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CADTH OPTIMAL USE REPORT

HPV Testing for Primary Cervical Cancer Screening — Project Protocol

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Revision History

Section	Date	Description/Changes Made	Reason for Change

Rationale and Policy Issues

It is estimated that more than 80% of sexually active women will acquire a human papillomavirus (HPV) infection in their lifetimes, with the majority (about 90%) of these infections being relatively benign and resolving within one to two years.[1-3] Approximately 40 HPV genotypes are known to be involved in HPV infections, of which 13 have been designated as high-risk HPV (HRHPV) types due to their strong oncogenic potential.[2,4] A persistent infection with one or more of the HRHPV types is recognized as a main factor in the development of cervical intraepithelial neoplasia (CIN); i.e., cervical precancerous lesions and invasive cervical cancer.[1,4] In particular, HRHPV types 16 and 18 are responsible for approximately 70% of all cervical cancer cases worldwide.[1] This strong causal link between HPV infection and cervical cancer provided the impetus for using HPV testing in screening for CIN and invasive cancer.

HPV assays detect the presence of HPV DNA or ribonucleic acid in a sample of cervical cells, with a positive result indicating an HPV infection.[1,2] In contrast, in a Papanicolaou (Pap) test, conventional or liquid-based cytology is used to examine the sample and determine if the cervical cells show abnormal changes, which may indicate CIN or invasive cervical cancer.[2,5] The 2001 Bethesda System is most commonly used in Canada to classify Pap test results.[5] Test results of 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. 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*).[6] As CIN2 and CIN3 cannot be differentiated reliably in a clinical setting, a pan-Canadian consensus document on histopathology reporting recommends a two-tiered naming system for cervical dysplasia, specifically squamous intraepithelial lesions, in which CIN2 and CIN3 lesions are collectively referred to as high-grade squamous intraepithelial lesions (HSIL), and CIN1 is classified as low-grade squamous intraepithelial lesions (LSIL).[7] Approximately 1% of CIN1 and 12% to 30% of CIN2 or CIN3 cases progress to invasive cervical cancer.[4]

HPV testing can be used as a primary tool for screening (alone or with cytology triage for HPV-positive results), as an adjunct to Pap cytology in co-testing, or for triage of cases with ASCUS or LSIL cytology results.[5] HPV testing used as the primary screening method is also termed HPV primary screening. HPV primary screening has not been implemented in Canada, although it is under consideration in a number of jurisdictions. Notably, 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,[8] though this practice has not yet been funded.[9] A pilot study comparing HPV primary screening with Pap cytology screening, the HPV FOCAL trial, is ongoing in British Columbia; the results are expected to influence future policy decisions on cervical cancer screening in the province and other Canadian jurisdictions.[5]

Internationally, transition to HPV primary screening is proceeding or planned in several countries, such as Mexico, Italy, the Netherlands, Australia, Sweden, and Scotland.[4,10] European guidelines recommend HPV primary screening for organized, population-based screening.[11] In the US, HPV testing in combination with Pap cytology (co-testing) is recommended at five-year intervals for women between the ages of 30 and 65.[3,12] The growing adoption of HPV-based screening can be explained by some advantages that HPV testing is expected to offer over cytology, such as higher sensitivity and reproducibility, the possibility to safely increase the time between screening visits, the potential for the screening process to be more efficient and cost-effective, and the opportunity to implement self-sampling to encourage screening participation in under- and never-screened populations, among others.[4,13]

There appears to be a consensus in the literature that, based on the evidence, HPV testing as standalone primary screening or in co-testing should not be used for women under 30 years of age; the higher rate of transient HPV infections among that younger age group, 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 women without precancerous cervical lesions) and unnecessary interventions, such as referral to colposcopy.[3,4,8,11,14] Due to insufficient evidence on the matter, there is no firm consensus on the age at which HPV primary screening should be discontinued; however, the aforementioned Ontario guidelines recommend the age of 65, provided a woman has remained HPV-negative in the preceding 10 years.[8] It has been suggested that, with HPV testing, the screening interval can be extended to at least five years for women 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 Pap test.[3,4,8,11,14]

In contrast, existing guidelines in the provinces and territories recommend that women be screened with the Pap test every two to three years starting at age 21 and until age 65 to 70, depending on the jurisdiction.[5] The Canadian Task Force on Preventive Health Care published guidelines in 2013 that now recommend routine screening with Pap cytology every three years for women 25 years to 69 years of age.[15] The Pan-Canadian Cervical Screening Network established the following target for cervical cancer screening participation: ≥ 80% of women aged 21 years to 69 years should be screened in the preceding 42 months,[5] which would correspond to approximately 9.5 million women.[16]

According to a recent report[5] published by the Canadian Partnership Against Cancer, there were an estimated 1,500 new cases of cervical cancer and 380 deaths from the disease in Canada in 2015. On a per-population basis, the age-standardized incidence of invasive cervical cancer ranged from 8.8 to 17.8 per 100,000 women in the eight provinces that reported on this aspect. In another report produced by the Canadian Cancer Society's Advisory Committee on Cancer Statistics, the age-standardized incidence and mortality rates for cervical cancer in 2015 are estimated at 7.5 and 1.6

cases per 100,000 Canadian women, respectively.[17] According to the report from the Canadian Partnership Against Cancer, from January 1, 2010 to June 30, 2013, the percentage of abnormal Pap test results, classified according to the 2001 Bethesda System, ranged from 3.9% of women in British Columbia and Prince Edward Island to 14.7% in New Brunswick. These results are reported for a 12-month period and, for calculation purposes, include only the most severe Pap test result when a woman has had multiple Pap tests in the period examined. From January 1, 2010, to June 30, 2013, women aged 21 years to 69 years had a participation rate in cervical cancer screening that ranged from 62.9% to 71.3% in the 10 provinces for which data are available. This rate is uncorrected for a previous hysterectomy, which, as explained in the report, may represent an underestimation of screening rates. Participation rates corrected for hysterectomy ranged from 64.9% to 73.8% in the three provinces that reported this data (British Columbia, Manitoba, and Ontario).[5]

Cervical cancer screening aims to reduce risk of the disease and associated mortality by detecting and treating precursor lesions before they progress to invasive cervical cancer.[5,8] Indeed, a recent analysis of a wide pool of data on the subject concluded that screening is beneficial and contributes to a lower risk of developing or dying from invasive cervical cancer.[18] In Canada, the lifetime risk of dying from cervical cancer is one in 100 in women who do not undergo screening and one in 500 for those who do undergo screening. Therefore, screening improves survival from cervical cancer.[19]

The evaluation of screening procedures can be considered using six criteria: validity, reliability, yield, cost, acceptance, and the availability of follow-up services.[20] The first three criteria are related to the performance of the screening test. Validity refers to the ability of the screening test to separate those with and without the condition of interest. Diagnostic test accuracy outcomes, such as sensitivity and specificity, are measures of screening test validity that are commonly reported in studies evaluating the performance of HPV assays in cervical cancer screening.[14,21] In the context of using HPV testing as a screening tool for cervical cancer, a true-positive would be an HPV-positive result in a woman with high-grade CIN (or HSIL), and a false-positive would be an HPV-positive result in a woman without HSIL. This is distinct from the scenario of screening for a sexually transmitted infection of HPV itself, in which case a true-positive would be an HPV-positive test result when the virus is present, and a false-positive would be an HPV-negative result when the virus is not present. As the focus of this review is on HPV testing for cervical cancer screening, true-positives and false-positives will be defined in reference to the presence of HSIL unless otherwise specified.

A primary outcome in several cervical cancer screening studies is the rate of CIN or HSIL that HPV testing-based strategies are able to detect (i.e., true-positives) in one or more rounds of screening as a standalone screening method or combined with cytology.[21-24] Additional diagnostic test accuracy or validity outcomes for cervical cancer screening are the negative predictive value[21] and positive predictive value[21] of the screening test. Yield from screening refers to the number of cases that are newly identified as a result

of screening and are referred to treatment as appropriate.[20] In the context of cervical cancer screening, this includes colposcopy referral rates.[21,23] The ultimate value of a screening test extends beyond its diagnostic test accuracy to the effect of its use on long-term clinical outcomes as a result of appropriate disease identification and subsequent treatment. While it is anticipated that most available evidence on a screening test stops at the level of diagnostic test accuracy, relevant clinical outcomes include the impact of the screening method on cervical cancer incidence and mortality.[14]

The available evidence indicates that HPV testing may yield sensitivity as high as 95%, compared with 55% for conventional Pap cytology.[4] However, HPV testing has been found to have lower specificity than cytology,[4] although a meta-analysis[25] reported that the two testing methods showed similar specificity in screening women aged 30 years and older. A systematic review[21] of randomized controlled trials (RCTs) evaluating the performance of HPV testing over two or more rounds of screening reported that in the first screening round, significantly higher numbers of CIN2, CIN2+, and CIN3+ were detected in women who were screened with HPV testing compared with those who had cytology. In the second round, lower numbers of CIN2+ and CIN3+ were detected in the women who underwent HPV testing at first screening.

An interpretation of these results proposes that HPV testing performs better than cytology as a tool for early detection of clinically significant CIN, allowing prompt follow-up and treatment and leading to a reduction of these high-grade lesions in the screened population over time.[21,22] Additionally, limited evidence suggests that HPV testing may be associated with lower rates of cervical cancer incidence and mortality, although caution is advised in interpreting these results.[21] Of note, due to the enhanced sensitivity of HPV testing, there is concern that it may lead to over-diagnosis and unnecessary interventions for transient HPV infections and less serious cervical lesions that would have otherwise self-resolved, subjecting the affected women to undue physical and mental burdens.[4,8] The guidelines developed for the Ontario Cervical Screening Program highlight that educating women and practitioners will be an important component of implementing HPV primary testing.[8] Current evidence indeed suggests that HPV testing as a standalone screening tool (or combined with cytology) is associated with higher rates of referrals to colposcopy compared with cytology alone.[21,26]

In addition to issues regarding test accuracy and the clinical use of the results, 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. PROGRESS-Plus[27] defines, in a general way, the relevant population characteristics that may be of interest in health technology assessments (HTAs), including place of residence and socioeconomic status. It also invites consideration of other situational, contextual, and personal characteristics subject to discrimination

or structural disadvantage. An example of a relevant population characteristic would be indigeneity.

Examples of other relevant situational, contextual, and personal characteristics that have been studied for screening disparities in other jurisdictions include intellectual disability,[28,29] incarceration,[30] HIV status, insurance status,[31] sexual orientation,[32] gender identity, experience in sex work,[33] sexual life history (which places some populations at risk of new HRHPV infection earlier than the population norms that guide screening policy; i.e., children subject to sexual abuse),[34] experience with intimate partner violence,[35] and membership in certain immigrant groups (e.g., Hmong, Vietnamese, and Haitian in the US).[36] These important considerations are discussed throughout the report.

Policy Issues

Currently, women in all Canadian provinces and territories have access to opportunistic or organized cervical cancer screening with the Pap test.[5] While the implementation of the Pap test 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.[2,5] In view of the higher sensitivity of HPV testing, some experts and stakeholders have called for it to be adopted in Canada as the primary screening tool, replacing the Pap test in eligible women.[4,8] As noted, to date, no Canadian jurisdiction has implemented routine HPV primary screening.[5] However, a number of Canadian jurisdictions are currently considering, planning, or piloting HPV primary screening programs.[5,8,37] In this context, this HTA will be conducted to inform decision-making, policy development, capacity planning, and recommendations around HPV testing for primary screening.

Policy Question

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 ages to start and stop screening, should guide HPV-based cervical 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, patient experience and perspectives, ethical issues, implementation issues, and environmental impact of HPV testing as a primary screening tool for cervical cancer screening.

Research Questions

The proposed HTA will address the following research questions. For the purposes of this review, 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 HRHPV testing, with or without cytology triage, compared with primary cytology-based testing for cervical cancer screening of asymptomatic women?
2. What are the diagnostic efficacies of primary HRHPV testing strategies compared with each other for cervical cancer screening of asymptomatic women?
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 cervical cancer screening of asymptomatic women in Canada?
4. What are the perspectives of women, 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?
7. What is the environmental impact associated with the use of HPV testing as a primary screening tool for cervical cancer?

Methods

Search Strategy

The literature search will be performed by an information specialist using a search strategy peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist.[38] The complete search strategy is presented in Appendix 1.

For the clinical search, published literature will be 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 will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be human papillomavirus (HPV) testing, cervical cancer, diagnostic test accuracy, and screening.

No filters will be 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.[39] Retrieval for the current search will be limited to documents published since January 1, 2002, supplemented with relevant studies from the previous CADTH report. The search will also be limited to English-language and French-language publications. Conference abstracts will be excluded from the search results.

Three additional searches will also be performed:

- Information related to patient perspectives and experiences will be 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 Scopus. A hybrid qualitative filter will be applied to limit retrieval to qualitative studies. The validation of this filter has been published.40 Conference abstracts will be excluded from the search results.
- Ethics-related information will be identified by searching the following databases: MEDLINE (1946–) via Ovid, PsycINFO (1967–) via Ovid, CINAHL (1981–) via EBSCO, and PubMed.
- Implementation-related information will be identified by searching MEDLINE (1946–) via Ovid, Embase (1974–) via Ovid, CINAHL (1981–) via EBSCO, and PubMed. Conference abstracts will be excluded from the search results.

These additional searches will be limited to English-language or French-language publications. Retrieval will be limited to documents published since January 1, 2002, except for the ethics search, which will not be limited by date.

The initial searches will be completed by March 2017. Regular alerts will be established to update the searches until the final report is published. Regular search updates will be performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified prior to the completion of the stakeholder feedback period of the final report. Any studies that are identified after the stakeholder feedback period will be 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) will be 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 will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Clinical Review

This protocol was written a priori and will be followed throughout the review process. Any deviations from the protocol will be disclosed in the final report. Updates to the PROSPERO submission will be made accordingly.

Study Design

An informal scoping review of existing HTAs, systematic reviews (SRs), and evidence-based guidelines, supported by a Rapid Response Reference List,[41] was conducted to inform the preparation of this protocol — in particular, to guide a decision regarding how to integrate existing, published SRs into the current clinical study. Four SRs[21,25,42,43] and one evidence-based guideline by the US Preventive Services Task Force[12] with its supporting SR[44] identified by the Rapid Response Report were examined in more detail to determine their relevance to the policy question for this review as well as the comprehensiveness of their literature searches.

While all SRs included comparisons of primary HPV testing with cytology for cervical cancer screening, reporting of the study characteristics of included primary studies was limited in two SRs.[21,42] In addition, two of the SR publications did not provide sufficient details regarding their literature search strategies for them to be rerun by CADTH information specialists or for the quality of the search strategies to be thoroughly evaluated;[25,43] two SRs placed restrictive study designs on the search that are not ideal for diagnostic testing.[21,43] Mustafa et al.[42] was published in 2016; however, the literature search was conducted up to 2012. The SR supporting the US Preventive Services Task Force recommendations had more limited inclusion criteria than CADTH considered for this review and did not evaluate all currently relevant comparisons, as determined based on feedback from clinical experts. As the field of research on HPV testing for cervical cancer screening is rapidly expanding and evolving, it is likely that additional primary studies have been published since the end of the literature search for these existing SRs. Therefore, it was decided that conducting a new SR of primary studies would be the most appropriate approach for CADTH to address the diagnostic efficacy of primary HRHPV testing for cervical cancer 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 adult women 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[27a] Exclusions: ○ Women with known cervical cancer or previous treatment for HSIL ○ Women without a cervix ○ High-risk women (e.g., immunocompromised, HIV-positive)	
Index Test	
Diagnostic Test Accuracy • Primary HRHPV testing[b] with HPV nucleic acid tests[c] alone • Primary[b] HRHPV testing with HPV nucleic acid tests[c] followed by LBC or conventional cytology-based testing for HPV-positive samples *Clinical Utility* • Primary HRHPV testing[b] with HPV nucleic acid tests[c] and subsequent management of patients with confirmed disease[d] • Primary[b] HRHPV 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 HRHPV 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* • Primary conventional cytology-based testing (Pap smear) alone[e] • Primary conventional cytology-based testing (Pap smear)[e] followed by HRHPV testing of cytology-positive samples • Primary LBC testing alone[e] • Primary LBC testing[e] followed by HRHPV 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]	***Q2*** *Diagnostic Test Accuracy* • Primary HRHPV testing strategies[b] compared with each other • HRHPV and cytology co-testing *Clinical Utility* • Primary HRHPV testing strategies[b] and subsequent treatment of patients with confirmed disease[d] compared with each other • HRHPV and cytology co-testing and subsequent treatment of patients with confirmed disease[d]

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

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 patients who accepted screening
• Diagnostic test accuracy
  ○ Number and proportion of patients 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 patients (e.g., unnecessary referral to colposcopy)
  ○ Over-diagnosis, including treatment, and related impacts on patients (e.g., cervical incompetence, adverse pregnancy outcomes)
  ○ Any other reported harms
• Clinical utility
  ○ Number or proportion of patients referred to colposcopy
  ○ Number or proportion of patients 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

• RCTs
• Non-RCTs
• Cohort studies
• Cross-sectional 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

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

Country
• Canada, US, Australia, New Zealand, UK, European Economic Area countries
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; HRHPV = 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 HRHPV testing means that the HRHPV test is the initial test in a screening pathway. This includes pathways in which positive results on the HRHPV test are followed directly by colposcopy or a cytology-based triage test.

[c] Commercial HPV tests will be considered for inclusion if they detect at least some of the following identified HRHPV types: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.[4] 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 HRHPV 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.[39]

The main population of interest is asymptomatic women with a cervix; however, studies of persons with a cervix who do not identify as women will also be included. Studies with mixed populations of individuals who meet and do not meet the review inclusion criteria will be included if the results pertaining to the subgroup who do meet inclusion criteria are reported separately. If results for the population of interest are not reported separately, studies with a mixed study population will be included if at least 80% of the population meets the inclusion criteria.

Studies will be 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 are evaluated. Eligibility for inclusion will be limited to studies conducted in Canada, the US, Australia, New Zealand, the UK, or a member of the European Economic Area.

Commercial HRHPV nucleic acid tests will be considered for inclusion if they detect at least some of the following HRHPV 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., Digene Hybrid 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). Subgroup analyses will be performed by functional class of assay (i.e., generic, partial genotyping,

and full genotyping) and threshold of HPV test positivity (e.g., 1 pg/mL or 2 pg/mL), if possible.

Eligible cytology tests include Pap tests with conventional cytology-based methods and liquid-based cytology methods (e.g., ThinPrep, SurePath). There is a range of abnormal cytology results that may be variably used in the included studies as the threshold for further investigation in the screening pathway (e.g., ASCUS, ASCH [atypical squamous cells, cannot exclude HSIL], LSIL, HSIL). The categories and thresholds for cytology results provided in the included studies will be clearly reported, where possible. Sensitivity analyses including and excluding studies using different cytology result thresholds may be performed as appropriate given the data identified.

The reference standard is colposcopy with histologic examination of tissue specimens, when indicated. Tissue specimens are typically sampled by biopsy, but in some cases, may be taken during the loop electrosurgical excision procedure (LEEP) for HSIL, which may be performed at the time of first colposcopic examination when HSIL is observed and there are concerns that the patient may not return for follow-up. There is no restriction on the number of biopsy specimens required to determine a true-positive or true-negative result; however, sensitivity analyses may be performed based on the number of tissue specimens used for the reference standard in each study.

There is no restriction regarding therapy duration or length of follow-up.

Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified before the end of the stakeholder feedback period of the final report. Any studies identified after the stakeholder feedback period will be 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. Exceptions may be made to include major studies published after the end of the stakeholder feedback period if their findings are considered important and if they could significantly change the review results and overall conclusions.

Exclusion Criteria

Studies will be excluded if they do not meet the selection criteria outlined in Table 1 or if they are duplicate publications. If there are multiple publications of the same study, the less recent will be excluded unless it provides additional information on the outcomes of interest. Studies that select samples for inclusion on the basis of cervical cytology results (e.g., known ASCUS, known LSIL cytology results) will be excluded. Studies will also be excluded if they focus exclusively on HPV types not listed in Table 1 or exclusively evaluate screening interventions with a focus on in situ hybridization, p16 immunostaining, and HPV viral load. Evaluations of earlier versions of commercial tests that have been replaced (e.g., Hybrid Capture 1) will be excluded. Studies comparing HRHPV testing with visual inspection with acetic acid or visual inspection with Lugol's iodine will be excluded, as

these screening methods are more common in low-resource settings and are not representative of current cervical cancer screening practices in Canada. Studies will also be excluded if patients progress to treatment for high-grade cervical lesions or invasive cancer based on screening test results without first receiving colposcopy. A list of excluded studies, with reasons for exclusion after full-text review, will be provided.

Screening and Selecting Studies for Inclusion

To address the diagnostic efficacy of primary HRHPV testing as a screening tool for cervical cancer, primary studies that evaluate diagnostic test accuracy or clinical utility and report results related to diagnostic accuracy efficacy or clinical outcomes will be considered for inclusion. Reviewers will use the systematic review management software DistillerSR[45] to facilitate title and abstract screening, as well as full-text study selection.

Two reviewers will independently screen titles and abstracts of all citations retrieved from the literature search relevant to research questions 1 and 2, as well as any articles identified by content experts. In addition, the included and excluded studies listed in the 2003 CADTH Technology Report on Liquid-Based Cytology and Human Papillomavirus Testing in Cervical Cancer Screening[39] will be ordered to determine their relevance to this review. The full text of all studies identified for further review will be examined independently by two reviewers based on the predetermined selection criteria outlined in Table 1. The two reviewers will then compare their selections from the full-text review and resolve any disagreements through discussion until consensus is reached, involving a third reviewer if necessary. A final draft list of included studies will be posted for stakeholder review for 10 business days, and feedback and any additional studies identified for potential inclusion will be reviewed following the above process. Additional references of potential interest that do not meet the pre-specified selection criteria, including SRs or guidelines identified during the informal scoping review, may be discussed in the report.

The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. A full-text screening checklist for research questions 1 and 2 is reported in Appendix 2.

Data Extraction

A data extraction form (Appendix 3) has been designed to document and tabulate all relevant information from included studies for research questions 1 and 2. Reviewers will use the systematic review management software DistillerSR[45] to facilitate data extraction. Relevant information includes both descriptive data and results reported in all included studies; the form may be updated during the data extraction phase to reflect additional details reported by the included studies that are relevant to the outcomes of interest.

Two reviewers will pilot the extraction forms in duplicate among individual included studies until consistency between reviewers is reached. For

example, data extracted from pilot studies by independent reviewers will be compared for major discrepancies regarding the type of data extracted or the interpretation of each outcome, as well as the level of detail provided for the data extracted for each outcome. Discrepancies in these areas will be resolved through discussion until consensus is reached and a common approach to data extraction has been established, involving a third reviewer if necessary. If the form is updated during the data extraction phase, the form will be re-piloted for the new data elements.

Data from each included study will then be extracted by one reviewer and checked for accuracy by a second reviewer (i.e., two reviewers will independently extract data from one-half of the included studies and review the data extracted from the other half the studies). Disagreements will be resolved through discussion until consensus is reached, involving a third reviewer if necessary. Data will not be extracted from figures that do not explicitly provide numerical data. Authors of the studies included in this review will be contacted to provide any missing information or clarify any issues.

Methodological Assessments

Primary studies that investigate diagnostic test accuracy will be evaluated used the QUADAS-2 instrument.[46] The quality of clinical RCTs that evaluate clinical utility and downstream patient outcomes will be assessed using the Cochrane Risk of Bias Tool.[47] Clinical non-randomized studies will be assessed using the Risk of Bias Assessment Tool for Nonrandomized Studies (ROBINS-I).[48]

Two reviewers will pilot the quality assessment tools on pairs of randomly chosen, appropriately designed studies for each tool until consistency in assessments is reached. For example, quality assessments or ratings for piloted studies will be compared to identify major disagreements in the assessments for each item of the tool. Through discussion, the reviewers will clarify the source of the disagreement (e.g., different interpretations of the assessment tool item or the study methods) until consensus is reached and a common approach to quality appraisal has been established, involving a third reviewer if necessary. Once consistency in assessments is reached, the quality of the included studies will be assessed by one reviewer and verified by a second reviewer (i.e., two reviewers will independently conduct the quality assessment from one-half of the included studies and review the results of the assessment from the other half the studies). Disagreements will be resolved through discussion, involving a third reviewer if necessary.

Summary of Evidence

Description of Study Characteristics and Findings

A summary of study characteristics — including the total number of studies by population, intervention, comparator, outcomes, and study design (PICOS) elements; years of publication; and countries of development — will be provided in the form of tables and a narrative summary.

Description of Methodological Assessments

A narrative summary of the results of the methodological assessments for each included study will be provided. Specifically, tables will be developed to present the answers to the questions within the risk-of-bias tools, along with a narrative description of the strengths and limitations of the included studies within the main text of the report to provide the reader with an overview of the quality of the literature.

Data Synthesis Methods

The results of included primary studies will be pooled using meta-analysis if appropriate. The decision to pool all studies or subsets of studies will be made after reviewing and exploring heterogeneity. Clinical and methodological heterogeneity will be assessed in consultation with the clinical experts. This assessment will consider patient and study design factors that might be expected to affect test performance, including but not limited to age at screening, type of testing, and testing strategy. This may include assessments of statistical and clinical heterogeneity among thresholds for detection of disease. If pooling is not appropriate — due to significant clinical heterogeneity or to methodological or statistical heterogeneity that cannot be addressed analytically — the findings will be synthesized narratively.

For each outcome of interest, analysis will be conducted for the overall study population. This will also be done for each subgroup listed in Table 1, as the data permit.

Meta-Analysis of Diagnostic Test Accuracy Studies

Selected studies that evaluate diagnostic test accuracy and are considered for pooling of results will undergo assessments of between-study heterogeneity using graphical presentations — including forest plots and plots of sensitivity and specificity in receiver operating characteristic (ROC)-space — and calculation of between-study variance tau squared, summary, and predictive confidence intervals (CIs).[49] If meta-analysis is deemed inappropriate, studies that report on diagnostic accuracy will be reviewed and results reported narratively.

Where required, the diagnostic two-by-two table will be derived from the available data (e.g., sensitivity, specificity, number of confirmed cases, and number of people contributing to the diagnostic data).[50] Exclusions between women screened and women contributing to the diagnostic test group will be documented and the potential for bias assessed.

Reasons for observed heterogeneity will be explored by subgroup or multivariate regression analyses, given the availability of covariate data. Individual comparisons (e.g., for all HPV testing as compared with cytology-based testing, and for individual classes of tests compared with cytology-based testing) will be summarized separately (including those that compare tests through a common reference standard rather than directly) and the consistency assessed. Additional sensitivity analyses dealing with study

outliers, study size, study quality, study design, and other study-related or design-related factors will also be considered to establish the robustness of the findings. As some variation in the patient population and associated detection of high-grade cervical lesions is anticipated, the risk of verification bias as determined during critical appraisal will be assessed in sensitivity analysis. If substantial verification bias is detected, models will be adjusted using the de Groot et al. method.[51]

There are no established thresholds to determine the appropriateness of pooling diagnostic testing studies,[49] so the findings related to the above will be appraised in terms of their usefulness in answering the clinical and policy questions. Should it be decided that meta-analysis is appropriate, the data will be pooled using a statistical model that takes into account the bivariate nature of diagnostic test accuracy data. The choice of primary model (bivariate random-effects[52] or hierarchical summary receiver operating characteristics [HSROC][53]) will be determined by the properties of the data to be pooled, particularly sources of heterogeneity.[54] The rationale for model selection will be documented. Possible summary results include summary ROC curves, pooled sensitivity, specificity, diagnostic odds ratios, and their 95% CIs and prediction intervals. Where the area under the curve is used as a quantitative measure of the diagnostic accuracy of primary HPV testing or cytology-based testing for cervical cancer screening, values closer to 1.0 indicate better diagnostic performance, and values closer to 0.5 indicate poor performance.[55] Positive and negative likelihood ratios above 10 and below 0.1, respectively, will indicate low misdiagnosis rates. If the pretest probability of CIN2+ or HSIL is available (i.e., prevalence of CIN2+ or HSIL in Canada), the likelihood ratios will be used to calculate the post-test probability and absolute differences in effect between HPV and cytology-based screening strategies per 1,000 patients per year screened. Network meta-analyses will not be performed.

Explorations of heterogeneity, plotting, and meta-analysis will be conducted using the statistical software R,[56] with packages mada[57] and HSROC.[58]

If pooling is not appropriate, a narrative synthesis will include the presentation of findings within summary tables alongside study and clinical characteristics believed to contribute to heterogeneity, as determined during the exploration of the data. A narrative description will aim to synthesize observed test performance in the absence of a meta-analysis.

Meta-Analysis of Primary Clinical Utility Studies

The clinical utility of primary HPV testing strategies for cervical cancer screening will be based on findings about the benefits (e.g., diagnostic test accuracy and its influence on appropriate progression to treatment, and the indirect effects on clinical outcomes) and harms (e.g., unnecessary referral to colposcopy or treatment and associated impacts on patients).

Dichotomous outcomes (e.g., mortality) will be summarized using relative risks and 95% CIs. Continuous outcomes will be summarized using differences in means and 95% CIs, if appropriate. If indicated (e.g., for

quality-of-life scales), standard methods for converting between units of measurement will be used, and standardized mean differences will be calculated if possible. For outcomes reported as time-to-event, and given available individual patient data in the form of a survival curve or table of events per patients at risk, analyses will be performed using Kaplan–Meier curves and Cox regression. If studies report adjusted effects measures, the adjusted results in the primary analysis will be used, with the unadjusted result in the exploratory analyses presented and comments on any differences between the two. If required measures of variance are not available, variances will be imputed if possible.[59] Forest plots will be shown for all individual summary estimates.

Between-study heterogeneity within the groups of studies being considered for pooling will be assessed using graphical presentations (including forest plots and plots of outcomes against covariates) and calculations of the I^2 and Cochran's Q test statistics. An $I^2 \geq 75\%$ will be interpreted to indicate considerable heterogeneity across studies, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*. Cochran's Q test statistic — based on chi-squared, where I^2 = (Q – degrees of freedom)/Q — will be based on a level of significance of 10%. Clinical and methodological heterogeneity will be assessed in consultation with the clinical experts.

Reasons for observed heterogeneity will be explored by subgroup or multivariate regression analyses, given the availability of the data. Individual contrasts (e.g., for all HPV testing compared with cytology-based testing, and for individual classes of tests compared with cytology-based testing) will be summarized separately and the consistency assessed. Additional sensitivity analyses dealing with study outliers, study size, study quality, study design, and other study-related or design-related factors will also be considered to establish the robustness of findings.

If pooling of outcome data is appropriate, summary measures and CIs for the reported outcomes will be reported. Random-effects models will be used. In the event that both randomized and non-randomized studies report on the same outcome, RCTs will be considered separately from non-randomized studies. The influence of study design will be explored in sensitivity analyses, e.g., prospective non-randomized studies compared with retrospective non-randomized studies. Meta-analyses will be carried out using the Cochrane Review Manager software, version 5.3, or using R with package metafor.[60]

If pooling is not appropriate, a narrative synthesis will include the presentation of findings within summary tables alongside study and clinical characteristics believed to contribute to heterogeneity, as determined during the data exploration. A narrative description will aim to synthesize the direction and size of any observed effects across studies in the absence of a meta-analysis and will include an assessment of the likelihood of clinical benefit or harm.

Publication bias will be assessed using visual funnel plots and tested using Egger's regression test and Begg's rank correlation test.[61]

Economic Review

Study Design

A primary economic analysis will be conducted to evaluate the cost-effectiveness of different cervical cancer screening strategies for women in Canada.

Primary Economic Analysis

A decision-analytic model will be developed to assess the costs and health outcomes associated with cervical cancer screening strategies for women in Canada. The economic analysis will determine the most cost-effective screening strategy. This will include considerations related to the screening tools (i.e., type of test and, if applicable, triage schedule) and screening policy (i.e., start and end ages for screening, frequency of screening). Of note, the use of HPV testing for cervical cancer screening can fall under primary screening, triage, or an adjunct to Pap cytology in co-testing. In alignment with the clinical review, the scope of this economic analysis is to explore the role of HPV testing within a primary or triage screening strategy.

Given that the clinical purpose of cervical cancer screening is to detect patients with high-grade cervical lesions who can be treated before the condition develops into cervical cancer, the economic model will cover the full clinical spectrum, from screening to diagnosis and treatment.

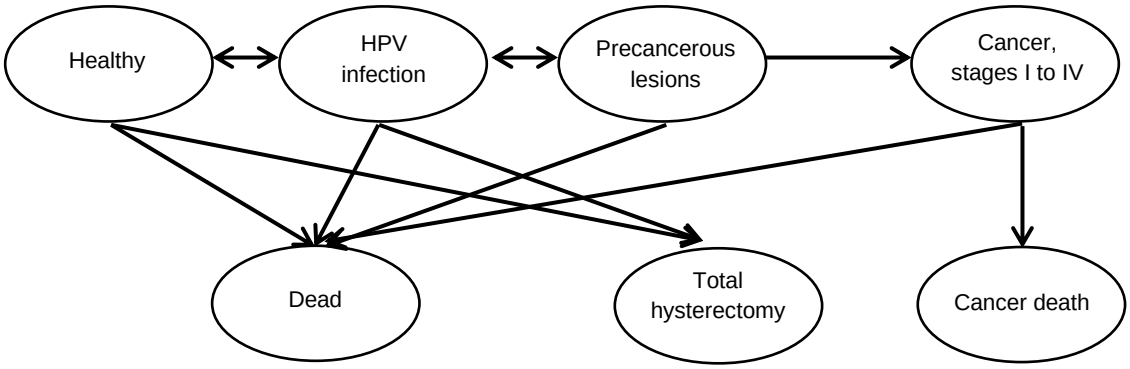
Model Design

A hybrid model with two components will be adapted based on an existing Canadian, published decision-analytic model.[62] To address the research question, a lifetime Markov model will simulate the natural history of cervical cancer among Canadian women in the absence of screening; a decision tree will capture the outcomes of screening.

The Markov model follows a cohort of women aged nine years to 100 years throughout their lifetimes. Distinct health states representing HPV infection, precancerous changes to the cervix, and cervical cancer will be used to model the progression of HPV infection and the mechanism of cervical carcinogenesis (Figure 1). At the model's initiation, all women are clear of infection and have no prior history of cervical cancer (defined as "healthy"). As the model progresses, women can become infected with low-risk HPV (i.e., never develops into cervical cancer) or high-risk HPV (i.e., oncogenic, with the potential to develop into cervical cancer). Once the individual is infected with a high-risk HPV strain, this can lead to the development of precancerous abnormalities of the cervix, classified according to the Bethesda system. Precancerous lesions can spontaneously regress to a lower severity, clear completely, or progress to cervical cancer, with both squamous cell carcinoma and adenocarcinomas modelled. Cervical cancer may be asymptomatic (in which case it can progress to higher cancer stages) or symptomatic (in which case it would be detected and treated). Women who have undergone a total hysterectomy unrelated to cervical

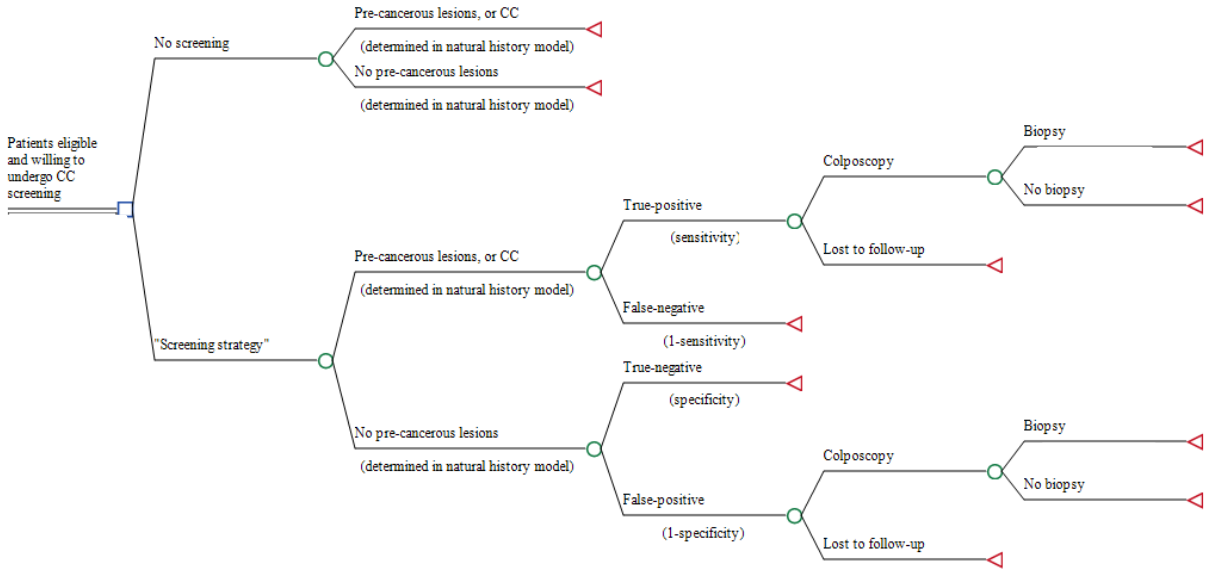
dysplasia are removed from the analysis, as they are no longer at risk of developing cervical cancer.

Figure 1: Disease States and Allowed Transitions for the Natural History Component of the Cervical Cancer Model



To evaluate the cost-effectiveness of the various screening strategies, the screening model is applied to the epidemiological model. The proportion of women screened during each model cycle is based on a predefined screening interval and the initiation age for screening that is specific to each strategy. Women who are not screened at that particular cycle continue to progress and regress into other health states in the natural history model. Women undergoing screening will continue in the natural history model while also progressing through the decision tree for screening. Progression through the screening model depends on a patient's health state within the natural history model at the time the screening test is applied (e.g., healthy, precancerous lesion, cervical cancer) as well as the sensitivity and specificity of the various tests and the patient's compliance (e.g., the number of women not lost to follow-up). Figure 2 outlines the structure of the decision tree. The screening model will further capture diagnostic confirmation and the associated management for pre-invasive cervical lesions and cervical cancer.

Figure 2: Proposed Structure of the Screening Component of the Cervical Cancer Model



CC = cervical cancer.

An existing Canadian model will be adapted,[62] as necessary, to reflect the current Canadian setting based on feedback from the CADTH clinical team and the clinical co-authors. In addition, clinical experts and members of the Health Technology Expert Review Panel will be consulted to ensure the model structure reflects existing clinical literature and Canadian clinical practice patterns. Checks on internal and external validity of the model will be performed to assess for any logical discrepancies. The model will be constructed in Microsoft Excel 2010.

Perspective

The primary perspective will be that of a Canadian publicly funded health care system (i.e., provincial Ministry of Health).

Resource Use and Cost Data

The costs captured will reflect the analysis perspective. These costs include those related to the screening tests, diagnosis, and treatment of pre-invasive lesions and cervical cancer. Canadian-specific costs will be used when available; if Canadian costs are unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs will be adjusted to 2017 Canadian dollars using the health care component of the consumer price index.

Utilities

Utilities associated with each health state will be obtained from the literature and from Canadian sources when possible. A literature search performed by an information specialist will provide the basis for identifying suitable utility values.

Clinical Parameters

Natural history: Estimates on the incidence of HPV infection and the progression and regression of HPV lesions to cervical cancer will be revised with the latest Canadian estimates, where possible. Canadian age-dependent mortality rates and hysterectomy rates will be applied to the model. Mortality rates from cervical cancer will be taken from Canadian literature.

Screening accuracy: The characteristics of each screening test (e.g., sensitivity and specificity) will be taken from the clinical review.

Outcomes

The model will estimate the expected costs and quality-adjusted life-years (QALYs) of different screening strategies for cervical cancer over the model's time horizon. QALYs will be the primary clinical outcome measurement, as this single measure can capture both morbidity and mortality impacts relating to a diagnosis of cervical cancer. The primary results of this model will be the incremental cost-effectiveness ratios of the screening strategies on the efficiency frontier, measured in terms of the incremental costs per QALY gained. In addition, a disaggregate number for resource utilization (e.g., number of colposcopies) and the number of HPV infections will be reported.

Time Horizon and Discounting

As the model follows patients over their lifetimes, discounting will be set at 1.5% per year.[63]

Sensitivity Analysis

The base-case analysis will represent the probabilistic findings, capturing the impact of parameter uncertainty, with results presented on the cost-effectiveness acceptability curve (CEAC). The CEAC will highlight interventions on the efficiency frontier across different willingness-to-pay thresholds. Uncertainty in the model will be further evaluated in a number of ways. Scenario and subgroup analysis will be performed to evaluate key model assumptions while retaining the model's probabilistic element. Potential scenarios and subgroups of interest may include:

- Adherence to screening protocol
- Different HPV tests; e.g., generic assays versus partial genotyping assay versus full genotyping assay

- Risk of HPV infection; i.e., incidence of HPV infections
- Vaccination status

Other analyses to address parameter uncertainty may include varying sets of related inputs (e.g., sensitivity and specificity of screening tests) or extreme scenarios (e.g., best-case and worst-case analysis, threshold scenarios). This may help identify key inputs driving the results of the cost-effectiveness analysis.

Assumptions

While developing the model, assumptions and limitations will be identified and acknowledged in the report. Where possible, assumptions will be tested by conducting appropriate sensitivity analyses.

Patient Perspectives and Experience

Study Design

A systematic review and qualitative meta-synthesis of primary qualitative empirical studies that describe the perspectives of women eligible for HPV screening will be conducted. When these studies include the perspectives of family members or caregivers, these perspectives will also be included. Using the methodology of qualitative meta-synthesis, the results of these primary studies will be synthesized to provide both interpretive and descriptive findings that will be useful to decision-makers.

Research Question

The initial research question is this: What are the perspectives of women, 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?

The predefined topic (HPV testing as a primary tool for cervical cancer screening) and research question will guide the research collection, data extraction, and analysis. The topic and research question originate with the policy issue, consultation with clinical experts, and consultation with the authors of other sections of this HTA. However, it will be refined in an iterative process as relevant literature is identified and reviewed. It is not uncommon in the field of HTA to identify research questions for which no relevant qualitative research exists, as it is rare to find qualitative research about new technologies that have not yet diffused into society. This potentiality will be accommodated by composing a research question and corresponding methods plan that are relevant to the aims of this HTA but that are answerable from the existing body of qualitative research.

Refinement of the research question will begin only after the initial literature search is conducted to ensure that the research question is both relevant to and useful for the aims of the HTA and is answerable based on the data that exist. The iterative process of research question refinement will proceed as

follows: First, all qualitative research relevant to the technology under analysis (HPV screening) will be retrieved, as described in the literature search strategy (Appendix 1), and then screened for eligibility. If this literature is insufficient, the search may be broadened to include qualitative research relevant to cervical cancer screening. This body of literature will form the "topic-specific library." After reviewing the titles and abstracts of the topic-specific library, a specific research question will be written, and input and feedback from the other HTA authors and clinical experts will be solicited.

The sufficiency of the research data will be judged at two points. The first question of sufficiency is whether there are enough eligible data to answer a question similar to the initial research question. This first threshold is a rough quantitative estimate based on the number of eligible articles included in the topic-specific library. If fewer than 50 primary qualitative research studies on the topic of HPV screening are retrieved, a wider search that includes cervical cancer screening more generally will be conducted.

The second judgment of sufficiency comes at the point of forming the specific research question and asks whether the initial research question is the best one for this HTA with this data. At this point, an iterative stance will be adopted to refine the question in conjunction with an appraisal of the available evidence.[64] This iterative refinement is typical of many qualitative approaches, and requires familiarity with the data set.[65,66] This process starts with the initial research question stated above. The titles and abstracts of included articles will be reviewed to pull aside potentially relevant articles for full-text review. As articles are reviewed, notes on the topics, emphases, and populations of the articles will be kept to develop an understanding of what type of information is present in the topic-specific library.

At this point, an assessment will be made about whether the initial research question is answerable with this data set. This consideration includes whether this question overlooks any particular areas of strength in the literature. The refinement of the research question remains an open question as analysis continues. As data are extracted from relevant studies and analyzed, the analysts will continue to reflect and consider whether these data provide the necessary breadth and depth to answer the proposed question, and whether the question could be refined to optimize the strengths of the available data. Of course, the HTA context and decision-makers' priorities are primary considerations during these assessments. The analysts document the evolution of the question and search strategy in order to maximize the authenticity of the final account.[67]

Eligibility Criteria

Eligible studies include English-language and French-language studies of any qualitative design that explore or assess perspectives of women eligible for HPV screening. To be eligible, studies must explore or assess participants' own perspectives directly, not indirectly (i.e., through another person). Due to insufficient evidence and a lack of firm consensus on optimal times to begin and end HPV screening,[3,8,14,68] eligibility for HPV

screening in Canada differs by province.[5] For the purpose of article selection, eligibility for HPV screening is defined as 21 years to 70 years of age (the age where screening programs are typically offered in Canada) or, if age is not specified, "adult" women. Only studies conducted in countries with comparable health care systems are included. These are defined as Canada, the US, New Zealand, Australia, and European Economic Area countries. Studies that assess clinician perspectives only will be excluded. Selection criteria follow.

Inclusion Criteria

- English-language and French-language full-text publications
- Studies published from January 1, 2002, to the present
- Primary qualitative empirical research (using any descriptive or interpretive qualitative methodology, including the qualitative component of mixed-methods studies)
- Studies involving adult women (21 years to 70 years of age) and women outside this age group who are eligible for HPV 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 US, Australia, New Zealand, UK, and European Economic Area countries)

Exclusion Criteria

- Animal and in vitro studies
- Editorials, case reports, or commentaries
- Studies addressing topics other than HPV 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 perspective of women eligible for HPV 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 (71 years or older), adolescent, or pediatric populations

Screening and Selecting Studies for Inclusion

Two reviewers will independently screen the titles and abstracts of all citations retrieved from the literature search based on the eligibility criteria.[69,70] For citations that appear eligible for inclusion and for which it is difficult to determine eligibility on the basis of title and abstract alone, the full text of these articles will be retrieved and assessed before determining

eligibility. Discrepancies between the two reviewers will be resolved through discussion until consensus is reached. The study selection process will be presented in a PRISMA flow chart. All eligible studies will be included.

Iterative Process of Searching and Research Question Refinement

If, after screening and selection, reviewers deem the available body of qualitative research insufficient to answer the proposed research question, the question will be refined and iterated. This may include a new search with a focus on a broader topic (e.g., cervical cancer screening).

As explained in the research question section, the decision on whether the available data are sufficient requires an iterative assessment of the data alongside a refinement of the research question. Familiarity with the data is required to judge sufficiency; therefore, these two activities must proceed together and cannot be predefined.

Data Collection and Extraction

Data collection will involve extracting two types of data from each primary report: study characteristics and study results relevant to the research question.[69] From each eligible article, descriptive data about features of the study are extracted by one reviewer into a standardized electronic form (Appendix 4). The qualitative results of the study will be extracted using the qualitative data management software NVivo 11.[71] Extraction of both types of data will subsequently be verified by a second reviewer.

Descriptive data extracted into a form will include items such as first author, article title, study objectives, participant characteristics, study design and methodology, publication date, and nation in which the study was conducted. Specific information about participant characteristics collected include age range, sex or gender, role (e.g., woman eligible for screening), and other sampling characteristics (e.g., woman diagnosed with cervical cancer, woman who has experienced an abnormal HPV screening result). Given the interest in equity of access, reviewers will record demographic information when authors identify participants as belonging to a socially marginalized group — for example, by virtue of Indigenous status, income level, immigration status, or rural or remote location.

The data extracted into NVivo 11[71] will serve as the main source of information for the analysis. Reviewers will extract findings from each study that are relevant to this 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."[72] In addition to the researchers' findings, reviewers will extract 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,[73] only results presented within the main report will be extracted. NVivo 11[71] will be used to extract and manage this data.

Methodological Assessments

Qualitative meta-synthesis researchers typically do not exclude qualitative research on the basis of independently appraised "quality." This approach is common to multiple types of interpretive qualitative synthesis.[66,72,74-79] However, to help readers assess the trustworthiness of the conclusions, each study will be appraised for quality using the Critical Appraisal Skills Programme (CASP) Qualitative Checklist.[80] Two reviewers will assess each study, with a third joining if needed for consensus. Results will be reported narratively in the report and individual results included as an appendix.

Given the lack of consensus in the field of qualitative research as to methods and standards for critical appraisal of research quality,[65] the CASP tool will not be used to exclude studies from consideration. For this review, the academic peer review and publication processes are assumed to have eliminated scientifically unsound studies, according to current standards. Beyond this, all topically relevant, accessible, and published research using any qualitative interpretive or descriptive methodology will be included. The value of the research findings will be appraised for inclusion or exclusion solely in terms of their relevance to the research questions and the presence of data that supported the authors' findings.[81,82]

Data Analysis

Analysis of Study Characteristics

To begin, a descriptive analysis of study characteristics will be conducted. These will be reported in tabular form. Typically, this includes the number and type of participants, information about study design and methodology, and distribution of studies by national context. The purpose of this analysis is to describe the set of included studies and understand the range of study designs and methods that will inform the resulting synthesis. Concerning study design, there is significant heterogeneity in the reporting of qualitative research methods; some authors may report a methodology, while others may only name an analytic approach. Information about study design made available by the authors will be extracted and described, focusing on methodology if one is provided or describing the analytic approach if that is the only information available. Further, information about study design and methodology will not be imputed, but will rely on the information the authors provide through explicit statements about study methods. As a result of the variable approaches to reporting qualitative methods, the summary of this information typically includes both study designs and analytic approaches. Examples of these tables are provided in Appendix 5 (Table A1, Table A2, and Table A3). A table that describes the features of each individual study will be compiled for quick reference (see example Table A4 in Appendix 5).

Analysis of Study Findings

Published qualitative research will be analyzed using techniques of integrative qualitative meta-synthesis,[72,75,83] 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.

A staged coding strategy adapted from grounded theory[84] will be employed. This approach compares research findings across primary included studies, categories, and co-investigators' interpretations of the studies. All analytic interpretations will be negotiated during regular meetings with the whole research team.

The goal of qualitative meta-synthesis is to produce a report that yields succinct findings that accurately reflect both the aggregated results and the interpretive depth of the component studies, providing the reader a sense of the complexity and richness of the original work.[85] At the same time, mindful of the context of this HTA, analysts will strive to remain relevant to the policy concern, offering descriptive and interpretive findings that are useful in the context of HTA. Reported findings will include both themes and contrasting perspectives. The report will outline findings that are significant for reasons of prominence as well as those that may be less prevalent but are still insightful or relevant to the policy question. Findings related to all stages of the life cycle of a technology, including implementation, will be included.

A note on the terminology of coding for qualitative meta-synthesis: The codes, themes, and categories offered by the author of each study will be considered, but new codes, themes, and categories to synthesize the information across studies will be developed.[86] A "code" will be considered as the initial unit of qualitative analysis. A code can capture any type or level of idea. It is a label that allows one to apply both descriptive and interpretive summaries to a piece of data. Codes can be grouped and regrouped to form categories. Themes are the most abstract level of analysis, and are identified in the data by looking across both categories and codes.[84,86] The process may move in a linear fashion from code to category to theme, but sometimes the process of identifying categories and themes happens simultaneously, especially in the middle and later stages of coding. At times, analysis may require deconstruction and reconstitution — for instance, when thinking about a theme catalyzes the deconstruction of a category and the recoding of it to identify or organize the data in a different way. This is all part of the iterative nature of analysis.[84]

Initial Coding

Using a staged coding process similar to that of grounded theory,[84,87] findings will be broken into their component parts (i.e., the author's key themes, categories, concepts) and regrouped across studies according to themes and categories inductively developed by the research team. Coding begins with a line-by-line open code to identify meaning and content. The process of initial coding is completed by multiple coders working separately on the same body of data (with approximately five studies to start) and then meeting to discuss their emerging insights. At this stage, a descriptive coding will be conducted, although the team will start to see some "focused

coding" work accomplished as the initial codes are condensed and grouped into categories through discussion. The same group of coders will individually code five more papers and will meet to discuss the list of categories and potentially identify initial themes, suggesting a direction for refinement and evolution. At this point, some categories may be grouped into themes, or the team may proceed with more descriptive coding and categorization. Categories are formed based on both the prevalence of information across a large number of studies and the usefulness or importance of information that appears in a smaller number of studies. Once the research team is confident that the coding of individual analysts is sufficiently aligned, the coding will proceed with one researcher acting as the primary coder and the other verifying the coding.

Taxonomic Analysis

Central to the qualitative meta-synthesis technique is an inductive form of domain analysis that Sandelowski has named taxonomic analysis.[83] It is similar to grounded theory's theoretical coding stage; therefore, it is congruent with the process outlined above. Taxonomic analysis aims to demonstrate the conceptual range of findings to provide a foundation for developing conceptual descriptions or theories.

Taxonomic analysis at the beginning of the focused coding stage will help refine a direction for focused and theoretical coding (described below). A taxonomy of findings will be created by inductively identifying domains of interest within the data and then categorizing the findings into these domains.[83] A taxonomy is formed by concepts that have "semantic relations, either within the same or between different categories in each domain"[83] (p.200). Sandelowski describes a semantic relation as an interpretative assessment of the findings detailing how disparate findings are conceptually related. The purpose of this work is to identify underlying conceptual relationships, especially those that may not be explicitly expressed in individual studies, but which may be visible when findings are compared across the broader data set. This work can help to identify the unifying primary theme described by Charmaz in the process of theoretical coding.[84] Taxonomies are an analytic exercise and may not be part of the final analysis or published in the report.

Focused and Theoretical Coding

Focused and theoretical coding are second-cycle stages of coding and may occur both together or separately.[84] 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 in order to provide a unifying primary theme (which may be called a core or central category) that helps to order, understand, and explain the relationships between other categories.[84,86]

While many methodological texts explain these as separate processes, in practice they often develop simultaneously, either in tandem or in alternating sequences. As the reviewer develops familiarity with the data through

immersion in analysis, ideas about different concepts begin to crystallize, sometimes pushing one idea quite far theoretically while others remain at an initial coding stage. Although it is easier on paper to describe coding and analytic thinking as though they proceed in a linear fashion, in practice they are interdependent.

There is iteration between the initial, focused, and theoretical coding stages, especially when working with very large data sets. For example, the reviewer may not complete the initial coding for the whole data set before completing the focused coding. A reviewer may use a smaller number of studies to develop a tentative schema for focused coding and then apply and elaborate that schema on a larger number of studies. This strategy is particularly helpful when qualitative meta-synthesis is conducted on a large number of studies. This technique has been applied in the past, for instance in synthesizing 120 primary qualitative studies.[88] If working with a smaller number of studies, it may not be necessary to take this staged approach. An initial and a focused coding may be conducted on the whole data set in separate stages, iterating more frequently between focused and theoretical coding after initial coding has been completed. Experience has shown that 30 included studies tends to be the tipping point for choosing how to manage the analytic process. Of course, this varies depending on the richness and relevance of the studies and the heterogeneity of the ideas expressed.

Focused or theoretical coding begins with a research team meeting to review the initial coding and discuss potential directions for further analysis. At this point, the initial codes and any preliminary categories or themes are reviewed, thinking about the relationship between these items and deciding upon a theoretically relevant direction in which to proceed. “Theoretically relevant” means a direction that is supported by the initial analysis, is judged likely to be rich enough for further inquiry, and is 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.[72,76] The goal of focused or theoretical coding is to develop a comprehensive list of categories or themes that can be applied to the data set to answer the research question. Of course, like most other aspects of qualitative research, this is an iterative process, with a focused coding schema suggested, implemented, elaborated, discussed, and refined many times over.

This iterative analytic cycle starts with multiple coders working individually and meeting regularly to discuss (1) whether the developed list of categories is sufficiently abstract to include all the initial descriptive themes and to answer the policy question and (2) whether theoretical coding aligns between reviewers. If the team does not agree on both points, the list of categories, themes, and their relationships is refined, and the coders continue to try to apply these ideas to the data independently before meeting to reassess sufficiency and alignment. As the team becomes more

comfortable with the coding schema and the way it is being applied to the data, focused coding can continue with fewer analysts.

Throughout the process of coding, reviewers will remain alert to new codes and ideas. When new themes or categories are identified, all data will be recoded to search for further instances of the meaning captured by that code. When all codes are applied to the full sample of results, they will be assessed for consistency in interpretation and application.

Throughout all stages of analysis, regular meetings between members of the research team will take place to discuss emerging results and preliminary analytic ideas. Further, to help ensure rigour in the analysis, explicit notes will be kept using the memo and annotation features in NVivo 11[71] to record decisions made regarding coding and theme development. 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 subgroups.

Ethical Review and Analysis

Ethical Issues

Normative questions regarding the implementation of HPV testing as a primary screen for cervical cancer may be divided into three broad categories:

1. What ethical issues have been identified in cervical cancer screening, and how might a change to primary HPV screening influence them?
2. What new ethical issues are raised by the use of HPV testing as a primary screening tool for cervical cancer?
3. If HPV testing is adopted as a primary screening tool, what considerations should guide its adoption to best address the identified issues?

These questions are matters of systems-level (population-level or public health) ethics, which examines questions that will affect a large number of people and in which outcomes and interests are considered in aggregate. (Organizational ethics, policy ethics, and public health ethics are all domains of systems-level ethics.) For systems-level ethics, instead of asking “Does this technology benefit the patient?” and “Does this technology disadvantage vulnerable individuals?” one asks, “Does this technology create overall benefit with minimized and proportional harms for the population?” and “Does this technology disadvantage marginalized groups?”

The framework of public health ethics places a greater emphasis on achieving benefits at the population level than does clinical ethics; nonetheless, questions arise in public health ethics as to the scope of legitimate public interest in prevention and health promotion and the scope for individual autonomy in the context of a social decision to pursue a public good. Is there a tension between fully informed screening program participation (or non-participation) and the public health goal of maximizing

screening uptake? If there is such a tension, how should it be resolved? Does the population health goal of cancer prevention warrant persuasive framing, incentivizing choice, pressure, or soft or hard coercion? If decision-making is driven by granting too much or too little salience to some of the risks of screening decisions and not others (the risk of cancer versus the risks of over-diagnosis), what harms might this cause, and how should the problems be addressed?

Furthermore, responding to the question of how a technology should be implemented or provided also requires considering the nature of the technology from the individual perspective. Adopting a new technology changes communication and decision-making: the invitation to screen or not, the choice to take up the invitation or not, the opportunity and choice to return for follow-up, and the opportunity and choice for specific treatment approaches. Hence, individualist considerations that are dominant in clinical ethics — such as respect for persons, benefit, autonomy, dignity, and fairness from the individual perspective — also arise in the context of public health intervention. Such considerations inform recommendations on how to implement or deliver the technology such that it lives up to key values or principles. If the analysis determines that the technology cannot be implemented in a way that sufficiently lives up to these core values, this may influence the technology's acceptability at the systems level.

Interests

One relevant group whose interests need to be considered when identifying and addressing the ethical issues associated with HPV as primary screening for cervical cancer is the public, whose members fund the system, are at risk of cervical cancer, and stand to benefit from a reduction in disease burden as well as the opportunity to fund other priorities (when screening and treatment are successful and efficient) or to suffer harms and lost opportunity costs (when they are not). Also relevant are persons targeted for screening across life cycles; those in their families and communities with whom they are interdependent and who may not be targeted for screening, including sexual partners; and communities that might be differentially affected by changes in screening technology and the resultant changes in organization and delivery. It is also necessary to consider the perspectives of patients, including both those with risk factors typically not represented by advocacy groups and those already experiencing the clinical condition that the screening program seeks to prevent (who are more typically represented by patient advocacy groups). Two other relevant groups are health care providers, including primary and tertiary care and laboratory services, and other care systems that might or might not be implicated, such as public health and health care funders.

Inquiry

This project will proceed in two stages. The first stage will be a review of the ethics, clinical, and public health literatures to identify existing ethical analyses of the new technology or (if there are too few such analyses available) of existing technology deployed in cervical cancer screening. The

second stage involves novel ethical analysis based on gaps identified in the ethics literature and the results of concurrent reviews. This may require reviewers to conduct selective searches to provide the basis (in theoretical ethics, in applied ethical analyses of similar technologies, and in evidence) for the ethical analysis of emerging issues specific to this technology. This approach will identify and assess the relative importance and strength of the identified concerns and proposed solutions, identify and assess issues that have not yet come to the attention of ethics researchers, and delineate ethical desiderata for possible solutions to the issues for which such solutions have not yet been proposed.

Applied ethics typically relies on the specific details of community and patient perspectives, clinical utility, economic analysis, environmental impacts, and implementation considerations. As such, the ethical review involves an iterative process whereby the ethical analysis responds to results emerging from clinical, implementation, patient perspective, and economic reviews.

Review of Existing Ethical Analyses

A review of the ethics, clinical, and public health literatures will be conducted to identify normative analyses and qualitative research that directly address ethical issues in HPV primary screening. In addition, the reviewers will include overview or opinion articles that explicitly identify ethical issues without presenting primary research or normative analysis. If this search generates fewer than 30 results, the search parameters will be widened to search for identification and analysis of ethical issues in cervical cancer screening in general.

In addition to literature that explicitly identifies or analyzes ethical issues, the clinical, patient experience, economic, implementation, and environmental reviews may raise ethical issues. For example, an empirical investigation of patient attitudes toward HPV testing for cervical cancer screening, when read through an ethics lens, may raise ethical issues even if the participants and researchers did not formulate them as such. Where research into patient perspectives does reveal a shared preference for a specific solution, this solution may nonetheless need normative analysis in relation to the perspectives of other relevant stakeholders. A clinical decision analysis may raise questions about the trade-off of mortality risk reduction and the cascade effects of screening and intervention, and this trade-off may benefit from ethical analysis. An economic analysis might raise questions about equity due to its chosen methods for determining QALYs for particular outcomes. An implementation question may highlight professional values that are emphasized differently in different areas of practice, such as the emphasis of clinical medicine on individual benefit and of public health on the public good. An environmental study may raise normative questions about the appropriate stewardship of resources and management of risk in the context of public safety.

Screening and Selecting Articles for Inclusion

To select relevant literature, two reviewers will independently screen the title and abstracts of citations. An article will be categorized as "retrieve" if it meets at least one of the following criteria:

- Provides normative analysis of an ethical issue arising in the use of HPV testing for cervical cancer screening
- Presents empirical research directly addressing an ethical issue arising in the use of HPV testing for cervical cancer screening
- Explicitly identifies but does not analyze or investigate empirically an ethical issue arising in the use of HPV testing for cervical cancer screening.

If it is impossible to determine eligibility based on abstracts, full text will be retrieved and assessed for eligibility.

If fewer than 30 articles are identified, and these are considered by the reviewers to inadequately indicate the range of ethical issues involved in primary HPV screening for cervical cancer, the search will be broadened to ethical issues in cervical cancer screening.

The goal in a review of bioethics literature is to canvass what arises as an ethical issue from a broad range of relevant perspectives. As such, the quality of normative analysis does not figure in the article selection criteria; any identification of an issue by the public, patients, health care providers, researchers, or policy-makers is of interest, whether presented through rigorous ethical argumentation or not. For example, academic ethicists may focus on certain issues because they relate to theoretical trends in their discipline, while an opinion piece by a clinical or policy leader (or a patient experience) may bring to the fore ethical questions that are neglected by academic ethicists but are highly pertinent to the assessment of the technology in the relevant context. Despite the different standards of normative argumentation for each kind of report, the importance of the issues raised cannot be assessed solely by these standards; therefore, literature cannot be excluded based on methodological standards.

Reports meeting the criteria will be included in the analysis. Reports that do not meet the criteria will be excluded.

Disagreements between reviewers will be resolved by discussion and consensus. In the event of persistent disagreement, a third assessor will adjudicate.

Data Extraction

The bibliographic details for each report (e.g., author, publication date, journal), the potential ethical issues raised, and the report's conclusions (issues identified, values at stake identified through normative analysis, and solutions proposed, and their normative justification if presented) will be summarized in a table.

Analysis

The ethical issues identified, values described, and solutions proposed in the literature will, at this stage, be evaluated using the methods of ethical (applied philosophical) analysis, which include applying standards of logical consistency and rigour in argumentation, particularly where specific implications are identified and specific solutions advocated; responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; adequacy to the context for which the technology is being considered; and the representation of perspectives from diverse relevant communities, with particular attention to the possibility of the neglect of marginalized and vulnerable populations.

In the area of population or systems-level ethics, important values include justice (equity in access and outcomes, resource allocation in relation to community needs, and social justice concerns about voice and control); the (feasible) minimization of harms and maximization of benefits in the implementation of technology, and the acceptability of residual harms given realistically anticipated benefits; the responsibility, accountability, and trustworthiness of health care providers, health care systems, and those responsible for public safety and environmental stewardship; the tension between individual autonomy and pursuit of a public good (in this case, cancer prevention); and cultural, social, and religious values and mores that may be engaged by a given technology in the context of a public health program.

Summarizing and Presenting Results

Review of the existing ethics literature and communication with other reviews in progress may identify issues that have not yet been analyzed or possible solutions that have not yet been explored in the literature that explicitly address ethical issues in primary HPV screening for cervical cancer or in cervical cancer screening more broadly. This is to be expected when assessing an emerging technology. Where the report undertakes analysis that is not derived from the peer-reviewed literature, this will be noted in the interests of transparency.

Ethical issues are multidimensional. Their reporting can be organized procedurally (i.e., through a patient or clinical care continuum), structurally (i.e., through the levels of the health care system at which they emerge, as micro, meso, and macro level issues), according to the key values standardly identified in the relevant (in this case, public health) ethics literature, or according to the specific issues and concerns identified in the analysis and in communication with other review processes. The ethical review and analysis will be organized according to whichever of these four frameworks best suits the results and facilitates its use by decision-makers.

Ethical analysis assists in social and policy decision-making but is not itself the site of legitimate social decision-making, which requires consultation and deliberation on the part of relevant stakeholders in a given context. Decisions will also be sensitive to emerging empirical evidence.

Furthermore, the ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, for example, are determined by facts about how health care services are arranged and provided.

Given these features of ethical decision-making, results of the ethics review will be presented in a way that helps decision-makers better understand the ethical implications of their decisions and recommendations. For example, a number of contextualizing questions will be developed based on the identified issues so that decision-makers can assess localized impact, and proposed solutions will be analyzed to indicate the relevant ethical trade-offs at stake and mitigation strategies that could be employed to manage them.

Implementation Issues

A change from Pap testing to HPV testing as the primary screening strategy for cervical cancer in Canada is predicted to be a transformational and disruptive change for the laboratory setting, for clinical and screening workflows, and potentially for clinicians and patients. A preliminary review of the literature indicates that there are significant implementation issues that should be considered before a decision is made to adopt this technology. Certain factors need to be examined to understand how they could facilitate or challenge successful implementation.

Methods

A review of the implementation issues associated with HPV testing for primary cervical cancer screening will be conducted. This will involve a narrative literature review and consultations with targeted experts and stakeholders.

Targeted Literature Search

Targeted literature searches will be performed, as per the strategy described in the “Methods: Search Strategy” section of this protocol. Canadian literature will be searched first and, if insufficient information is found, the search will be expanded to include literature from European Economic Area countries, US, Australia, and New Zealand.

It is likely that an iterative strategy will be followed, such that, as the reviewers begin to understand important issues and strategies, more targeted searches will be conducted to identify more information on these new and currently unexpected issues.

Screening and Selecting Articles for Inclusion

Articles will be screened and selected for inclusion by one reviewer, who will identify articles that describe implementation issues, factors that influence implementation, and examples of evaluations of previously implemented programs.

Data Extraction

Data extraction will be performed by one reviewer. The data extracted will include bibliographic details of included papers, population and intervention information, the identified implementation barriers and facilitators, results of evaluations of existing programs, and other key findings related to implementation.

Perspectives

When analyzing data, the items coded and summaries written will be those most relevant at the health services delivery level. The aim is to provide information to policy-makers regarding the operational requirements that should be in place or could be used to help facilitate the effective implementation of the recommendations of the expert committee.

Consultations

To fully answer the implementation issues research question, consultations will be conducted with targeted experts and stakeholders to augment the literature. These stakeholders may include representatives from Canadian cancer organizations; representatives from the laboratory, pathology, and hospital sectors; primary care physicians; and women from the eligible screening populations and subgroups of interest. Consultations will also be considered with representatives from countries that have already implemented HPV primary screening. Manufacturers of self-testing kits may be consulted to enquire about details related to the Canadian context (e.g., whether sample transportation could be affected by Canadian weather extremes). The determination of which stakeholders to consult will depend on the nature of outstanding questions; one or two stakeholders from each relevant group may suffice, but this number might change depending on the information provided or lacking.

To guide the consultations, an interview guide will be developed. Interview questions related to implementation will be developed based on gaps identified in the literature and to obtain more information on key issues, including those arising from the patient preferences or ethics sections. Consultations will be conducted by phone by a knowledge mobilization officer; follow-up questions or clarifications will be conducted by email. Consent to publish comments and names will be sought. For consultations with women from eligible screening populations, ethics board approval will be obtained in advance.

Descriptive Analysis

Each article identified through the literature search, or information provided through the consultations, will be analyzed using the methods of content analysis and sorted into the relevant INTEGRATE-HTA[89] categories. Specifically, INTEGRATE-HTA[89] 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 INTEGRATE-HTA[89] framework, as well as an additional domain of "patient," will comprise a coding template that will be applied to all data. Once all data have been coded by one researcher, a second researcher will verify the coding assignments. Literature and data from the patient preference and experience, ethics, and other sections may also inform this analysis.

Once all data have been read and coded, text coded within each domain will be summarized by one reviewer; if necessary, subcategories within each code will also be identified. For example, subcategories may be developed to account for issues relevant to special populations or those with the potential to be differentially affected by implementation. The summary will include a description of the domain (and its subcategories where relevant) and how the factor relates to the implementation of HPV screening programs. Once all summaries have been written, they will be read and compared with the original data by a second reviewer to ensure comprehensiveness and consistency within the accounts.

Given the emergent nature of this review and the open-ended data that will be collected, it is possible that adaptations to this planned analytic strategy will be required to accommodate the data obtained and the needs of stakeholders. The final report will detail the actual analytic methods used.

A list and description of factors that have the potential to facilitate or challenge successful implementation will be presented, as well as a summary of potential strategies that could be used to implement or increase the uptake of the technology, if the decision is made to do so. Additionally, a summary of how each factor influences implementation will be provided and, where possible, strategies will be identified that could be used to ensure these factors are taken into consideration or mitigated.

The implementation issues identified will guide the development of knowledge mobilization activities, tools, and tactics to support the uptake of recommendations and the implementation of any resulting decisions or changes to the health care system or health service delivery.

Environmental Impact

Study Design

A narrative review of the literature on the potential environmental impact associated with HPV testing for primary cervical cancer screening will be conducted.

Selection Criteria

Articles that provide insights into the potential environmental impact of HPV testing for primary cervical cancer screening will be included. For example, the impact may relate to resource use, waste issues, or recycling schemes related to HPV testing for primary cervical cancer screening.

Screening and Selecting Articles for Inclusion

Citations arising from the literature searches conducted to address research questions 1 to 6 will be screened for information related to potential environmental impact; the reviewers of the clinical, economic, patient preferences and experiences, ethics, and implementation issues sections of the assessment will screen for their respective sections.

Data Extraction

From each relevant article, the bibliographic details (i.e., authors, year of publication, and country of origin), population and intervention information, and potential environmental impacts identified will be captured by one reviewer in an Excel spreadsheet.

Descriptive Analysis

Information from relevant studies will be summarized narratively and will not be systematically reviewed.

Areas for Potential Amendments

If amendments to the protocol are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported in the final study report. If necessary, rescreening or updating of the previous literature search will be performed to capture additional data according to the amendments.

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CADTH

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/
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/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
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 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"/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
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.
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/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
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 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/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
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
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

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
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

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
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.
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/

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
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.
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

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
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$).mp.
114	(humanistic or existential or experiential or paradigm$).mp.
115	(field adj (study or studies or research)).tw.
116	human science.tw.

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
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/

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
155	Papanicolaou Test/
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

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experience Search Strategy**
189	188 use psyb
190	161 or 185 or 189
191	139 and 190
192	191 not 141
193	192 not conference abstract.pt.
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

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

MULTI-DATABASE STRATEGY	
#	**Ethics Database Search Strategy**
	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/
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

MULTI-DATABASE STRATEGY	
#	**Ethics Database Search Strategy**
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.
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

MULTI-DATABASE STRATEGY	
#	**Ethics Database Search Strategy**
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.

CADTH

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 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.

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
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.
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/

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
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/
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

MULTI-DATABASE STRATEGY	
#	**Implementation Search Strategy**
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)
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

CADTH

Appendix 2: Full-Text Screening Checklist — Clinical Review

Reviewer: _____ **Date:** _____

Ref ID: **Author:** **Publication year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include or Exclude)[a]**	**No (Exclude)**
1. The population of interest: Asymptomatic adult women eligible for cervical cancer screening (≥ 21 years of age, or age at which screening starts in the jurisdiction) Exclusions: • Women with known cervical cancer or previous treatment for HSIL • Women without a cervix • High-risk women (e.g., immunocompromised, HIV-positive)	☐	☐	☐
2. The interventions of interest: • Primary HRHPV testing with HPV nucleic acid tests alone • Primary HRHPV testing with HPV nucleic acid tests and cytology triage for HPV-positive samples • Primary HRHPV testing with HPV nucleic acid tests alone and treatment of patients with confirmed disease • Primary HRHPV testing with HPV nucleic acid tests and cytology triage for HPV-positive patients and treatment of patients with confirmed disease	☐	☐	☐
3. The comparators of interest: *Q1* • Primary conventional cytology-based testing (with or without HPV triage of cytology-positive samples) • Primary liquid-based cytology testing (with or without HRHPV triage of cytology-positive samples) • Primary conventional cytology-based testing (with or without HPV triage of cytology-positive samples) and treatment of patients with confirmed disease • Primary liquid-based cytology testing (with or without HRHPV triage of cytology-positive samples) and treatment of patients with confirmed disease *Q2* • Primary HRHPV testing strategies compared with each other • HRHPV and cytology co-testing • Primary HRHPV testing strategies and subsequent treatment of patients with confirmed disease compared with each other • HRHPV and cytology co-testing and subsequent treatment of patients with confirmed disease	☐	☐	☐
4. The reference standard of interest for Q1A and Q2A:	☐	☐	☐

Ref ID: **Author:** **Publication year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include or Exclude)[a]**	**No (Exclude)**
Colposcopy with histologic examination of tissue specimens when indicated Exclusions: • Reference standard applied to a subset of screening test-positive patients			

5. The outcomes of interest:
• Number or proportion of patients who accepted screening
• Diagnostic test accuracy
  ○ Proportion of patients positive and negative on each test (TP, TN, FP, 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)
  ○ Number or proportion of patients referred to colposcopy
  ○ Number or proportion of patients treated or referred for treatment
• Harms of screening
  ○ Anxiety
  ○ Adverse pregnancy outcomes
  ○ Impacts of false-positives and false-negatives on patients
  ○ Over-diagnosis, including treatment, and related impacts on patients
• Clinical utility outcomes
  ○ Quality of life
  ○ Cervical cancer incidence
  ○ Cervical cancer-related morbidity
  ○ Cervical cancer-related mortality
	☐	☐	☐

6. The study designs of interest: • RCTs • Non-RCTs • Cohort studies • Cross-sectional studies	☐	☐	☐
7. The setting of interest: • Settings where cervical cancer screening may be offered (e.g., internal medicine, family medicine, obstetrics/gynecology, university-based health clinics, mobile clinics, sexually transmitted infection clinics, family planning clinics, correctional facilities, worksites)			
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No or inappropriate comparator ☐ No or inappropriate reference standard ☐ No relevant outcomes ☐ Irrelevant study design		

Ref ID: Author: Publication year:			
Did the study include:	**Yes (Include)**	**Unclear (Include or Exclude)[a]**	**No (Exclude)**
	☐ Study description only ☐ Other (describe):		

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; HRHPV = high-risk human papillomavirus; HSIL = high-grade squamous intraepithelial lesions; NLR = negative likelihood ratio; NPV = negative predictive value; PLR = positive likelihood ratio; PPV = positive predictive value; RCT = non-randomized controlled trial; TN = true-negative; TP = true-positive.
[a] This will be discussed with a second reviewer.
[b] If all items above are answered "yes" or "unclear," then the study will be included.

Did the study report any data relevant to another research question (RQ)? □ Yes: RQ# _____ □ No

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Appendix 3: Data Extraction Form — Clinical Review

Reviewer: _____ **Date:** _____

Study Characteristics		
Ref ID:		
Author(s):		
Publication title:		
Publication year:		
Country where the study was conducted:		
Funding:		
Methodology		
Study design:	☐ RCT ☐ CCT	☐ Cohort
Study objectives:		
Inclusion criteria:		
Exclusion criteria:		
Recruitment method:		
Overall sample size: • **Consecutive patients considered for the study** • **Total number recruited** • **Total number screened**		
Duration of study:		
Program start and stop age for screening:		
Program screening interval:		
Number of rounds of screening:		
Screening pathway (order of testing):		
Clinical setting:		
Method of sample collection:	☐ Physician-collected	☐ Self-collected
Repeat testing criteria:		
Treatment threshold:	☐ CIN2+ ☐ CIN3+	☐ HSIL ☐ Other (describe):
Patient Characteristics		
Age:		
Race:		
Income:		
Education:		
Relationship status:		
History of sexual activity:		
HIV+ or other STI:		
Prior screening status:		
HPV vaccination status:		
Other (describe):		

Comparison	
Primary screening test evaluated (specify type of assay, disease threshold, manufacturer, technological specifications):	
Comparator (specify type of assay, disease threshold, manufacturer, technological specifications):	
Reference standard:	
Application of reference standard:	☐ All patients ☐ All screening test-positive patients and a subset of screening test-negative patients ☐ All screening test-positive patients only
Definition of cytology-positive threshold:	☐ ASCUS+ ☐ Persistent ASCUS ☐ LSIL+ ☐ Persistent LSIL ☐ CIN1+ ☐ HSIL ☐ CIN2+ ☐ AGC ☐ Other (describe):
Timing between index test and reference standard:	
Reported Outcomes	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

Results (To be Completed for Each Screening Method)	
Number or proportion of patients who accepted screening	
Number or proportion of patients referred to colposcopy	
Total number of patients in 2×2 table	
Number with indeterminate reference	
True positives[a]	
True-negatives	
False-positives	
False-negatives	
Indeterminate index, known case[a]	
Indeterminate index, known non-case	
Indeterminate index, unknown status	
Total number of cases[a]	
Sensitivity	
Specificity	
Positive predictive value	
Negative predictive value	
Positive likelihood ratio	
Negative likelihood ratio	
Diagnostic odds ratio	
Confidence or credible intervals	
Number or proportion of patients referred for treatment	
Anxiety	
Adverse pregnancy outcomes (specify)	
Quality of life	
Cervical cancer incidence	
Cervical cancer-related morbidity	
Cervical cancer-related mortality	

[a] Including description of whether this includes cases of invasive cancer or only cases of high-grade squamous intraepithelial neoplasia.
AGC = atypical glandular cells; ASCUS = atypical squamous cells of undetermined significance; CCT = controlled clinical trial; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesions; LSIL = low-grade squamous intraepithelial lesions; RCT = randomized controlled trial; STI = sexually transmitted infection.

Did the SR report any data relevant to another research question (RQ)? □ Yes: RQ# _____ □ No

CADTH

Appendix 4: Data Extraction Form — Patient Perspectives Review

Reviewer: _____ **Date:** _____

STUDY CHARACTERISTICS	
Ref ID:	
First author:	
Publication title:	
Publication year:	
Country of publication (where data were generated):	
Setting (where data were generated):	
Funding sources:	
Ethics approval:	☐ Yes ☐ No Comments:
Study design:	☐ Ethnography ☐ Phenomenology ☐ Grounded theory ☐ Qualitative description ☐ Other (specify):
Study objectives:	
Eligibility criteria:	
Recruitment method:	
Sample size:	
Participant characteristics:	
Age	
Sex or gender	
Income	
Education	
Relationship status	
Other	
Data collection methods:	☐ Interview ☐ Focus group ☐ Observation ☐ Document review ☐ Other (specify):
Data analysis methods	
STUDY RESULTS	
Results statements will typically, but not always, be presented within the "results" section of a report. Results statements do not include raw data, study methods, external data, or researchers' conclusions and implications. Results statements from the eligible articles relevant to the research question will be captured for analysis using NVivo qualitative data analysis software (QSR International Pty Ltd., Version 11, 2015).[90]	

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Appendix 5: Sample Tables — Patient Preferences Review

Table A1: Example Table of Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
Ethnography	5
Grounded theory	7
Other (PhotoVoice, qualitative description)	4
Phenomenology	4
Qualitative (otherwise unspecified)	11
Total	31

Table A2: Example of Body of Evidence Examined According to Study Location

Study Location	Number of Eligible Studies
Australia/New Zealand	3
Canada	0
Europe	21
US	7
Total	31

Table A3: Example of Body of Evidence Examined According to Type and Number of Participants

Type of Participant	Number of Participants
Patient	752
Caregiver or family member	103
Clinicians	10
Total	865

Table A4: Example of Table of Characteristics of Included Studies

First Author, Publication Year	Country	Methodology	Participant Characteristics, Sample Size	Data Collection	Study Objectives
Smith, J.	Canada	Grounded theory	24 women who tested positive at HPV screening	In-depth interviews	Examine women's reactions and preferences upon receiving an initial abnormal result from HPV screening.