA	Qualitative description	32 Korean immigrant women	Interviews	To explore decision making about Pap smears among Korean immigrant women.
Kue et al. (2014)	USA	Qualitative, not otherwise stated	44 Hmong women; 39 Hmong men	Interviews	To explore Hmong women and men's perceptions of breast and cervical cancer and cancer screening, women's experiences with breast and cervical cancer screening, and health care system barriers to screening.
Kwok et al. (2011)	Australia	Content analysis	18 Chinese immigrant women	Interviews	To understand the different facilitators and barriers to screening for Chinese Australian women.
Laranjeira (2013)	Portugal	Constant comparative analysis	25 women	Interviews	To investigate Portuguese women's knowledge and beliefs about cervical cancer screening.
Lee et al. (2014)	USA	Thematic content analysis	30 Korean and Vietnamese women	Interviews	To explore multilevel factors that may underlie low screening rates among Vietnamese American Women and Korean American women living in a city where their ethnic communities are relatively small.
Lee et al. (2017)	USA	Thematic analysis	16 Korean immigrant women	Focus groups	To identify major barriers to Papanicolaou (Pap) test uptake and human papillomavirus (HPV) vaccine acceptability for Korean immigrant women.
Lewis et al. (2002)	USA	Qualitative, not otherwise stated	47 African American and Hispanic women	Focus groups	To understand the barriers to breast and cervical cancer screening among New Jersey African Americans and Latinas.
Logan et al. (2011)	UK	Thematic content analysis	48 women from a "socially deprived area"	Focus groups	To explore women's knowledge, experiences and perceptions

					of cervical cancer screening in an area of social deprivation.
Lor et al. (2013)	USA	Qualitative description with content analysis	16 Hmong women	Interviews	To describe the beliefs, feelings, norms, and external conditions regarding breast and cervical cancer screening in a sample of Hmong women.
Lovell et al. (2007)	New Zealand	Thematic analysis	17 Maori women, Chinese women; Korean women; Women of low socioeconomic status; 9 clinicians	Interviews	To investigate why underscreening persists in a country where cervical screening has a high profile and how the promotion of cervical screening has impacted on the decisions of women to undergo a smear test.
Lyytle et al. (2006)	USA	Qualitative, not otherwise stated	69 low-income women from a rural area	Focus groups	To obtain an understanding of attitudes about breast and cervical cancer screening among women aged 25 to 64 years; to determine factors that motivate women to be screened for breast and cervical cancer; and to evaluate educational materials about breast and cervical cancer screening for use in this population.
MacDonald et al. (2015)	Canada	Thematic analysis	18 Indigenous (Mi'kmaq) women; 3 clinicians	Talking circles; interviews	To explore Mi'kmaq women's experiences with Pap smears within the contexts that shaped their experiences using postcolonial feminist perspectives and Indigenous principles.
Magee et al. (2005)	USA	Thematic analysis	42 prison inmate women; 4 clinicians	Interviews	To determine what is and is not working with the Pap smear and follow-up treatment for women in prison.
Manderson et al. (2006)	Australia	Community-based collaborative research; Case study	323 Australian Indigenous women; 45 community members; 179 clinicians	Interviews; focus groups, community meetings; case histories	To explore the different cultural and structural factors affecting understanding and awareness of cervical cancer and Indigenous women's use of and access to health services for screening, diagnosis and treatment.
Marlow et al. (2009)	UK	Framework analysis	21 women	Interviews	To identify the key questions about HPV that British women will ask when considering having an HPV test or vaccination.
Marlow et al. (2015)	UK	Framework analysis	43 women representing various ethnic minorities (Indian,	Interviews	To explore self-perceived barriers to cervical screening attendance among ethnic minority women compared to

			Pakistani, Bangladeshi, Caribbean, African, Black)		white British women.
Matin et al. (2004)	USA	Qualitative, not otherwise stated	20 Muslim women	Focus groups	To examine the impact of religious and cultural values on health care behavior of Muslim women from immigrant backgrounds in the San Francisco Bay Area, particularly with regard to cervical cancer screening; to determine whether these women would welcome discussing values and beliefs regarding sexuality and reproductive health.
Matthews et al. (2006)	USA	Thematic analysis	94 African-Americans	Focus groups	To evaluate the CDC Racial and Ethnic Approaches to Community Health (REACH) 2010 faith-based breast and cervical cancer early detection and prevention intervention for African American women living in urban communities.
McAlearney et al. (2011)	USA	Grounded theory and adapted approaches	36 women from a rural area	Focus groups	To explore Appalachian women's perceptions of trust and distrust of healthcare providers and the medical care system as they relate to views about cervical cancer and screening.
McCaffery (2003)	UK	Framework analysis	71 Indian women; Pakistani women; African-Caribbean women	Focus groups	To examine attitudes to HPV testing among a purposively selected sample of women from four ethnic groups: white British, African Caribbean, Pakistani and Indian.
McCaffery (2006)	UK	Framework analysis	74 South Asian (including Pakistani, Indian, and east African Asian) and African Caribbean women	Interviews	To examine the social and psychological impact of HPV testing in the context of cervical cancer screening.
McDowell et al. (2017)	USA	Thematic analysis	31 transmasculine individuals (interviews); 32 transmasculine individuals (surveys)	Interviews; online survey with open-ended questions	To elucidate cervical cancer screening preferences among trans-masculine individuals.
McLachlan et al (2018)	Australia	Grounded theory	40 women 7 health professionals	Interviews	To identify and understand clinical and personal enablers that assisted women to complete self-collection cervical

					screening pathways successfully.
McRae et al. (2014)	Ireland	Thematic analysis	59 women	Focus groups	To investigate Irish women's attitudes towards the transformation of cervical cancer prevention.
Menard et al. (2010)	USA	Grounded theory	15 Haitian immigrant women	Interviews	To understand the barriers to cervical cancer screening among Haitian immigrant women.
Miller et al. (2007)	USA	Thematic analysis	32 women with a mental illness; 35 clinicians	Interviews; focus groups	To explore challenges to accessing and providing breast and cervical cancer screening for women with mental illness.
Moravac (2018)	Canada	Thematic analysis	26 homeless women with severe mental health challenges	Interviews	To explore the factors influence breast and cervical cancer screening decisions among homeless women and women with mental health challenges residing in Toronto, Canada.
Ndukwe et al. (2013)	USA	Qualitative, not otherwise stated	38 African immigrant women	Interviews; focus groups; sociodemographic questionnaire	To investigate knowledge and awareness levels of breast and cervical cancer screening practices among female African-born immigrants to the USA residing in the Washington D.C. metropolitan area.
Nolan et al. (2014)	USA	Grounded theory	17 African-American women; 42 clinicians	Focus groups	To explore factors that might lead to delays in appropriate cervical cancer screening and diagnosis among Black women in Massachusetts.
O'Brien et al. (2009)	Canada	Ethnography	8 Indigenous (Cree) women	Focused ethnography; interviews	To explore Attitudes and beliefs of First Nation Cree women living in a reserve community to gain insights into how cervical screening could be better utilized.
Oelke et al. (2007)	Canada	Qualitative description	53 Sikh women	Interviews; focus groups	To investigate Sikh women's perspectives on cervical cancer screening.
Oscarsson et al. (2008)	Sweden	Content analysis	14 women	Interviews	To describe and interpret why women with no cervical smear taken during the previous 5 years choose not to attend a cervical cancer screening (CCS) program.

Penaranda et al. (2014)	USA	Thematic analysis	21 Hispanic women	Focus groups	To investigate attitudes toward self-sampling for cervical cancer screening among primary care attendees living on the USA-Mexico border.
Peitzmeier et al. (2017)	USA	Grounded theory and adapted approaches	32 transmasculine individuals	Interviews	To examine the factors influencing Pap test utilization among transmasculine individuals to inform evidence-based interventions to promote regular cervical cancer screening in this medically underserved population.
Pinzon-Perez et al. (2005)	USA	Phenomenology	51 Latina women from a rural area	Interviews	To identify alterable determinants of Pap smear screening for Latino women living in a rural area of California.
Pratt et al. (2017)	USA	Constructivist grounded theory	34 Somali women, 20 Somali men	Focus groups	To investigate the views of Somali women and men on the use of faith-based messages promoting breast and cervical cancer screening for Somali women.
Racey et al. (2016)	Canada	Thematic analysis	25 women from a rural area	Focus groups	To explore the initial reaction and perception to HPV self-collected testing, in the context of current barriers and facilitators to cervical cancer screening, among women in an underscreened community in rural Ontario.
Redwood-Campbell et al. (2011)	Canada	Case study	77 immigrant women of low socioeconomic status	Focus group	To describe the similarities and differences among multiple groups of immigrant women and Canadian-born women of low socio-economic status regarding barriers and enablers associated with cervical cancer screening, in order to inform core elements of a strategy that would be acceptable across multiple underscreened groups.
Scarini et al. (2013)	USA	Qualitative, not otherwise stated	96 African-American women	Focus groups; discussion group	To inform the development of interventions to promote cervical cancer screening in African American women in the Mississippi Delta by examining the acceptability and usability of self-collected sampling for HPV testing.

Schoenberg et al. (2005)	USA	Grounded theory and adapted approaches	25 women from a low-income, rural area	Interviews	To investigate the determinants of cervical cancer screening among central Appalachian women.
Schoenberg et al. (2013)	USA	Qualitative, not otherwise stated	60 rural women; 19 clinicians	Interviews; focus groups	To better understand barriers to, and facilitators of, breast and cervical cancer screening among Appalachian women and to identify strategies to increase cancer screening.
Seo et al. (2017)	USA	Phenomenology	12 Chinese American immigrant women	interviews	To understand the experiences and perceptions of having cervical cancer screening tests and to explore the extant barriers to having the tests among first-generation Chinese-American women in the United States.
Smith et al. (2003)	USA	Thematic analysis	68 women	Focus groups	To explore attitudes, beliefs, and perceived barriers to risk-based cervical cancer screening through focus group interviews of patients.
Stewart et al. (2010)	Australia	Content analysis	24 women	Interviews	To explore patient expectations and experiences regarding Pap smear and associated screening activities.
Szalacha et al. (2016)	USA	Content analysis	47 Mexican women	Focus groups	To qualitatively examine an alternative framework for examining cultural influences on Mexican-heritage Latinas' understandings of breast and cervical cancer screening and how to leverage their beliefs to positively influence screening practices.
Szarewski (2009)	UK	Framework analysis	28 Muslim women	Focus groups	To explore Muslim women's attitudes to self-sampling for HPV in the context of cervical cancer screening and their responses to two self-sampling devices.
Thorburn et al. (2013a)	USA	Content analysis	44 Hmong women; 39 Hmong men	Interviews	To explore sources of information about breast and cervical cancer, including screening, and identified barriers to seeking such information for Hmong women and men.
Thorburn et al. (2013b)	USA	Content analysis	44 Hmong women; 39 Hmong men	Interviews	To explore family and clan influences on Hmong women's breast and cervical cancer screening attitudes and behavior.

Van Til et al. (2003)	Canada	Thematic analysis	60 Older women	Focus groups	To understand the barriers to cervical cancer screening among older women.
Vanslyke et al. (2008)	USA	Thematic analysis	54 Hispanic women	Focus groups	To investigate the knowledge, beliefs, and attitudes among Hispanic women towards HPV and cervical cancer testing and prevention.
Wakewich et al. (2016)	Canada	Qualitative, not otherwise stated	69 Indigenous women; 16 clinicians	Interviews; focus groups	To investigate the Colonial legacy and the experience of First Nations women in cervical cancer screening.
Waller et al. (2005)	UK	Framework analysis	74 South Asian (including Pakistani, Indian, and east African Asian) and African Caribbean women *This might be the same population of women used in McCaffery 2006	Interviews	To examine how women make sense of information about HPV in the context of cervical cancer screening.
Waller et al. (2012)	UK	Framework analysis	46 women; 12 clinicians	Interviews	To examine how women make sense of information about HPV in the context of cervical cancer screening.
Williams et al. (2015)	USA	Content analysis	20 HIV-positive African-American women	Interviews	To examine sociocultural and structural factors associated with cervical cancer screening among HIV-infected African American in Alabama.
Wittenberg et al. (2015)	USA	Thematic analysis	42 Homeless women	Focus groups	To assess homeless women's preferences for cervical cancer screening interventions.
Wollin et al. (2003)	Australia	Qualitative, not otherwise stated	13 low-income deaf women	Interviews	To assess baseline knowledge about mammograms and pap smears among Australian deaf women, to investigate their participation in breast and cervical cancer screening services, and to explore, where relevant, their perceptions about their access to breast and cervical screening services.
Wong et al. (2010)	USA	Qualitative, not otherwise stated	10 Chuukese women	Interviews	To describe the knowledge, attitudes, and beliefs of Chuukese women in Hawai'i regarding cervical cancer prevention and screening.
Wu et al. (2010)	USA	Ethnography	55 Samoan women	Focus groups	To gain a better understanding of

	(American Samoa)				issues that may prevent women in American Samoa from using available cancer screening resources.
Zehbe et al. (2016)	Canada	Qualitative, not otherwise stated	69 Indigenous women; 16 clinicians	Interviews; focus groups	To investigate the challenges and barriers associated with designing screening programs aimed to specifically reach Indigenous women.
Zehbe et al. (2017)	Canada	Qualitative, not otherwise stated	69 Indigenous women; 16 clinicians	Interviews; focus groups	To investigate whether First Nations women preferred HPV self-sampling over healthcare provider-administered Pap screening.

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Studies	1. Was there a clear statement of the aims	2. Is a qualitative methodology appropriate?	3. Was the research design appropriate to address	4. Was the recruitment strategy appropriate to the aims of the	5. Was the data collected in a way that addressed	6. Has the relationship between researcher and participants	7. Have ethical issues been taken into consideration?	8. Was the data analysis sufficiently rigorous?	9. Is there a clear statem ent of	10. How relevant is the research to the current

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	of the research?		the aims of the research?	research?	the research issue?	been adequately considered?			finding s?	review?
Abdullahi et al. (2009)	2	2	1	2	2	0	2	2	2	Highly Relevant
Ackerson (2010)	2	2	1	2	2	0	2	2	2	Relevant
Ackerson et al. (2011)	2	2	2	2	2	0	2	2	2	Relevant
Ackerson (2012)	2	2	1	2	2	0	2	2	0	Highly Relevant
Ackerson et al. (2008)	2	2	1	1	1	0	2	0	0	Relevant
Adegboyega et al. (2016)	2	2	1	2	2	0	2	2	2	Highly Relevant
Agenor et al. (2015)	2	2	0	2	2	0	2	2	2	Highly Relevant
Agenor et al. (2016)	2	2	0	1	2	0	2	2	2	Somewhat relevant
Anaman-Torgbor et al. (2017)	2	2	2	2	2	2	0	2	2	Relevant
Andrasik et al. (2008)	2	2	1	1	2	0	2	0	2	Highly Relevant
Andreassen et al. (2017)	2	2	2	1	2	2	2	2	2	Relevant
Anhang et al. (2004)	2	2	2	2	2	0	2	2	2	Relevant
Armstrong (2005)	2	2	2	2	2	0	0	0	0	Somewhat relevant
Armstrong (2007)	2	2	2	2	2	0	0	2	2	Somewhat relevant
Armstrong (2012)	2	2	2	2	2	2	2	2	2	Somewhat relevant
Baker et al. (2012)	2	2	1	2	2	1	0	2	2	Highly Relevant
Barata et al. (2008)	2	2	1	2	2	0	2	2	2	Highly Relevant

Bellinger et al. (2015)	2	2	2	1	2	2	2	2	2	Somewhat relevant
Black et al. (2011)	2	2	2	2	2	0	2	2	2	Highly Relevant
Blake et al. (2015)	2	2	0	1	1	0	1	2	2	Somewhat relevant
Blomberg et al. (2008)	2	2	0	0	2	2	2	2	2	Highly Relevant
Blomberg et al. (2011a)	2	2	2	2	2	0	1	2	2	Highly Relevant
Blomberg et al. (2011b)	2	2	2	2	2	2	0	2	2	Somewhat relevant
Brown et al. (2007)	2	2	0	2	2	0	0	2	2	Highly Relevant
Brown et al. (2011)	2	2	1	2	2	0	2	2	0	Somewhat relevant
Buetow et al. (2007)	2	2	2	2	2	0	0	2	0	Relevant
Burke et al. (2004)	2	2	2	1	2	0	2	2	2	Somewhat relevant
Byrd et al. (2007)	2	2	2	2	2	0	2	2	2	Highly Relevant
Chang et al. (2013)	2	2	2	1	2	0	2	2	2	Somewhat relevant
Cohen et al. (2016)	2	2	0	2	0	2	0	2	2	Relevant Relevant
Curmi et al. (2014)	2	2	2	1	2	2	2	0	2	Highly Relevant
Curmi et al. (2016)	2	2	2	2	1	2	2	0	2	Relevant
Donnelly (2006)	2	2	1	1	2	0	2	2	0	Relevant
Donnelly et al. (2009)	2	2	0	2	1	0	2	2	2	Relevant
Fernandez et al. (2009)	2	2	2	2	2	2	2	2	2	Relevant
Fletcher et al. (2014)	2	2	1	2	2	0	2	2	2	Somewhat relevant
Flores et al. (2011)	2	2	2	2	1	0	2	0	2	Somewhat relevant

Freenan et al. (2018)	2	2	2	1	2	0	0	0	2	Somewhat relevant
Friedman et al. (2012)	2	2	1	2	2	0	2	2	2	Relevant
Gele et al. (2017)	2	2	2	1	2	0	0	2	2	Relevant
Ghebre et al. (2015)	2	2	2	1	2	0	0	2	2	Relevant
Goldman et al. (2004)	2	2	2	1	2	1	1	2	2	Highly Relevant
Grandahl et al. (2012)	2	2	2	2	2	0	0	2	2	Highly Relevant
Gregg et al. (2011a)	2	2	2	2	2	1	1	2	2	Somewhat relevant
Gregg et al. (2011b)	2	2	2	2	2	1	1	2	2	Somewhat relevant
Guilfoyle et al. (2007)	2	2	2	2	2	1	2	2	2	Highly Relevant
Hanlon & Payne (2018)	2	2	1	0	2	0	0	0	2	Relevant
Head et al. (2017)	2	2	2	2	2	0	1	2	2	Somewhat relevant
Howard et al. (2009)	2	2	2	2	2	0	1	2	2	Somewhat relevant
Hulme et al. (2016)	2	2	2	2	2	1	2	2	2	Highly Relevant
Johnson et al. (2016)	2	2	2	2	2	0	1	1	1	Somewhat relevant
Katz et al. (2016)	2	2	2	2	2	0	1	2	2	Relevant
Kim et al. (2004)	2	2	2	2	2	1	1	2	2	Highly Relevant
Kim et al. (2016)	2	2	2	2	2	1	1	2	2	Highly Relevant
Kue et al. (2014)	2	2	2	2	2	0	1	2	2	Highly Relevant
Kwok et al. (2011)	2	2	2	2	2	0	1	1	2	Relevant
Laranjeira (2013)	2	2	2	0	1	0	1	1	1	Highly Relevant
Lee et al. (2014)	2	2	2	2	1	1	0	2	2	Highly Relevant
Lee & Lee (2017)	2	2	2	0	2	0	0	2	2	Somewhat Relevant

Lewis et al. (2002)	2	2	2	2	2	2	0	0	2	Somewhat relevant
Logan et al. (2011)	2	2	2	2	2	0	2	2	2	Relevant
Lor et al. (2013)	2	2	2	2	2	1	1	2	2	Relevant
Lovell et al. (2007)	2	2	2	2	2	1	1	1	2	Somewhat relevant
Lyytle et al. (2006)	2	2	2	2	2	2	0	2	2	Relevant
MacDonald et al. (2015)	2	2	2	2	2	0	2	2	2	Highly Relevant
Magee et al. (2005)	2	2	2	2	2	0	1	2	2	Relevant
Manderson et al. (2006)	2	2	2	2	2	0	2	2	2	Relevant
Marlow et al. (2009)	2	2	2	1	1	0	2	1	1	Relevant
Marlow et al. (2015)	2	2	2	2	2	0	1	2	1	Relevant
Matin et al. (2004)	2	2	2	2	2	0	2	2	2	Highly Relevant
Matthews et al. (2006)	2	2	2	2	2	1	0	2	2	Somewhat relevant
McAlearney et al. (2011)	2	2	2	2	2	2	2	2	2	Somewhat relevant
McCaffery (2003)	2	2	2	2	2	0	2	2	2	Relevant
McCaffery (2006)	2	2	2	2	2	0	0	0	0	Somewhat relevant
McDowell et al. (2017)	2	2	2	1	2	0	0	2	2	Relevant
McLachlan et al. (2018)	2	2	2	2	1	0	0	1	2	Highly relevant
McRae et al. (2014)	2	2	2	2	2	0	2	2	2	Highly Relevant
Menard et al. (2010)	2	2	2	2	2	0	0	2	2	Relevant
Miller et al. (2007)	2	2	2	2	2	0	2	0	2	Somewhat relevant
Moravac (2018)	2	2	1	1	1	0	0	0	2	Highly relevant

Ndukwe et al. (2013)	2	2	2	2	2	0	2	2	2	Somewhat relevant
0lan et al. (2014)	2	2	2	2	2	2	2	2	2	Relevant
O'Brien et al. (2009)	2	2	2	2	2	0	2	0	2	Highly Relevant
Oelke et al. (2007)	2	2	2	2	2	0	2	2	2	Relevant
Oscarsson et al. (2008)	2	2	2	2	2	0	2	2	2	Highly Relevant
Peitzmeier et al. (2017)	2	2	2	2	2	2	0	2	2	Relevant
Penaranda et al. (2014)	2	2	2	0	2	0	2	2	2	Relevant
Pinzon-Perez et al. (2005)	2	2	2	2	2	0	2	2	2	Relevant
Pratt et al. (2017)	2	2	2	2	2	0	2	2	1	Somewhat relevant
Racey et al. (2016)	2	2	2	2	2	2	2	2	2	Relevant
Redwood-Campbell et al. (2011)	2	2	2	2	2	2	2	2	2	Somewhat relevant
Scarini et al. (2013)	2	2	2	2	2	0	2	2	2	Somewhat relevant
Schoenberg et al. (2005)	2	2	2	2	2	2	2	2	2	Relevant
Schoenberg et al. (2013)	2	2	2	2	2	2	2	2	2	Relevant
Seo et al. (2017)	2	2	2	2	2	0	1	2	2	Relevant
Smith et al. (2003)	2	2	2	2	2	2	2	2	2	Highly Relevant
Stewart et al. (2010)	2	2	2	2	2	0	2	2	2	Highly Relevant
Szalacha et al. (2016)	2	2	2	2	2	2	2	2	2	Highly Relevant
Szarewski (2009)	2	2	2	2	2	0	2	2	2	Relevant
Thorburn et al. (2013a)	2	2	2	2	2	2	2	2	2	Somewhat relevant
Thorburn et al. (2013b)	2	2	2	2	2	2	2	2	2	Somewhat relevant

Van Til et al. (2003)	2	2	2	2	2	0	2	2	2	Highly Relevant
Vanslyke et al. (2008)	2	2	2	2	2	0	2	2	2	Relevant
Wakewich et al. (2016)	2	2	2	2	2	2	2	2	2	Highly Relevant
Waller et al. (2005)	2	2	1	2	2	0	0	2	2	Somewhat relevant
Waller et al. (2012)	2	2	2	2	2	0	2	2	2	Highly Relevant
Williams et al. (2015)	2	2	2	2	2	0	2	2	2	Relevant
Wittenberg et al. (2015)	2	2	2	2	2	2	2	2	2	Somewhat relevant
Wollin et al. (2003)	2	2	2	2	2	0	2	0	2	Somewhat relevant
Wong et al. (2010)	2	2	2	0	2	2	2	0	2	Somewhat relevant
Wu et al. (2010)	2	2	2	2	2	0	2	2	2	Somewhat relevant
Zehbe et al. (2016)	2	2	2	2	2	0	2	2	2	Somewhat relevant
Zehbe et al. (2017)	2	2	2	2	2	2	2	2	2	Highly Relevant

5495 Each paper was assessed independently by two reviewers. Each reviewer assigned a score of 1 or 0 for each criterion of each paper and the sum of these scores is presented in this
5496 table. A score of 0 means that the reviewer was unable to see evidence that a particular criterion was achieved. We decided on the relevance of each paper after the analysis was
5497 completed, by examining how broadly that paper was used in the analysis.

Appendix 12: Methods of included Studies – Patient Experiences review

Study design	Number of studies
Thematic analysis/thematic content analysis	32 (27.4%)
Qualitative not otherwise specified	28 (23.9%)
Content analysis	15 (12.8%)
Grounded theory and adapted processes/constant comparative analysis	16 (13.7%)

Framework analysis	10 (8.5%)
Other (interpretive description, community-based participatory research, phenomenology, case study)	7 (6.0%)
Qualitative description	6 (5.1%)
Ethnography	3 (2.6%)
Total	117 (100%)

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Appendix 13: National Context – Patient Experiences Review

Study Location	Number of Studies
USA and US territories	63 (53.8%)
Canada	18 (15.4%)
United Kingdom	15 (12.8%)
Australia	8 (6.8%)
Sweden	5 (4.3%)
New Zealand	3 (2.5%)
Romania	2 (1.7%)
Norway	1 (0.9%)
Portugal	1 (0.9%)
Poland	1 (0.9%)
Total	117 (100%)

Appendix 14: Participant Characteristics – Patient Experiences

Participant type	Number of studies
Women	4835
Family members or unpaid caregivers	258
Clinicians	433

Appendix 15: Social Identity – Patient Experiences Review

Description of social identity	Number of studies
Minority ethnicity or culture	64 (54.7%)
Low socioeconomic status	13 (11.1%)
Indigenous peoples	10 (8.5%)
Other (obese, incarcerated women, homeless women, mental health challenges, HIV positive, Deaf)	11 (9.4%)
Rural	6 (5.1%)
LGBTQ	7 (6.0%)
Older women	3 (2.6%)
Any type of marginalization	102 (87.2%)
Total	117 (100%)

Appendix 16: Additional Findings from Sensitivity Analyses of the Economic Evaluation

Table 54: Additional Sensitivity Analyses Findings for Future Incident Cohort

Analysis	Strategy	Expected		Incremental		Sequential ICER
		Cost($)	QALYs	Cost($)	QALYs	
Future Incident Cohort						
Reference Case	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,471	39.956	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	2,021	39,961	551	0.005	112,717
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,580	39.956	109	0.000	Ex. dom
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,601	39.957	130	0.001	Ex. dom
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,744	39.957	273	0.001	Ex. dom
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,847	39.958	376	0.002	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	1,855	39.958	384	0.002	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,857	39.959	387	0.002	Ex. dom
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	2,065	39.960	594	-0.001	Dominated
Vaccination Uptake (12.40%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,665	39.944	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	2,241	39.953	575	0.0100	60,345
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,784	39.945	119	0.0071	Ex. dom
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,784	39.945	119	0.0068	Ex. dom
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,946	39.946	281	0.0068	Ex. dom
	A3: Primary cytology (3 yrs; 30 – 69)	2,045	39.949	380	0.0062	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	2,046	39.950	381	0.0059	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	2,061	39.950	396	0.0062	Ex. dom
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	2,262	39.952	21	0.0058	Dominated
Vaccination Uptake (88.20%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,356	39.966	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	1,868	39.968	512	0.001	428,893
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,461	39.966	105	-0.001	Dominated
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,478	39.967	122	0.001	Ex. dom
	B1: Primary cytology w/ HPV	1,609	39.966	253	-0.001	Dominated

	triage (3 yrs; 25 to 69)					
	A3: Primary cytology (3 yrs; 30 – 69)	1,722	39.967	366	0.000	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	1,725	39.967	368	0.000	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,742	39.967	386	0.001	Ex. dom
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	1,935	39.967	67	-0.001	Dominated
Discount Rate (0%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	2,689	63.606	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	3,473	63.616	784	0.010	76,279
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	2,862	63.607	173	0.001	Ex. dom
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	2,863	63.605	174	-0.000	Dominated
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	3,088	63.607	399	0.001	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	3,264	63.611	575	0.005	Ex. dom
	A3: Primary cytology (3 yrs; 30 – 69)	3,270	63.610	581	0.004	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	3,340	63.612	650	0.006	Ex. dom
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	3,619	63.615	146	-0.001	Dominated
Discount Rate (5%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	447	19.462	Reference		
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	684	19.463	237	0.001	318,284
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	487	19.462	40	0.000	Ex. dom
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	514	19.462	67	0.000	Ex. dom
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	572	19.462	125	0.000	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	572	19.462	126	0.000	Ex. dom
	A3: Primary cytology (3 yrs; 30 – 69)	594	19.462	147	0.000	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	616	19.462	169	0.001	Ex. dom
	A1: Primary cytology (3 yrs; 21 – 69)	417	19.463	31	-0.000	Dominated
Alternative Incidence Rates	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,480	39.956	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	2,025	39.961	5454	0.005	119,689
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,589	39.956	109	0.000	Ex. dom
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,611	39.957	131	0.001	Ex. dom
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,751	39.957	271	0.001	Ex. dom
	A3: Primary cytology (3 yrs;	1,856	39.958	376	0.002	Ex. dom

	30 – 69)					
	A2: Primary cytology (3 yrs; 25 – 69)	1,863	39.958	383	0.002	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,865	39.958	385	0.002	Ex. dom
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	2,073	39.960	48	-0.001	Dominated
Screening participation rate (80%)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,479	39.957	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	2,056	39.961	576	0.005	124,553
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,606	39.957	127	-0.000	Dominated
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,609	39.957	130	0.001	Ex. dom
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,770	39.958	291	0.001	Ex. dom
	A3: Primary cytology (3 yrs; 30 – 69)	1,868	39.959	389	0.002	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,881	39.959	402	0.002	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	1,883	39.959	404	0.003	Ex. dom
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	2,093	39.961	37	-0.001	Dominated
Missed screening	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,349	39.953	Reference		
	A1: Primary cytology (3 yrs; 21 – 69)	1,823	39.959	473	0.006	80,599
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,455	39.954	106	0.001	Ex. dom
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,458	39.955	109	0.002	Dominated
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,588	39.955	239	0.002	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	1,682	39.956	333	0.003	Ex. dom
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,683	39.957	334	0.004	Ex. dom
	A3: Primary cytology (3 yrs; 30 – 69)	1,713	39.957	364	0.004	Ex. dom
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	1,863	39.958	40	-0.001	Dominated
Alternate Utility Values (based on TTO)	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,471	39.953	Reference		
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	**2,065**	**39.956**	**594**	**0.003**	**215,497**
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,580	39.953	0.0037	109	Ex. dom
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,601	39.953	0.0039	130	Ex. dom
	B1: Primary cCytology w/ HPV triage (3 yrs; 25 to 69)	1,744	39.953	0.0038	273	Ex. dom
	A3: Primary cytology (3 yrs; 30 – 69)	1,847	39.953	0.0033	376	Ex. dom

	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,855	39.954	0.0032	384	Ex. dom
	A2: Primary cytology (3 yrs; 25 – 69)	1,857	39.953	0.0034	387	Ex. dom
	A1: Primary cytology (3 yrs; 21 – 69)	2,021	39.954	0.0033	551	Ex. dom
	A3: Primary cytology (3 yrs; 30 – 69)	1,847	39.958	474	0.002	Ex. dom.
	A2: Primary cytology (3 yrs; 25 – 69)	1,857	39.959	485	0.002	Ex. dom.
Disutility from abnormal screening results	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,471	39.946	Reference		
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	**1,580**	**39.951**	**109**	**0.006**	**19,547**
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,601	39.944	21	-0.007	Dominated
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,744	39.951	164	0.000	Dominated
	A3: Primary cytology (3 yrs; 30 – 69)	1,847	39.945	267	-0.006	Dominated
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,855	39.942	275	-0.010	Dominated
	A2: Primary cytology (3 yrs; 25 – 69)	1,857	39.941	277	-0.010	Dominated
	A1: Primary cytology (3 yrs; 21 – 69)	2,021	39.941	441	-0.010	Dominated
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	2,065	39.940	485	-0.011	Dominated
HPV costs	C3: Primary HPV w/ cytology triage (5 yrs; 25 - 69)	1,373	39.956	Reference		
	C2: Primary HPV w/ cytology triage (3 yrs; 25 - 69)	1,877	39.960	504	0.004	127,316
	A1: Primary cytology (3 yrs; 21 – 69)	2,021	39.961	144	0.001	156,188
	C4: Primary HPV w/ cytology triage (5 yrs; 30 - 69)	1,484	39.957	111	0.001	Ex. dom.
	B2: Primary cytology w/ HPV triage (3 yrs; 30 to 69)	1,562	39.956	189	0.000	Ex. dom.
	C1: Primary HPV w/ cytology triage (3 yrs; 30 - 69)	1,696	39.958	324	0.002	Ex. dom.
	B1: Primary cytology w/ HPV triage (3 yrs; 25 to 69)	1,722	39.957	349	0.001	Ex. dom.
	A3: Primary cytology (3 yrs; 30 – 69)	1,847	39.958	474	0.002	Ex. dom.
	A2: Primary cytology (3 yrs; 25 – 69)	1,857	39.959	485	0.002	Ex. dom.

5517 Ex. Dom = extendedly dominated; HPV = human papillovirus; QALY= quality adjusted life years; TTO = time trade off

5518

5519 **Table 55: Sensitivity Analyses Results for the Prevalent Cohort.**

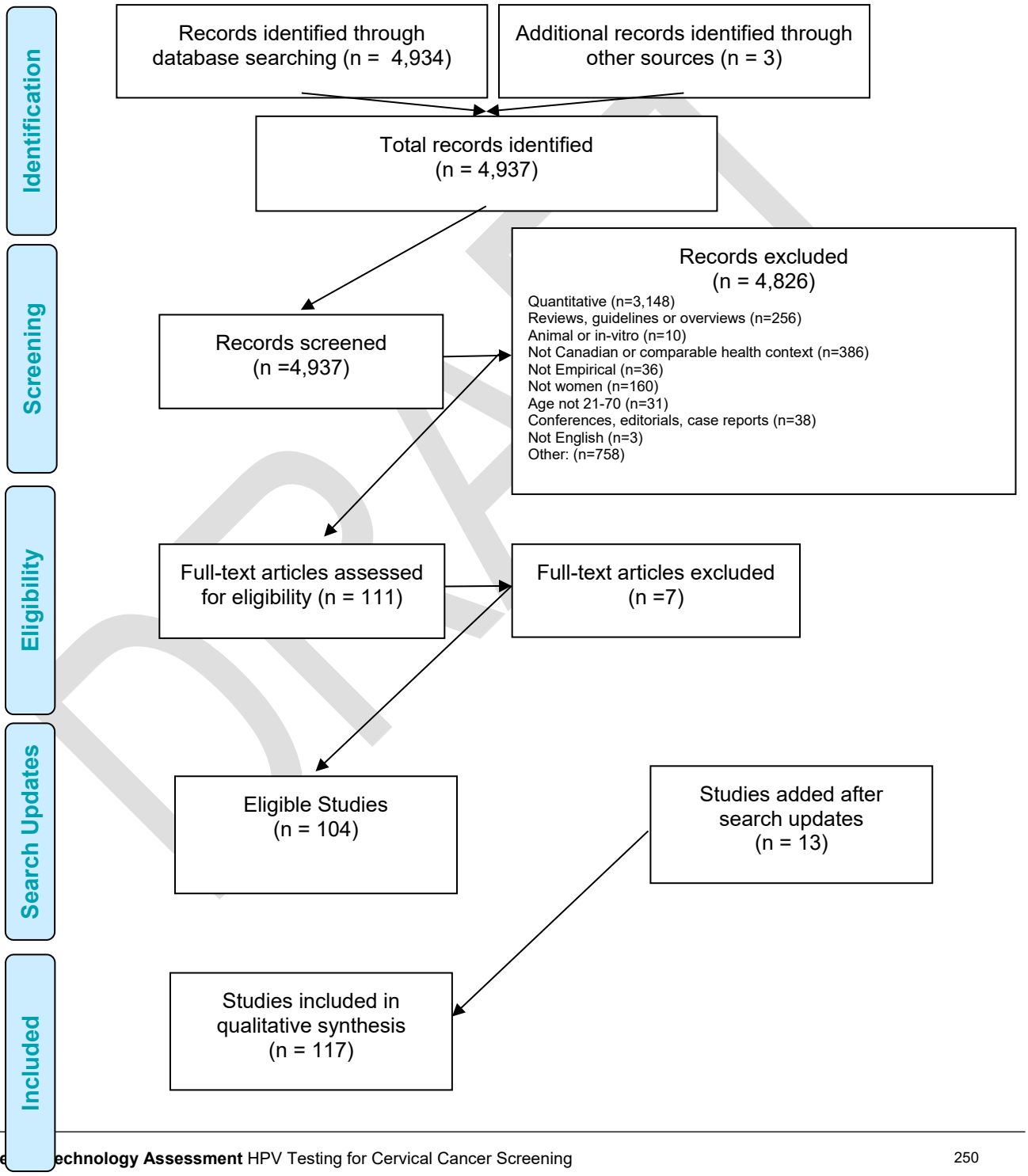
Analysis	Strategy	Expected		Incremental		Sequential ICER
		Cost($)	QALYs	Cost($)	QALYs	
Reference case	C3/C4 Primary HPV w/ cytology triage (5 yrs;)	2,241	31.546	Reference		
	C1/C2: Primary HPV w/	2,704	31.549	463	0.002	194,777

	cytology triage (3 yrs)					
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,381	31.546	139	-0.000	Dominated
	A1/A2/A3: Primary cytology (3 yrs)	2,427	31.544	186	-0.003	Dominated
Discount rate (0%)	C3/C4 Primary HPV w/ cytology triage (5 yrs;)	3,093	44.320	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	3,311	44.328	218	0.0084	25,885
	A1/A2/A3: Primary cytology (3 yrs)	3,394	44.330	83	0.0022	37,250
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	3,703	44.335	309	0.0046	67,749
Discount rate (5%)	C3/C4 Primary HPV w/ cytology triage (5 yrs)	1,172	17.292	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	1,298	17.293	126	0.0013	99,627
	A1/A2/A3: Primary cytology (3 yrs)	1,381	17.294	83	0.0004	224,807
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	1,538	17.294	156	0.0005	324,379
Alternative Incidence Rates	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,171	31.281	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,352	31.286	182	0.0047	38,510
	A1/A2/A3: Primary cytology (3 yrs)	2,438	31.287	86	0.0011	79,666
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,686	31.289	247	0.0024	105,202
Missed screening	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,023	31.272	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,199	31.280	176	0.0076	23,199
	A1/A2/A3: Primary cytology (3 yrs)	2,269	31.282	70	0.0027	25,583
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,481	31.286	212	0.0036	59,652
Screening participation rate (80%)	C3/C4 Primary HPV w/ cytology triage (5 yrs)					
	B1/B2: Primary cytology w/ HPV triage (3 yrs)					
	A1/A2/A3: Primary cytology (3 yrs)					
	C1/C2: Primary HPV w/ cytology triage (3 yrs)					
Alternative Utility Values (based on TTO)	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,171	31.271	Reference		
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,352	31.275	182	0.0041	43,789
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,686	31.277	333	0.0023	144,978
	A1/A2/A3: Primary cytology (3 yrs)	2,438	31.273	86	-0.0020	Dominated
Disutility from abnormal screening	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,171	31.266	Reference		
	B1/B2: Primary cytology w/	2,352	31.278	182	0.0124	14,681

results	HPV triage (3 yrs)					
	A1/A2/A3: Primary cytology (3 yrs)	2,438	31.265	86	-0.0128	Dominated
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,686	31.265	106	-0.0131	Dominated
HPV costs	C3/C4 Primary HPV w/ cytology triage (5 yrs)	2,031	31.281	Reference		
	C1/C2: Primary HPV w/ cytology triage (3 yrs)	2,460	31.289	429	0.0081	52,634
	B1/B2: Primary cytology w/ HPV triage (3 yrs)	2,324	31.286	293	0.0047	Ex. Dom
	A1/A2/A3: Primary cytology (3 yrs)	2,438	31.287	407	0.0011	Ex. Dom

Ex. Dom = extendedly dominated; HPV = human papillovirus; QALY= quality adjusted life years; TTO = time trade off

Appendix 17: Prisma Diagram – Patient Experiences Review



Appendix 18: Data Collection – Patient Experiences Review

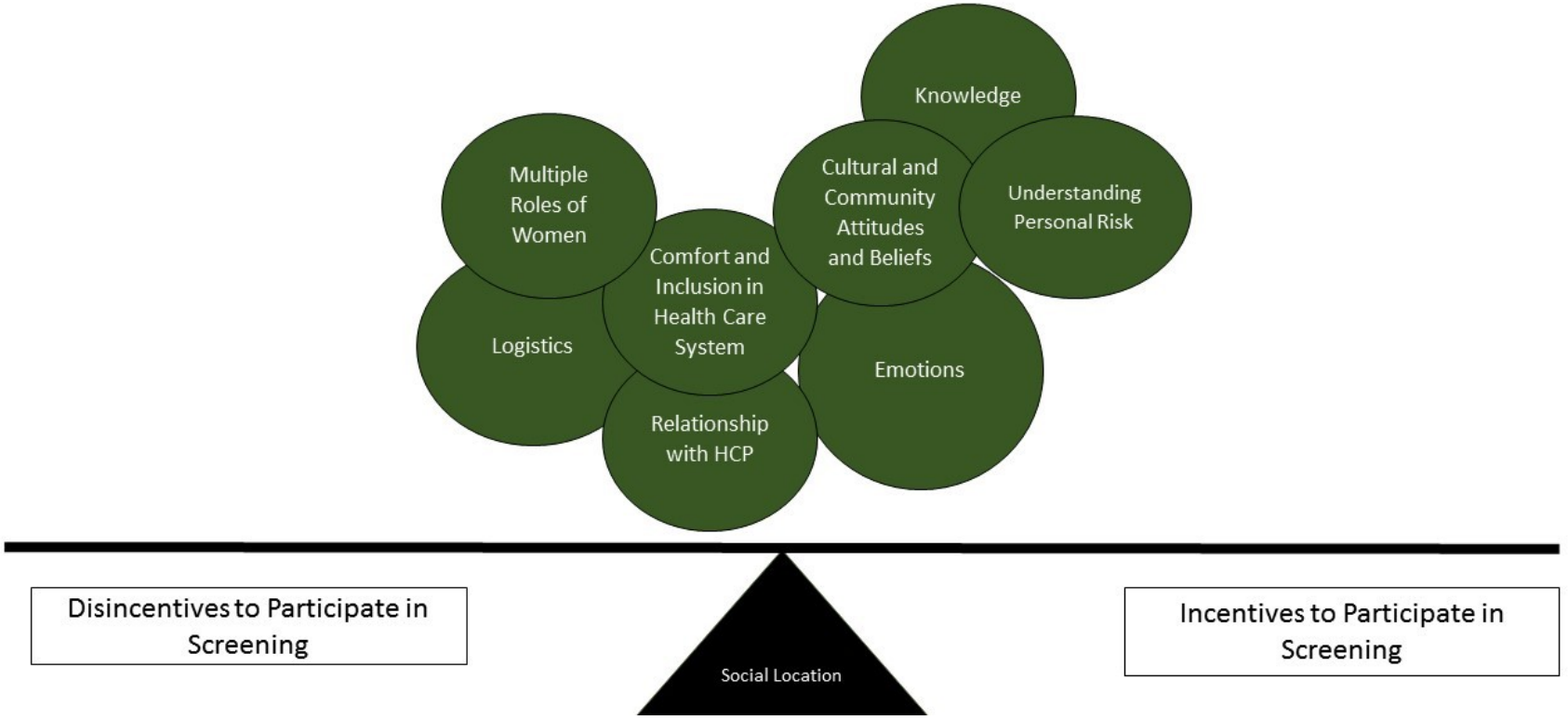
Method	Number of studies
Interviews only	52 (44.4%)
Focus group	42 (35.9%)
Interviews and focus groups	13 (11.1%)
Interview or focus group supplemented by another method	10 (8.5%)
Total	117 (100%)

Appendix 19: Factors and Themes – Patient Experiences Review

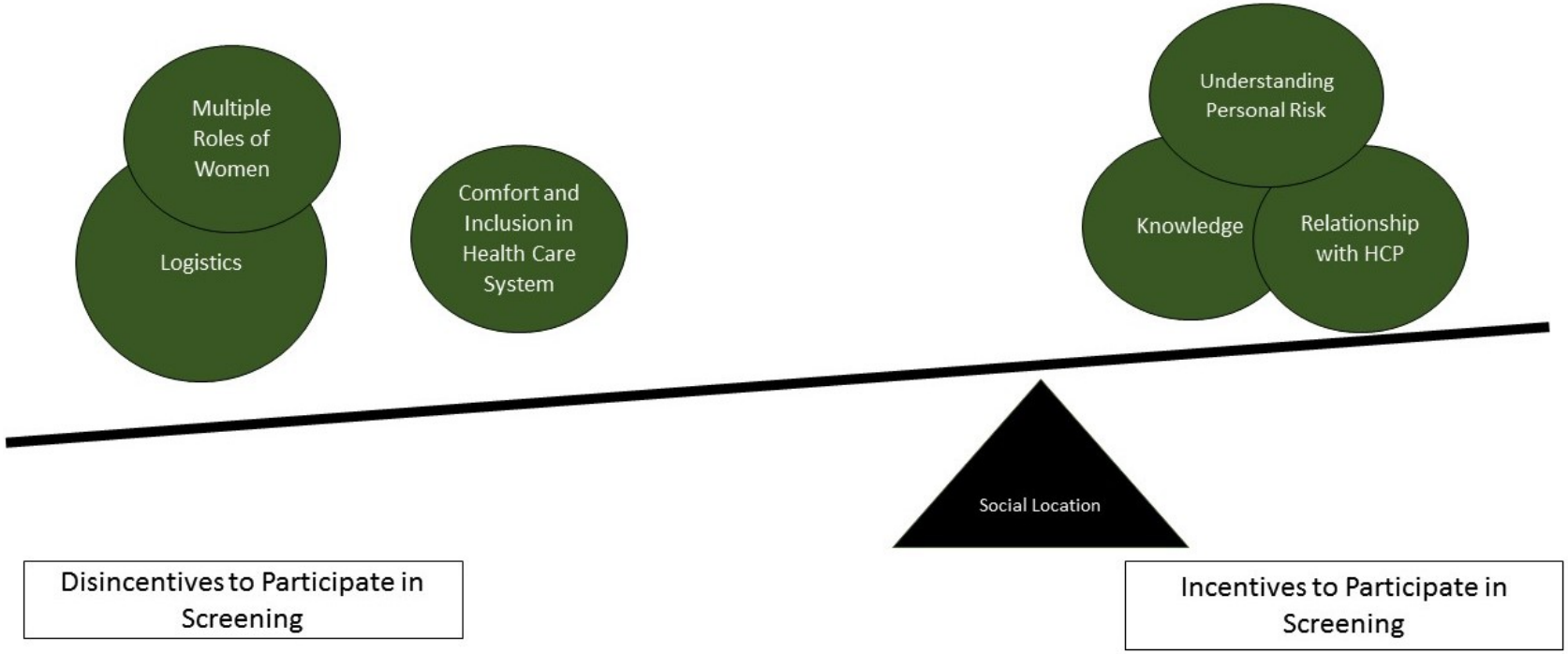
Factor	Themes
Emotions	• Emotional discomfort • Fear • Emotional orientation and values
Cultural and Community Attitudes and Beliefs	• Cultural Practices and Beliefs • Cultural (In)Congruency with HCP, System, Screening • Community Discussion • Community Understandings of Cervical Cancer Risk
Understanding Personal Risk	• Biological Risks • Physical and Behavioural Risks • Age and Life Stage Related Risks • General Well-being
Logistics	• Balancing Priorities • Scheduling Appointments • Communication • Finances
Multiple Roles of Women	• Familial Responsibilities • Communication
Relationships with Health Care Providers	• Satisfaction with HCP Communication • Personal Characteristics Influencing Experience of Care • Gender • Continuity of Care and Relationships • Initiation of CCS by HCP
Comfort and Inclusion in the Health Care System	• Relationships • Interactions with Health Care System • Organized Screening Programs
Knowledge	• Access to Information • Understanding of Purpose of Screening • General Knowledge about HPV • Screening Interval

HPV-Specific Factors	• Attitudes and Beliefs About HPV
	  ○ Link between HPV and cancer
	  ○ HPV as an STD
	• Screening Process
	  ○ HPV vs. Pap
	  ○ Accuracy of Screening
	  ○ Self-Sampling

Appendix 20: Patient Experiences – Balance of Factors that Encourage or Discourage Participation in Cervical Cancer Screening

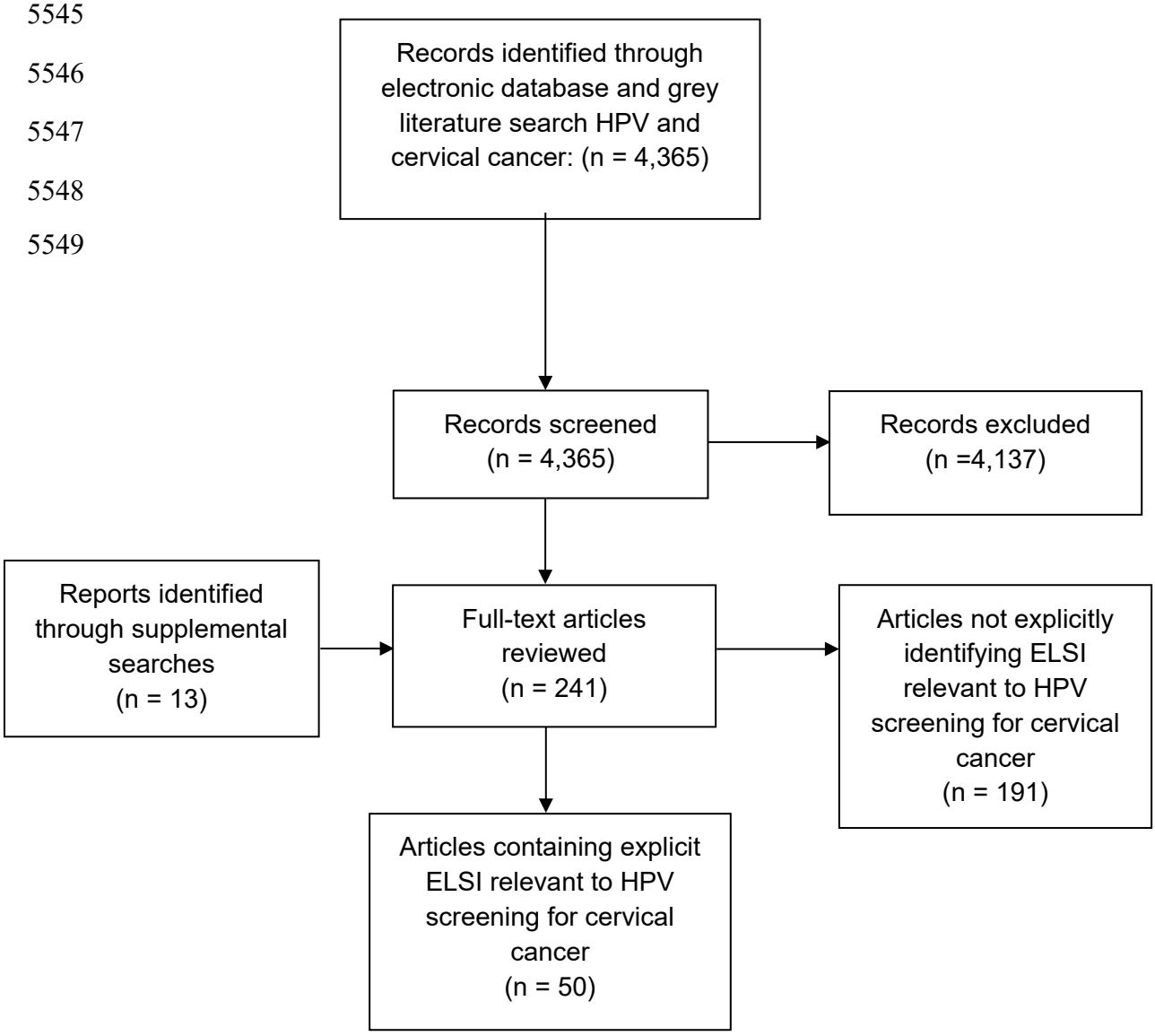


Appendix 21: Patient Experiences Review – Shift of Balance of Factors



Appendix 22: Ethics Review

Flow Diagram of ELSI Literature Search and Selection Process



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5551 **Table 56: Included Studies in the Ethics Review**

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Snadden, D. (1992). Ethical dilemmas of cervical cancer screening. Canadian Family Physician, 38:331-3, 1992 Feb, 331-3.	Canada	Opinion piece; normative analysis	Overview of ethical issues	Discusses issues of risk (harm vs. Benefit), economic costs, and patient autonomy; accepts that screening benefits weigh in favour of screening but that it is imperative to reduce harms where possible (in the organization, quality, and intensity of screening) and provide information adequate for informed choice.
Informed choice				
Alsobrook, H.B. (1972). Re: Medical-legal aspects of cervical cytology studies to detect uterine cancer. *Journal of Louisiana State Medical Society, 124(8),* 299.	US	Medicolegal Commentary	Disclosure of option	Physicians who fail to recommend annual screening to their relevant female patients by use of the Papanicolaou test (unless contraindicated) may be guilty of negligence and malpractice.
Annas, G.J. (1981). Pap smears: Physicians must disclose risk of refusal. *Hastings Center Report, 2(1),* 3.	US	Court Case Discussion & Commentary	Disclosure of option	Physicians have a legal duty to disclose information (including an explanation of any risks of any potential deadly consequences) to patients who refuse a recommended Pap smear test.
Chew-Graham, C., Mole, E., Evans, L. J., & Rogers, A. (2006). Informed consent? How do primary care professionals prepare women for cervical smears: A qualitative study. Patient Education and Counseling, 61(3), 381-388.	UK	Primary research; empirical ethics; qualitative - interviews with health professionals	Informed choice: Adequacy of information provision	Practice nurses followed a routine, while physicians varied information provision with clinical context and time available; practice nurses were persistent in achieving uptake due to commitment to program; GPs were more skeptical of value of screening and inclined to accept patients' declining screening but sometimes acted to meet targets; interviewees thought informed choice was implied by attendance and did not discuss the purpose and limitations of test in any detail.
Dixon, H. S. (2004). Pelvic exam prerequisite to hormonal contraceptives: Unjustified infringement on constitutional rights, governmental coercion, and bad public policy. Harv. Women's LJ, 27, 177.	US	Legal analysis	Informed choice; voluntariness	Argues against tying provision of contraception to willingness to undergo cervical cancer screening.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Doyal, L., & Schamroth, A. (1988). The ethics of paternalism and preventive screening. *Practitioner*, *232*(1452), 820-823.	US	Case discussion; Normative analysis	Disclosure of results	Argues that disclosure of abnormal test results, though it may cause short-term anxiety, respects patient autonomy and helps the patient respond appropriately to re-screen invitation; managing short-term anxiety should be a responsibility of physicians practicing preventive medicine.
Foster Jr., HH. (1969). The legal aspects of screening for cervical neoplasia. *Obstetrical & Gynecological Survey, 24(7)*, 1029-1035.	US	Law review	Informed choice: voluntariness	Informed consent is required for the Pap smear, including for women rendered vulnerable by incarceration and involuntary admission.
Jepson, R. G., Hewison, J., Thompson, A. G., & Weller, D. (2005). How should we measure informed choice? The case of cancer screening. Journal of Medical Ethics, 31(4), 192-6.	UK	Primary research; normative analysis	Informed choice: choice vs. uptake; voluntariness	The policy move towards informed choice in screening opens the question how this choice should be conceptualized in public health and measured. Adequacy of information is essential but so is voluntariness (options and the effective freedom to choose among options), the person's own desire for active or passive participation in decision-making, and the person's ability to match their decision to their values. Effective measures of informed choice should capture these dimensions.
Kolthoff, S. K., Hestbech, M. S., Jorgensen, K. J., & Brodersen, J. (2016). Do invitations for cervical screening provide sufficient information to enable informed choice? A cross-sectional study of invitations for publicly funded cervical screening. *Journal of the Royal Society of Medicine*, *109*(7), 274-281.	10 countries	Primary research; Empirical ethics; textual analysis of screening invitations	Informed choice: Adequacy of information provision; choice vs. uptake	Incomplete and biased information is common in screening invitations; many invitations are framed to motivate persons to attend screening rather than as decision aids to enable informed choice.
Raffle, A. E. (2001). Information about screening - is it to achieve high uptake or to ensure informed choice? *Health Expectations*, *4*(2), 92-98.	UK	Opinion piece; normative analysis	Informed choice: Adequacy of information provision; choice vs. uptake	Lack of understanding of limitations of screening violates autonomy, makes patients vulnerable to ignoring symptoms of interval cancers, worsens the experience of getting cancer despite screening by anger and blame, and distorts public debate about screening policy.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Slater, D. N. (2000). Are women sufficiently well informed to provide valid consent for the cervical smear test? *Cytopathology*, *11*(3), 166-170.	UK	Empirical ethics; questionnaire	Informed choice: Adequacy of information provision	Just under or over half of women attending colposcopy were not provided written information, or verbal explanation, of goals and limitations of CC screening.
Williams, J. H., Carter, S. M., & Rychetnik, L. (2014). Information provision in cervical screening in Australia. *Medical Journal of Australia*, *201*(5), 295-297.	Australia	Primary research; Empirical ethics - textual analysis; normative analysis	Informed choice: Adequacy of information provision; choice vs. uptake	Public information about screening overestimates benefits and understates harms and limitations (form content analysis); GPs are pressured by targets and limited time to provide inadequate consent (from narrative lit review); equity concerns include that harms of overtreatment are likely worse for younger women and information not tailored to highest risk groups, e.g. Aboriginal and Torres Island Straight women. Alternatives to promoting maximum uptake.
Equity				
Williams, J. H., & Carter, S. M. (2016). An empirical study of the 'underscreened' in organised cervical screening: Experts focus on increasing opportunity as a way of reducing differences in screening rates. *BMC Medical Ethics*, 17, 56.	Australia	Empirical ethics; interview study	Equity	Cervical cancer screening experts made use of different understandings of equity in discussing disparities in cervical cancer screening. Three main views emerged: a utilitarian view that valued high uptake and expected availability to translate into access; a view that barriers to access to mainstream services had to be addressed, and a view that services had to be tailored to communities. A single participant argued that disparities may be less concerning because underscreened persons may have other health priorities and the health system should be meeting those other priorities.
Issues in evidence				
Carter, S. M., Williams, J., Parker, L., Pickles, K., Jacklyn, G., Rychetnik, L., & Barratt, A. (2015). Screening for cervical, prostate, and breast cancer: Interpreting the evidence. *American Journal of Preventive Medicine*, *49*(2), 274-285.	N/A	Narrative review; normative analysis	Ethical issues in evidence interpretation	Review of issues in interpretation of evidence for policy-makers and physicians. CC screening evidence is largely observational; incidence of CC is low hence NNS high; reporting RRR exaggerates benefits; should improve our understanding of natural history (e.g. proportion of/which CIN 3 progress to cancer); impact of new technology (HPV) and vaccination unknown.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Grimes, D. A., & Schulz, K. F. (2002). Uses and abuses of screening tests. Lancet (London, England), 359(9309), 881-884	N/A	Opinion piece; normative analysis	Ethical analysis of harm-benefit tradeoff; issues in evidence	Argues for higher standards of evidence for screening compared to diagnostic testing (by listing screening-related harms) and reviews typical biases in evidence base (e.g. length and lead-time bias).
Polyzos, N. P., Valachis, A., Mauri, D., & Ioannidis, J. P. (2011). Industry involvement and baseline assumptions of cost-effectiveness analyses: Diagnostic accuracy of the Papanicolaou test. *Canadian Medical Association Journal*, *183*(6), E337-E343.	N/A	Primary research; analysis of methodological quality of cost-effectiveness studies	Ethical issues in evidence interpretation	Examined economic studies of HPV vaccination or screening compared to pap test and found that manufacturer funding correlated with bias in estimation of test characteristics of pap smear, to the benefit of manufacturer's product.
Ethical analysis and debate of harm-benefit tradeoff				
Austin, R. M. (2004). New cervical cancer screening guidelines: The other side of group health care "rights". Diagnostic Cytopathology, 30(3), 208-210	US	Opinion piece; normative analysis	Harm-benefit balance: individual vs. group perspectives	Argues against widening screening interval (given adoption of LBC) on the grounds that the decision is economically driven and results in net harms to patients.
Austin, R. M. (2003). Human papillomavirus reporting: Minimizing patient and laboratory risk. Archives of Pathology and Laboratory Medicine, 127(8), 973-977	US	Opinion piece; normative analysis	Harm-benefit balance: individual vs. group perspectives	Argues against widening screening interval on the grounds that the decision is economically driven and results in net harms to patients; skeptical of claims that the decision to widen screening interval is driven by non-maleficence.
Kinney, W. K., & Huh, W. K. (2017). Protection against cervical cancer versus decreasing harms from screening - what would U.S. Patients and clinicians prefer, and do their preferences matter? *Preventive Medicine*, *98*, 31-32.	US	Opinion piece; normative analysis	Harm-benefit balance	Level of cancer prevention provided by yearly cytology is acceptable; reduction of screening-related burden or harm that does not maintain that level of prevention is unacceptable

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Malm, H. M. (1999). Medical screening and the value of early detection: When unwarranted faith leads to unethical recommendations. Hastings Center Report, 29(1), 26-3	N/A	Primary research; normative analysis (all cancer screening)	Ethical analysis of harm-benefit tradeoff	In the absence of RCT evidence, early detection is over-valued and duties of non-maleficence not fulfilled: we fail to account for possibility that earlier treatment is not successful; risks of unnecessary overtreatment may outweigh benefits of early treatment; benefit of disease prevention belongs only to the individual whose disease is prevented while the burdens and harms of screening belong to a much larger group.
Massad, L. S. (2008). Assessing new technologies for cervical cancer screening: Beyond sensitivity. Journal of Lower Genital Tract Disease, 12(4), 311-315.	US	Opinion piece; normative analysis	Harm-benefit tradeoff; public acceptability, equity	HPV testing has limitations in specificity, in public acceptability, and in individual and system cost--which may worsen equity.
Raffle, A. E. (2004). Cervical screening: Recent changes in policy regarding age and frequency are a poor use of resources. BMJ (Clinical Research Ed.), 328(7451), 1272-1273	UK	Opinion piece; normative analysis	Harm-benefit tradeoff; health system opportunity costs	Argues against narrowed screening interval on the basis of negligible benefits, harms to patients, and opportunity costs for health system.
Legal liability				
Anonymous. (2006). Case #4: One settles; the other fights on. A misreported Pap smear brings two clinicians to court. Only one takes his case to the jury. *The Clinical Advisor, 9(8)*, 100-101.	US	Court Case Discussion & Commentary	Defenses to Legal Claims	Legal and patient-engagement risk-management strategies for defending physicians against malpractice cases based on a misreported Pap smear.
Anonymous. (1999). Double jeopardy for women in cervical screening. *The Lancet, 354 (9193)*, 1833.	UK	Court Case Discussion & Commentary	Compensation to Patients; Acceptable Error Rates	Discussion of UK court decisions, acceptable error rates, and patients' rights to compensation for damages caused by the national cervical cancer screening program.
DeMay, R.M. (2000). Should we abandon pap smear testing? *Am J Clin Pathol*, *114(Suppl 1)*, S48-S51.	US	Medicolegal commentary	False Negatives; Legal Liability; Litigation Standards; Zero Standard Problem	A zero-error standard for cytology would place cost-effectiveness in question; if so, we should consider abandoning cytology screening.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Derman, H. (1997) Quality and liability issues with the Papanicolaou smear: Lessons from the science of error prevention. *Arch Pathol Lab Med, 121*, 287-291.	US	Analytic review	Liability; Patients' Rights to Legal Recourse; Litigation Standards; Public Expectations	Recommends legal reform to address standard of care, role of expert witnesses, and the reasonable person standard.
Fitzgibbons , PL & Austin, M. (2000). Expert review of histologic slides and Papanicolaou tests in the context of litigation or potential litigation. *Arch Pathol Lab Med, 124 (November),* 1717-1719*.,*	US	Policy review	Expert Review Guidelines	Outlines conditions that must be met to ensure an unbiased screening review process in expert witness testimony.
Frable, WJ. (1997). Guidelines for experts reviewing Papanicolaou smear litigation cases. *Arch Pathol Lab Med, 121*, 331-334.	US	Policy review	Expert Witness Testimony Guidelines	Provides rationale and recommended guidelines for the physician expert witness to plaintiffs and defendants of legal claims involving Pap smear litigation cases.
Frable, WJ, Austin, RM, Greening, SE et al. (1998). Medicolegal affairs: IAC Task Force summary. *Acta Cytologica, 42(1),* 76-132.	US	Background & Policy review	Professional Practice & Legal Standards; Consensus Position; Public & Professional Education	Review of legal issues pertaining to cervical cytologic smears for cervical cancer detection. Recommends quality control and patient education about the limitations of the Pap test.
Freckelton, I. (2003). Gynaecological cytopathology and the search for perfection: Civil liability and regulatory ramifications. *Journal of Law and Medicine, 11*, 185-200.	Australia, UK	Analytic review & Case Law review	Professional Practice & Legal Standards	The liability crisis did not materialize; liability has only been found where culpable failure to adhere to practice standards has been established. Clarification of standards and greater understanding of practice by law still required.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Godfrey, SE. (1999). The Pap smear, automated rescreening, and negligent nondisclosure. *AmJ Clin Pathol, 111,* 14-17.	US	Medicolegal commentary	Automated Rescreening; Negligent Nondisclosure; Practice Standards; Reasonableness	Predicts that from medicolegal necessity, laboratories will have to include the informed option of automated rescreening, which will increase the price making for a 2-tiered system (in the US) with different levels of affordability.
Greening, S. (1997). Errors in cervical smears: Minimizing the risk of medicolegal consequences. *Monographs in pathology, 39*, 16-39.	US	Analytic review	Quality Control; Quality Assurances; Practice & Legal Standards; Minimizing Legal Liability	Argues that cytologists need to critically evaluate their practices and practice settings to withstand regulatory and legal scrutiny; laboratories need to observe quality control and assurance procedures to defend against malpractice claims; and that consumer education is key to limiting these claims in the future.
Kline, TJ. (1997). Liability issues with the Papanicolaou smear: General legal background. *Archives of Pathology & Laboratory Medicine, 121(3),* 250-252.	US	Medicolegal commentary	Insurance; Risk Management Against Malpractice Lawsuits	Explains the ramifications of malpractice coverage, risk management strategies linked to quality assurance and quality controls, and clarifies the processes related to malpractice lawsuits related to Pap smear testing results.
Koss, LG. (1998). An eye on malpractice: Risk and consequences of screening and reporting cervicovaginal smears. *Acta Cytologica, 42(1),* 127-131.	US	Medicolegal commentary	Quality Control; Minimizing Legal Liability	The most significant and practical way to protect laboratories from malpractice suits and litigation is to reduce or minimize errors. Proposes this be done by screening all cervical smears twice and convincing the relevant parties to pay for quality or risk the results of increased litigation.
McCoy, D.R. & Sidoti, M.S. (1999). The Pap smear liability crisis. *Am J Clin Pathol, 112,* 273-281.	US	Medicolegal commentary/Editorial	Informed Consent; Negligent Non-Disclosure	Information regarding the availability and limitations of new automated screening technologies is appropriate for laboratories to share with clinicians, but not required for meeting standards of care. The clinician is under an independent duty to keep abreast of new technologies and is the only appropriate decision-maker of what information to share with patients.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Mitchell, H. (1997). Report disclaimers and informed expectations about Pap smears. An Australian view. *Arch Pathol Lab Med, 121 (March)*, 327-330.	Australia	Medicolegal commentary	Standard of Practice; Minimizing Risk of Litigation	Proposes various measures laboratories and clinical personnel might take to minimize the risks of litigation, including better communication processes making information more comprehensive and accessible to patients and the public. Suggests that "the most urgent need is for an international definition of the reasonable standard of care for the average screening situation."
Perey, R. (1998). Cervical cancer and the misdiagnosed smear. *Acta Cytologica, 42(1),* 123-127.	US	Medicolegal commentary	Negligence; Malpractice	Claims that the CC test has the potential to virtually eliminate cervical cancer, but this has not been achieved largely owing to clinical and laboratory negligence.
Rosenthal, DL. (1998). Patient advocacy vs. cervical cytologic smear risk reduction: Are they mutually exclusive? *Acta Cytologica, 42(1),* 120-121.	US	Medicolegal commentary	Standard of Practice; Minimizing Risk of Litigation; Patient Advocacy	Argues that the pathology profession has focused on litigation "crisis control" and needs, instead, to take responsibility for mistakes and practice risk reduction. Most needed are the development of professional practice standards and the use of expert panels—"true peer review"—to review smears included in potential litigation.
Schumann, J.L. et al. (1992). Pap smear collection devices: technical, clinical, diagnostic, and legal considerations associated with their use. *Diagnostic Cytopathology*, 8(5), 492-503.	International	Medicolegal commentary	Liability; Lab Standards; Quality Assurances/Control	Reviews how new sampling devices might affect potential liability for laboratories and physicians as well as a selection of relevant case law.
Sidoti, MS. (1998). The role of clinical history and presuit screening. *Acta Cytologica, 42(1),* 121-123.	US	Medicolegal commentary	Clinical History; Presuit Screening; Minimizing Risk of Litigation	Argues that labs and clinicians share liability for errors. Argues that labs should ensure legal counsel present when rescreening specimens as requested for physical turnover by any third party).
Skoumal, S.M., & Maygarden, S.J. (1997). Malpractice in Gynecologic cytology: a need for expert witness guidelines. *Modern Pathology, 10(3),* 267-269.	US	Medicolegal commentary	Expert Witness Testimony Guidelines	Discusses the role and positive benefits of a proposed forum to develop guidelines for expert witness testimony in Pap smear cytology.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Slater, D.N. (1998). False-negative cervical smears: medico-legal fallacies & suggested remedies. *Cytopathology, 9,* 145-154.	UK	Medicolegal review	Professional Practice and Legal Standards; Zero Standard Problem	Argues for a reasonable standard of skill and care as the legal test and education around limitations of screening.
Somrak, T. (1998). Defending against the current liability crisis. *Acta Cytologica, 42(1),* 131-132.	US	Medicolegal commentary	Medical Liability Reform; Litigation Crisis	Argues quality improvement and risk management practices and guidelines .
Stanley, M.W. (1997). Quality and liability issues with the Papanicolaou smear: the role of professional organizations in reform initiatives. *Archives of Pathology & Laboratory Medicine, 121(3)*, 321-326.	US	Medicolegal commentary	Minimizing Legal Liability; Quality Assurances; Professional Standards	Argues for quality assurances to minimize legal liability. Suggests concerted action by societies to address educational and medicolegal issues.
Varner, C.D. (1997). Liability issues of Pap smear: a defense lawyer's perspective. *Arch Pathol Lab Med, 121 (March)*, 315-320.	US	Law review	Legal and Practice Standards; Quality Assurance/Controls	Recommends quality assurance measures as a response to medico-legal risk and to ensure public confidence in screening programs.
Wood, W.S. (1997). Liability issue with the Papanicolaou smear. *Arch Pathol Lab Med, 121 (March)*, 335-340 .	US	Law review	Liability; Expert Witness	Argues that organized, accessible expert witness databases (as provided, for example, by the Defense Research Institute) can help defense lawyers to better obtain high quality expert witnesses and to better prepare for cross-examining opposing experts.
Program organization				
Parker, L., Carter, S., Williams, J., Pickles, K., & Barratt, A. (2017). Avoiding harm and supporting autonomy are under-prioritised in cancer-screening policies and practices. European Journal of Cancer (Oxford, England : 1990), 85, 1-5.	N/A	Primary research; normative analysis	Prioritization of ethical issues	Argues that autonomy and non-maleficence are insufficiently implemented in organized cancer screening programs; makes specific recommendations for program governance to achieve a more balanced approach to cancer screening given its limitations.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Slater, D. N. (2001). For debate--ethical considerations of gynaecological liquid-based cytology and human papillomavirus studies. *Cytopathology*, *12*(4), 251-256.	UK	(Policy) case discussion; Normative analysis	Research vs. piloting	In implementing liquid cytology, NICE both argued that LBC had insufficient evidence for full implementation and that it should be implemented on a pilot basis. HPV testing has been piloted under similar circumstances, despite additional concerns about its nature as an STI test. Slater argues that this is a contradiction: either further research is needed, in which case women need freedom to choose not to participate (i.e. to have the old technology), or implementation (including piloting) is in order.
Wallis K. (2007). Cervical screening legislation is unethical and has the potential to be counter-productive. *New Zealand Medical Journal*, 120(1266), U2840.	New Zealand	Primary research; normative analysis	Program oversight vs. confidentiality and privacy	1956 Cervical Cancer Screening Program legislation permits the program to access personal health records of individual patients; this is a breach of patent privacy and physician duty of confidentiality; is unnecessary as consent for access for research is feasible; constitutes intrusive oversight of physician practice.
Williams, J., Carter, S., & Rychetnik, L. (2017). Contested guideline development in Australia's cervical screening program: Values drive different views of the purpose and implementation of organized screening. Public Health Ethics, 10(1), 5-18	Australia	Primary research; empirical ethics - interviews with expert informants	Values informing program implementation	Experts involved in the development of organized cancer screening in Australia had different goals and these goals were informed by different values, different understandings of harms and benefits, and different interpretaitons of evidence. Their goals were to eliminate cervical cancer, minimize cervical cancer, reduce harms of opportunistic screening, or ensure equitable access to screening. Although some argue that public health ethics is primarily utilitarian, this study shows the limitations of utilitarianism in public health policy.

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