

CADTH OPTIMAL USE REPORT

# HPV Testing for Primary Cervical Cancer Screening: Recommendations Report

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## Abbreviations

<b>AGC</b>	atypical glandular cells
<b>ASC-H</b>	atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion
<b>ASCUS</b>	atypical squamous cells of undetermined significance
<b>HPV</b>	human papillomavirus
<b>HSIL</b>	high-grade squamous intraepithelial lesion
<b>HTERP</b>	Health Technology Expert Review Panel
<b>LBC</b>	liquid-based cytology
<b>QALY</b>	quality-adjusted life-year

## Summary of Recommendation

Worldwide, cervical cancer is one of the most frequently diagnosed cancers.<sup>1</sup> In 2017, it is estimated there were 1,550 cervical cancer cases diagnosed and 380 deaths in Canada.<sup>2,3</sup> The incidence of cervical cancer has been decreasing in the past three decades, largely due to routine screening with cytology.<sup>2</sup>

Canadian data show that routine screening with cytology also improves mortality from cervical cancer; the lifetime risk of dying from cervical cancer is currently one in 100 for those who do not undergo screening with cytology and one in 500 for those who do.<sup>4</sup> Currently different screening programs and approaches have been adopted in Canada, which vary by province, all of which are currently based on regular cytology screening. Existing Canadian guidelines recommend that cervical cancer screening with cytology be done every two to three years starting at age 21 through to between the ages 65 and 70, depending on the jurisdiction.<sup>3</sup>

HPV is the major risk factor for the development of cervical cancer and can be directly detected with diagnostic tests that detect the presence of the virus.<sup>5</sup> Approximately 40 HPV genotypes are known to be involved in genital HPV infections, 13 of which have been designated as high-risk HPV types due to their strong oncogenic potential.<sup>6,7</sup> HPV types 16, 18, 31, 33, 45, 52, and 58 are estimated to account for more than 90% of invasive cervical cancer<sup>5</sup> and 99% of cervical cancer is associated with HPV.<sup>1</sup>

The strong causal link between HPV infection and cervical cancer provided the impetus for evaluating the use of HPV testing in screening for squamous intraepithelial lesions and invasive cancer.<sup>5</sup> Genetic HPV tests detect the presence of HPV DNA or RNA in a sample of cervical cells, with a positive result indicating an HPV infection.<sup>6,8</sup> Partial genotyping tests indicate both whether HPV is present and, if so, whether high-risk variants of the virus are present in the sample.<sup>5</sup> Full genotyping tests identify all of the HPV strains present in the sample.<sup>5</sup>

HPV tests can be used alone, administered at the same time as cytology testing (co-testing), or sequentially with one or more triage tests.<sup>9,5</sup> A triage strategy adopts two or more tests to increase the diagnostic accuracy.<sup>9</sup> Due to the concern about the potential for positive results related to transient infection associated with primary HPV testing alone, several triage strategies have been considered in the HPV testing pathway.<sup>5</sup> Triage testing can be done using cytology or genotyping for high-risk HPV strains.

CADTH undertook a Health Technology Assessment (HTA) to inform policy decisions through a review of the evidence relating to clinical effectiveness and safety, cost-effectiveness, patients' perspectives and experiences, ethical issues, and implementation issues regarding the use of HPV versus cytology-based primary cervical cancer screening programs. The HTA informed the following policy questions: Should HPV testing replace cervical cytology in Canadian jurisdictions as the primary screening tool for cervical cancer? If yes, what criteria, including appropriate screening interval and ages to start and stop screening, should guide HPV-based cervical cancer screening programs in Canada?

**HTERP recommends that all jurisdictions adopt or continue with robust, programmatic, population-based cervical cancer screening, but does not recommend a specific test type.**

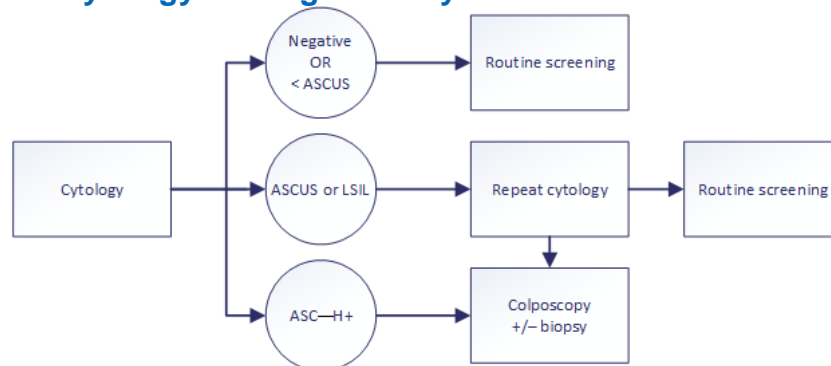
HTERP recommends that if a jurisdiction chooses to replace cytology with HPV-based testing as the primary test for programmatic cervical cancer screening, five-year testing intervals between the ages of 25 and 69 are appropriate. HPV-based screening should be done with a test with genotyping capability.

HTERP recommends a re-assessment of switching to HPV-based testing as the primary test for programmatic cervical cancer screening based on potential changes in test characteristics, emerging evidence on long-term clinical outcomes, the evolution of triage tests, and vaccination rates.

## Technology

With **cytology-based cervical cancer screening**, cytology tests are used to identify the presence of precancerous cell changes in the cervix.<sup>10</sup> There are two types of cytology: conventional (also known as the Pap test) and liquid-based. Conventional cytology involves the collection of cells from the surface of the cervix which are then spread on a slide and visually examined for abnormalities in a laboratory.<sup>5</sup> If more than one test is required for a repeat or a triage test, a separate sample is required for each test to be performed. For liquid-based cytology (LBC), cells are collected in liquid vials and are prepared semi-automatically in the laboratory and then examined. In contrast to conventional cytology samples, a single sample obtained for LBC can be used to perform multiple different tests. Different testing pathways are used to conduct cytology testing. With a cytology screening pathway, a positive result on cytology is a signal that further investigation is required (Figure 1). Colposcopy is a method used to take a closer look at the surface of the cervix under magnification.<sup>11</sup> This allows the clinician to visualize the cervix and identify any areas of abnormality or cervical lesions.<sup>11</sup> Colposcopy may be conducted with, or without, a biopsy to remove some of the abnormal cells for further examination under magnification (histology). If a high-grade squamous intraepithelial lesion (HSIL) or cervical cancer is identified, the patient is referred to treatment.

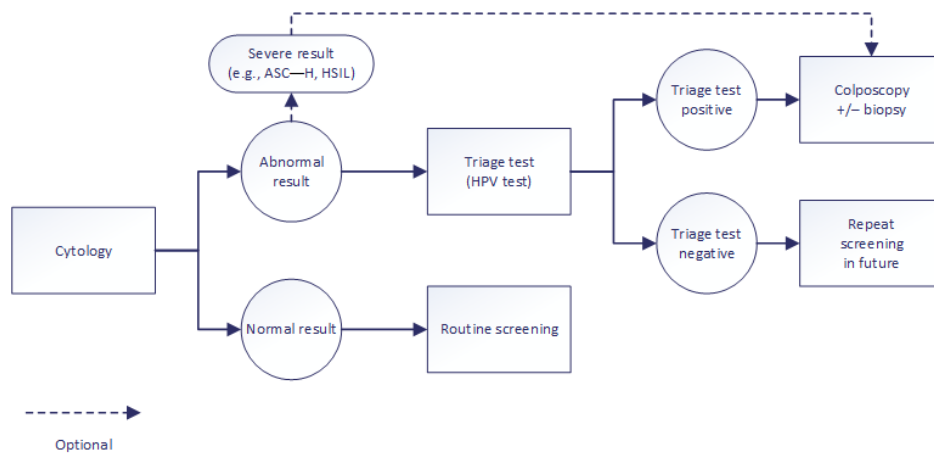
**Figure 1: Cytology Testing Pathway**



ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance.

Cytology testing can also be used in combination with other studies as a triage test, particularly HPV testing. When an abnormal result is detected with the cytology test, an HPV test may be used to identify the presence of oncogenic strains of HPV before deciding whether colposcopy is required (Figure 2).

**Figure 2: Cytology Triage Testing Pathway**

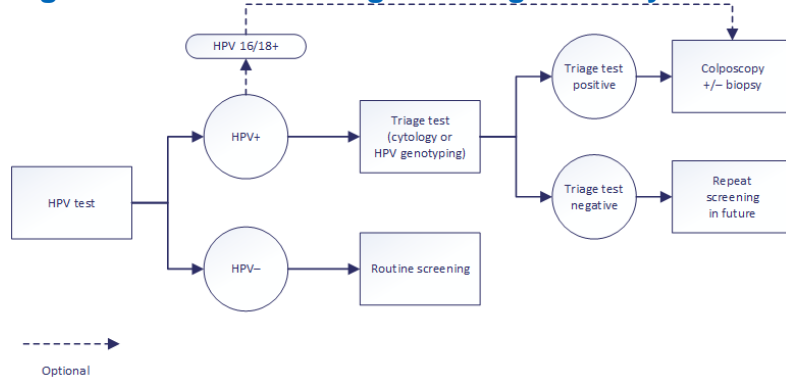


AGC = atypical glandular cells; ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; HSIL = high-grade squamous intraepithelial lesions.

**With HPV-based screening,** HPV tests detect the presence of HPV DNA or RNA in a sample of cervical cells, with a positive result indicating an HPV infection.<sup>6,8</sup> Partial genotyping tests indicate both whether HPV is present and, if so, whether high-risk variants of the virus (16 or 18 or others) are present in the sample.<sup>5</sup> Full genotyping tests identify all of the HPV strains present in the sample.<sup>5</sup> Unlike cytology testing, for which samples are collected solely by a health care provider, HPV-based tests can be collected either by a clinician or by the screening participants themselves.

HPV tests can be used alone, administered at the same time as cytology testing (co-testing), or in combination with one or more triage tests (Figure 3).<sup>9</sup> Co-testing was not assessed or in the scope of this project.

**Figure 3: HPV With Triage Testing Pathway**



## Methods

CADTH conducted an HTA on the clinical effectiveness, cost-effectiveness, patients' perspectives and experiences, ethical issues, and implementation issues regarding the use of cytology versus HPV-based testing for asymptomatic primary cervical cancer screening. The Health Technology Expert Review Panel (HTERP) developed recommendations on the use of HPV-based primary screening based on the evidence presented in the HTA report. HTERP members reviewed the evidence, discussed all elements of the HTERP deliberative framework,<sup>12</sup> and developed recommendations through discussion and deliberation. Additional information on the HTERP process is available on the CADTH website: <https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel>.

## Detailed Recommendations

The objective of these recommendations is to provide advice for Canadian health care decision-makers about primary cervical cancer screening programs. These recommendations are relevant for any person with a cervix who is asymptomatic for cervical cancer and who is eligible to be screened.

**HTERP recommends that all jurisdictions adopt or continue with robust, programmatic, population-based cervical cancer screening, but does not recommend a specific test type.**

### Rationale

The Canadian Partnership Against Cancer states that organized screening programs are the most important system-level strategy used to date for ensuring optimal screening participation.<sup>3</sup> Organized screening programs allow for more complete follow-up, for stronger organization of screening, links with a potential national registry, and would facilitate roll out of new testing modalities. The majority of Canadian jurisdictions have population-based screening programs, however not all do. The committee recommends that those that exist remain in place, and that jurisdictions that do not currently have a population-based screening program begin one.

There was insufficient evidence in the clinical review, when considered in the context of a low overall incidence of cervical cancer in Canada and when balanced against concerns regarding ethical and implementation challenges, to make a strong recommendation that HPV-based testing replace cytology-based testing immediately; however, there is also insufficient evidence to make a recommendation not to adopt an HPV-based strategy.

Adopting HPV as a primary screening test would change both the nature of the cervical screening test and the test characteristics in ethically significant ways. Due to changes in test characteristics, HPV-based testing increases referrals to colposcopy and biopsy; this entails more diagnostic testing, increased surveillance, and an increase in the distress of false positives. It is uncertain to what extent the greater detection of CIN 2 constitutes effective prevention or overdiagnosis (i.e., detecting CIN 2 that would have regressed if never detected and treated).

These burdens fall particularly heavily on younger screening participants. Primary testing with an HPV test increases referral rates to colposcopy, most substantially for those 25 to 29 (19.9% referral rate) and 30 to 34 (10.8% referral rate).<sup>13</sup> The main medical harms



associated with increased diagnostic and treatment biopsies tend to emerge in pregnancy and childbirth, underscoring the difficult challenge of achieving sufficient gains in cervical cancer reduction (prevention of disease; beneficence) to justify the associated harms of screening and to minimize those harms where possible (non-maleficence). Some jurisdictions have weighed the importance of these values differently (in addition to implementation concerns) and have made different choices about the age at which to begin offering screening, with European standards indicating a start age of 30 or 35 while Australia and England have chosen a start age of 25. There is currently discrepancy in Canadian guidelines for cytology; the Canadian Cervical Cancer Screening Network sets target participation rates for screening starting at age 21<sup>3</sup> while the Canadian Task Force on Preventive Health Care recommends a start age of 25.<sup>14</sup>

This balance of harms and benefits and the success of strategies to minimize harms will depend on provider and patient acceptance of recommendations (foregoing more frequent testing, earlier testing, and co-testing) or modifications in lab policy and treatment guidelines (e.g., reporting CIN 2+ and treating lower-risk CIN 2 the same as higher-risk CIN 3).

In addition, the change in the nature of the test substantially increases the proportion of those who will know their high-risk oncogenic HPV status and communicates this directly rather than leaving it to the participant to infer. Under a primary cytology testing scenario, those who receive true positive test results can infer their positive HPV infection status from their colposcopy and biopsy results. Under a primary HPV-testing scenario, the much larger group of all of those screened with both false and true positive screening test results will be directly informed of their positive high-risk oncogenic HPV status. In this context, patient information needs — both for informed choice and for mitigating the burden of knowledge of high-risk oncogenic HPV status or addressing the concerns of particular participants and communities around sexually transmitted infection (STI) test results — could change, as would the time and resources for primary or secondary care to manage these needs would change.

Decision-makers should be transparent about the basis for adopting or not adopting HPV testing as a primary screen on a given timeline. There appears to be mixed, and largely speculative, views about the effects on equity of HPV as a primary screen. Some underscreened groups may be especially concerned about HPV-based screening as an STI test, and this may lower uptake; some groups may benefit from self-sampling as an outreach strategy targeted to those who experience barriers to clinical sampling. Self-sampling for outreach to those who are underscreened is a separate policy question from adoption of HPV as the primary cervical screening test.

Some of the strongest patients' preferences would not be affected by a change in screening modality, as the potential for embarrassment, pain, and logistical inconvenience of both approaches is similar. However, the knowledge of STI status, as directly learned through the results of HPV testing, has been reported to be daunting, has led to associated problems of disclosure of STI status to sexual partners, has had an impact on relationships, and provoked fear of stigmatization. While HPV is not a reportable disease from a public health perspective, those with positive test results still face personal decisions with implications for partners about how to act on their knowledge of their status.

With respect to implementation, a switch to HPV-based screening would be a big operational and culture shift for clinicians, patients, and laboratories. If a switch is made, good planning, funding, and coordination will be needed to make sure implementation runs smoothly. One of the main challenges is acceptance of the new screening strategy by

patients and clinicians, and preventing a drop in screening participation rates. The other main challenge is the major changes required to laboratory configuration, workflow, and human resourcing. There are several facilitators that can help with overcoming these barriers; for example: education, step-wise rollout, organized screening programs, good IT systems, self-sampling. A change to HPV-based screening would be a significant culture shift. It is important to keep in mind the magnitude of the system change and the level of organization and funding that would be required to ensure all components are in place and functioning well. If a decision is made to adopt HPV testing for primary cervical cancer screening, implementation will need to be carefully planned, and sufficient time and resources will need to be allotted to ensure structures and supports are in place — at the patient, clinician, laboratory, and system level. The economic analysis within the HTA did not incorporate implementation costs, considering a switch from cytology-based to HPV-based testing, due to the difficulty in cost estimation and the variety in payers for various costs across jurisdictions.

Additionally, the majority of the clinical evidence assessed in the HTA pertained to a single test (HC2) and there was uncertainty regarding the effect on cervical cancer incidence and mortality (the purpose of screening programs is to reduce mortality due to cervical cancer, yet the rates are so low in countries with organized screening programs that measuring the effects of screening strategies on mortality through clinical trials is not feasible). As test characteristics change, and as more evidence becomes available regarding other tests used in the context of primary screening, the confidence in the clinical evidence may change. Thus, it is reasonable for jurisdictions to either choose to adopt or not adopt HPV-based testing, depending on the contextual and implementation factors within a jurisdiction at this time.

**HTERP recommends that if a jurisdiction chooses to replace cytology with HPV-based testing as the primary test for programmatic cervical cancer screening, five-year testing intervals between the ages of 25 and 69 are appropriate. HPV-based screening should be done with a test with genotyping capability.**

## Rationale

There is a trade-off between the sensitivities and specificities of cytology and HPV-based testing. HPV tests (including HC2, Multiplexed Genotyping, Aptima, Cobas, and Confidence) demonstrate higher sensitivity and lower specificity than either LBC or conventional cytology and the HC2 HPV test is less specific than cytology at the threshold of atypical squamous cells of undetermined significance (ASCUS) for the detection of CIN2+ and CIN3+. The high negative predictive value of the HPV test (which is higher than 99%), contributes to the recommendation to lengthen the screening interval.

The economic evaluation found that switching the primary test from cytology to HPV testing and decreasing the screening frequency decreases the overall cost of cervical cancer screening in Canada with limited harms in terms of lifetime risk of developing cervical cancer. Regardless of the population age or vaccination status, the model found that primary HPV with cytology triage, every five years, from the ages of 30 to 69 was associated with the lowest costs and lowest quality-adjusted life years (QALYs). The expected lifetime QALY difference between screening programs was small (ranges from 0.002 to 0.005), which can be interpreted as, at most, 1.8 additional days of full health gained per person.

While the economic model supported beginning screening at age 30, this would likely not be a strategy that would receive buy-in from clinicians or those eligible for screening. The

implementation review noted that reduced screening frequency and later start age may be met with reluctance by those who are eligible for screening. In Australia, where HPV-based screening is being introduced, more than 70,000 people signed an online petition to oppose the changes to the cervical screening program.<sup>15</sup> One of the changes that received the most strong opposition was the change in the start age of screening from 20 to 25.<sup>15</sup> It is speculated that some of the opposition was based on potential misunderstanding of the rationale for the change as well as misunderstanding of the effectiveness of screening and the role of HPV as a cause of cervical cancer.<sup>15</sup> In an opinion article, researchers in Australia stated that a reasonable message to take away from the petition was that communication and consultation have not been sufficient or effective.<sup>15</sup> In England, the introduction of a later start age, by increasing the age at which to begin screening from 20 to 25, was also not well received — it was perceived by some as rationing care.<sup>16</sup> As the clinical difference in terms of QALYs between screening strategies in the economic model was marginal, the committee concluded that at this time, a start age of 25 and end age of 69 was reasonable.

Samples for HPV tests can be self- or clinician- sampled, whereas cytology testing is clinician sampled only. This may be particularly important for populations who find the screening-process particularly embarrassing or invasive, or who are under- or never-screened for other reasons. There are individual studies showing high concordance or fair to high agreement between self- and clinician-sampled HPV tests, but as a whole, the evidence is uncertain. Self-sampled HPV tests may be less sensitive and specific than cytology at the threshold of ASCUS or more severe dysplasia for the detection of CIN2+. Thus, self-sampling is not currently appropriate for all of those eligible for screening, but rather, may be a tool to increase uptake for those who are underscreened.

An HPV test with genotyping capability would increase the certainty of identifying an oncogenic strain and reduce the need for additional testing following a positive HPV test result, which would also potentially reduce costs. HPV-based testing should be undertaken in the context of HPV as a primary test and with a triage test (currently cytology with genotyping) due to the lower specificity of HPV testing.

**HTERP recommends a re-assessment of switching to HPV-based testing as the primary test for programmatic cervical cancer screening based on potential changes in test characteristics, emerging evidence on long-term clinical outcomes, the evolution of triage tests, and vaccination rates.**

## Rationale

HPV infection can now be prevented with vaccination.<sup>5</sup> There are several brands of HPV vaccines available in the market and can target at least two highly oncogenic HPV strains (HPV 16 and 18).<sup>5</sup> The immunization strategies vary in Canadian provinces, as does uptake of immunization programs among those who are eligible.<sup>3</sup> School-based programs have been implemented in all Canadian provinces and territories with different eligible ages and dosing schemes.<sup>3</sup> Increased vaccination rates will further decrease the prevalence of HPV, which would likely influence both the clinical and cost-effectiveness of a population-based screening program. The increases in potentially unnecessary referrals to colposcopy are a noted barrier for HPV-based testing. Current thresholds for referral may not be relevant as the testing landscape changes and decreasing unnecessary referrals requires further study into the threshold for referral to colposcopy. Additionally, as evidence becomes available regarding newer tests (particularly triage tests and mRNA based HPV tests) and as self-sampled testing options likely improve, re-assessment will be needed.

## Considerations

HTERP worked the cervical screening policy issue through its deliberative framework and the following considerations were put forth as a part of their discussion.

HTERP considered the clinical evidence, which demonstrated that HPV-based screening tended to have higher sensitivity and lower specificity than cytology-based screening. Rates of invasive cervical cancer and of precancerous lesions, while supported by limited data, seem to be detected earlier using HPV-based testing. These outcomes were not commonly measured or reported in the included studies.

The committee discussed that longer-term data in the context of HPV-based screening as a part of co-testing, which was not within the scope of this review, is available based on a meta-analysis of four European RCTs.<sup>17</sup> While out of scope because co-testing as the primary screening strategy is not likely to be adopted in the Canadian context, HTERP discussed this meta-analysis at length as the only available long-term data with partial relevance. It was noted that the meta-analysis demonstrated that for the first 2.5 years of follow-up, detection of invasive carcinoma was similar between groups, however in those who received HPV-based co-testing at study entry, detection of invasive carcinoma was significantly less in the follow-up periods longer than 2.5 years; suggesting that the HPV-based co-testing detected abnormalities earlier than cytology-based co-testing.<sup>17</sup>

The 48-month follow-up of the Canadian FOCAL trial,<sup>18</sup> in which all participants who had a negative result from HPV-based testing at study entry or LBC-based testing at both study entry and the 24 month follow-up were further tested at 48 months with HPV and cytology co-testing was also discussed. While the authors of this study reported incidence of CIN3+ and CIN2+, rather than invasive cancers, at 48 months since initial testing, the incidence of both CIN3+ and CIN2+ was significantly lower in the group who had initial HPV testing than in those who had initially been screened using LBC. This suggests that HPV-based testing detected cancer precursors earlier.<sup>18</sup> The committee discussed these results along with those that were reported in the clinical evidence review.

The importance of the prevalence of cervical cancer was discussed. The prevalence of cervical cancer is low and will continue to be low with ongoing and population-based screening programs. A modelling study from Australia, where HPV-based screening is used and where HPV vaccination coverage is considered to be good was discussed.<sup>19</sup> Based on the model, the incidence of cervical cancer is predicted to reach six cases per 100,000 in 2020, fewer than four cases per 100,000 in 2028, and potentially less than one case per 100,000 in 2064 (assuming the current HPV screening and vaccination programs continue).<sup>19</sup> As vaccination rates increase and further cohorts of the vaccinated population enter screening age, the committee noted that these are important considerations for screening programs.

The committee discussed that the change to HPV-based testing would represent a significant implementation effort with respect to communication, education, and human resources; all of which come at a potentially significant cost, which could not be factored into the cost-effectiveness analysis. The cost estimation and the variety in payers for various costs across jurisdictions makes the implementation costs both difficult to estimate and jurisdiction specific. Further, HTERP discussed the potential opportunity cost of switching to an HPV-based strategy. It was felt that some jurisdictions with available resources to dedicate to cervical cancer screening might instead consider investing those resources into strategies to enhancing participation in vaccination or in existing cytology-based screening

programs. These alternative approaches were also not considered in the economic analysis, or HTA.

HTERP acknowledged that other jurisdictions have chosen to put forth a clear recommendation to adopt HPV-based testing. Overall, they found that, when balanced against concerns regarding ethical and implementation issues, there was insufficient evidence in the clinical review or the economic analysis, to make a strong recommendation that HPV-based testing be adopted immediately; however, there is also insufficient evidence to make a recommendation not to adopt an HPV-based strategy. Additionally, the majority of the clinical evidence assessed in the HTA pertained to a single test (HC2) and HTERP acknowledged that there was uncertainty regarding the effect on cervical cancer incidence and mortality. As test characteristics change and as more evidence becomes available regarding other tests, the confidence in the clinical evidence may change. Thus, the committee considered it reasonable for jurisdictions to either choose to adopt or not adopt HPV-based testing, depending on the contextual factors within the province or territory at this time.

While HTERP indeed considered it reasonable for jurisdictions to choose not to adopt HPV-based testing, they also noted that HPV testing is already becoming available as a fee-for-service test in some jurisdictions.<sup>1</sup> They discussed that for those who opt to pay for HPV testing, this removes them from the established screening program and may make it more difficult to follow-up with them and to continue to ensure participation in regular screening. Additionally, although there are currently tradeoffs between the sensitivities and specificities of cytology and HPV-based testing, there may be public perception that those who can pay for a test (or who belong to health plans that pay for the test) are getting superior care and are paying for better testing, when in fact the current evidence indicates that there are tradeoffs between negative predictive value, positive predictive value, sensitivity, and specificity. If a jurisdiction chooses not to adopt an HPV-based primary cervical cancer screening program, the availability of a fee-based HPV-testing system may carry a risk of magnifying perceived inequities.

HTERP discussed the need for education with respect to the nature of the test and what test results indicate at the public level. They acknowledged that due to the nature of testing for HPV rather than precancerous lesions, a switch to HPV-based testing will initially result in an increased number of positive test results. With education and infrastructure in place to manage more positive results efficiently, the harm and burden of positive test results can be reduced. Additionally, communication of test results may need to take into account patient confidentiality concerns, which are always important but likely to be heightened around an STI. Patient education with a focus on the etiology and risk factors of cervical cancer may improve screening participation. It may be particularly important to emphasize the relationship between high-risk oncogenic HPV strains and the cancer risk associated with a positive HPV test.

The committee discussed the potentially significant human resource change that is likely to result with a change from cytology to HPV screening programs. There is the likelihood of reduced cytology workload (and thus potential job losses for cytotechnologists and cytopathologists) and an increase in demand for molecular testing. Retraining, expanded roles, and career transition opportunities may be needed. HTERP emphasized that infrastructure and systems change are important for successful implementation. A switch to HPV testing would be a large operational and culture shift. Good planning, funding, and coordination would be needed to make sure implementation runs smoothly.

HTERP discussed that with changes in test characteristics and as the vaccinated cohorts become more prevalent, HPV-based testing may be more important.<sup>20</sup> As a switch to HPV-based testing requires education and health system change, which require time and potentially considerable costs, jurisdictions should begin the planning and budgeting for HPV-testing roll out, if that is their decision. HTERP emphasized that HPV-based testing represents an operational and culture shift for clinicians, patients, and laboratories. Planning, funding, and coordination are needed to ensure that implementation runs smoothly. Although the economic evaluation captured laboratory costs in terms of direct costs of performing and interpreting the test itself (e.g., assays kits, labour, specimen collection), other implementation costs such as the development of educational materials, changes in laboratory processes, and HR-level implications (e.g., retraining existing staff, hiring new staff) were not explicitly included in the economic model. These were not considered as the accuracy and completeness of these costs are difficult to estimate and the payers for the implementation changes are likely to vary across jurisdictions and even among licensed laboratories (e.g., hospital laboratories, public laboratories, private laboratories). HTERP recognizes that a switch to HPV-based testing is a switch both with respect to the nature of the test as well as the work load balance for health care personnel within the health care system. As HPV-based testing is STI screening rather than screening for precancerous lesions, education regarding what an HPV positive test means, both at the clinician and patient level, is important. For those who receive an HPV positive result, there may be a significant burden in knowing their status and in determining what their responsibility is with respect to informing others of their status. There are populations for whom STI testing represents a barrier and thus a switch may result in difficulty keeping them in the screening programs. STIs can carry stigma, particularly in certain cultural groups, and testing for STIs may be more acceptable for some than for others. While a self-sampled test may improve participation for some, the nature of the test as an STI test may ultimately prevent some individuals from participating in cervical cancer screening.

HTERP discussed that self-sampled HPV testing is not appropriate for everyone, as it still does not seem to be as accurate as clinician-sampled testing (in the context of primary cervical cancer screening); however, for those who are underscreened or have never been screened for cervical cancer, it represents a potential pathway to screening and may address some inequities by increasing participation in screening for those who do not normally present for testing. They recognize that a positive result requires follow-up with a health care professional and does not completely address inequities such as access to care or to culturally appropriate care.

HTERP discussed that while there is not strong evidence to support the choice of one particular HPV test over another, an HPV test with genotyping capability should be favoured over one that is not. When the test includes genotyping to identify the genotype of HPV, it would increase the certainty of identifying an oncogenic genotype and reduce the need for additional testing following a positive HPV test result. This would also potentially reduce costs and provide information regarding vaccine efficacy.

The testing interval that was supported by the economic model was a five-year testing interval. While the economic model supported beginning screening at age 30, HTERP discussed that this would likely not be a strategy with buy-in from clinicians or those eligible for screening. Additionally, as the clinical difference in terms of QALYs between screening strategies in the economic model was marginal, the committee concluded that at this time, a start age of 25 and end age of 69 was reasonable. From a cost perspective, the impact is also minimal — an additional \$130 over a lifetime time horizon when HPV-based screening

at five-year intervals starts at age 30 (\$1,471) versus at age 25 (\$1,601). HTERP discussed that it is important to note and to emphasize in educational materials, that HPV-based testing has different testing characteristics than cytology and therefore, the testing interval is different. The committee discussed that the negative predictive value of the HPV test as one reason for the testing interval change. As there was no evidence (modelled or otherwise) to suggest changes to age ranges of screening, particularly at the upper end of the age range, HTERP discussed age as a potential area for future research.

HTERP recommended that further research into the characteristics of self-sampled testing, individuals who are older than 69 and who have aged out of the screening programs, long-term clinical outcomes associated with testing, vaccination rates, and differences in screening outcomes based on vaccination status. They further recommended monitoring the international experience and international evidence, as HPV-based screening continues to be implemented in other jurisdictions.

## Background

The evidence regarding the clinical effects, cost-effectiveness, patients' perspectives and experiences, ethical, and implementation factors associated with HPV-based testing used for developing this guidance was derived from the CADTH HTA: *HPV Testing for Primary Cervical Cancer Screening*.<sup>21</sup>

## Research Questions

The research questions that guided the HTA were as follows, with separate methods developed a priori to address each question, as reported in publicly available published protocols:

1. What is the diagnostic efficacy of primary high-risk HPV testing, with or without cytology triage, compared with primary cytology-based testing for asymptomatic cervical cancer screening?
2. What are the diagnostic efficacies of primary high-risk HPV testing strategies compared with each other for asymptomatic cervical cancer screening?
3. What is the comparative cost-effectiveness of primary high-risk HPV testing, with or without cytology triage, compared with primary cytology-based testing for asymptomatic cervical cancer screening Canada?
4. What are the perspectives of adults eligible for cervical cancer screening, their family members, and their caregivers regarding the value and impact of HPV testing for cervical cancer screening on their health, health care, and lives?
5. What ethical issues are raised by HPV testing for cervical cancer screening and how might they be addressed?
6. What are the main challenges, considerations, and enablers to implementing HPV testing for primary cervical cancer screening in Canada?

## Summary of the Evidence

### Clinical Evidence

To assess empirical evidence relevant to the diagnostic test accuracy, clinical utility, and safety of cervical cancer screening, existing relevant and high-quality systematic reviews were integrated into an overarching review and supplemented with subsequently published primary studies. Published literature was identified by searching MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects (DARE), and PubMed. Retrieval of systematic reviews was limited to documents published since January 1, 2002. For supplemental primary studies, retrieval was limited to the earliest literature search cut-off date for each outcome assessed within the relevant systematic review. Results were limited to English- and French-language publications. The quality of systematic reviews, diagnostic test accuracy studies, randomized controlled trials and observational studies was assessed by two reviewers independently using the AMSTAR 2 tool, QUADAS-2 instrument, the Cochrane Risk of Bias Tool, and the Newcastle-Ottawa scale respectively. Data were extracted by one reviewer and verified by another. The results were summarized and categorized based on the outcomes. The heterogeneity of the results was assessed and potential sources of heterogeneity were discussed.

Four systematic reviews, nine randomized controlled trials, 10 prospective cohort studies, and one retrospective cohort study were identified as eligible for this review. For the comparison of the diagnostic test accuracy between HPV tests and cytology testing, Hybrid Capture 2 was the most extensively studied HPV test and was found to be more sensitive and less specific than cytology, including conventional or liquid-based cytology in most included studies. There is consistent evidence to show that other HPV tests were also more sensitive and less specific than cytology, including polymerase chain reaction-based tests, Multiplex Genotyping, Aptima, Cobas, and Confidence. Studies assessed participation rates in populations that were considered underscreened after participants were offered the chance to take samples by themselves at home or elsewhere. For the individuals who did not attend screening programs regularly, self-sampling HPV tests that were sent to individual residences were generally more acceptable than cytology. Higher colposcopy referral rates were observed among those screened by HPV tests, compared with cytology. While there was limited evidence available to address harms and clinical utility, overall, the evidence was consistent in demonstrating that primary high-risk HPV screening led to a statistically significantly increased detection of cervical intraepithelial neoplasia (CIN) 3+ in the initial round of screening versus cytology and that the relative risk for CIN 3+ detection between screening groups was similar to the overall findings in both the younger (younger than 35 years) and older (older than 35 years) age groups. After two to three years of follow-up, there were no serious adverse events observed that were related to the screening tests.

Regarding triage strategies, evidence relating to four triage strategies (primary HPV testing with cytology triage; primary HPV testing followed by triage with partial genotyping for HPV 16/18; primary HPV testing followed by triage with sequential partial genotyping for HPV 16/18 followed by cytology to further triage those positive for HPV 16/18; and primary HPV testing followed by co-testing triage [partial genotyping for HPV 16/18 and cytology]) was identified. The sensitivity and specificity of the primary HPV testing followed by cytology remained high after one to four years of follow-up. The longitudinal diagnostic test accuracies of the other three triage strategies of interest were compared with baseline



diagnostic test accuracy. Longitudinal sensitivities were lower than baseline for primary HPV testing followed by either cytology alone, sequential genotyping and cytology, or co-testing (with HPV genotyping and cytology). The longitudinal specificities were higher for primary HPV testing followed by cytology alone, and co-testing (with HPV genotyping and cytology), while they were lower than baseline for primary HPV testing followed by sequential genotyping and cytology.

## Economic Evidence

A decision-analytic hybrid model was developed to determine, from a health systems perspective, the lifetime cost-effectiveness associated with the following approaches to programmatic cervical cancer screening: primary cytology; primary cytology with HPV triage for equivocal cytology results, and primary HPV with cytology triage for HPV positive results. In addition, the model evaluated the potential impact from a strategy involving non-programmatic screening for cancer of the cervix. The model was based on a previously published decision-analytic model that was adapted to better capture existing Canadian guidelines on the clinical management of cervical cancer screening. It entailed a Markov microsimulation that reflected the natural history and epidemiology of HPV infection, cervical lesions and cervical cancer and, at the appropriate model cycles, a decision tree that captured the short-term screening outcomes that could modify the disease pathway if screening resulted in further clinical management. The clinical pathway and decision-analytic model were developed by reviewing existing clinical and economic literature, and the conceptualization of the model and its structure was subsequently validated by gynecologists. Single-cohort analyses were performed with three specific cohorts defined: a future incidence (entering model at an age younger than the screening program; i.e., baseline age of nine and partially vaccinated), an incident (entering model at the starting age of screening; i.e., baseline age of 20 and partially vaccinated), and a prevalent cohort (entering model at an age within the screening age range; i.e., baseline age of 30 and unvaccinated). The primary outcome was cost per quality-adjusted-life-years (QALYs) gained, in 2017 Canadian dollars. In total, nine different screening strategies were assessed that varied with respect to the screening interval (i.e., starting age of screening) and/or the frequency between screens (e.g., three or five years).

The current screening strategy of cytology every three years from the ages of 21 to 69 was found to reduce the lifetime risk of cervical cancer by 69% compared with no organized screening. The economic evaluation found that switching the primary test from cytology to HPV testing and increasing the screening frequency from three to five years could decrease the cost of cervical cancer screening in Canada with limited harm in terms of risk of developing cervical cancer. Regardless of the population age or vaccination status, the model found that primary HPV with cytology triage, every five years, from the ages of 30 to 69 was associated with the lowest costs and fewest QALYs. This strategy would be the most likely cost-effective strategy at willingness-to-pay thresholds of \$50,000 per QALY gained. The expected lifetime QALY difference between screening programs was small (ranges from 0.002 to 0.005), which can be interpreted as, at most, 1.8 additional days of full health gained per person. Sensitivity analyses on each of the evaluated three cohorts highlighted that the future incidence and incident cohorts were more robust to changes compared with the prevalent cohort. Overall, the model was most sensitive to lower rates of vaccination uptake, the removal of discounting of health effects and costs, or the application of disutilities to abnormal screening results.

## Patients' Perspectives and Experiences

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

A total of 117 primary empirical qualitative research studies were included in the meta-synthesis. Of these, 102 studies recruited participants based on particular aspects of their social or demographic identity including women who belonged to a minority ethnicity or culture, women of low socioeconomic status, Indigenous women, women who lived in rural areas, women who are lesbian, bi-sexual or transgender, older women, as well as other aspects of identity (e.g., those who have high BMI, those who are incarcerated, those who are homeless, those who are HIV positive). A number of factors were identified that act alternately as incentives or disincentives to decision-making about participation in cervical cancer screening: emotions, cultural and community attitudes and beliefs, understanding personal risk, logistics, multiple roles of women, relationships with health care providers, comfort and inclusion in the health care system, and knowledge. Many of the factors are closely related. Social location was highly influential on the way one experienced the incentivizing and disincentivizing factors. Few women understood the link between HPV and cervical cancer, which resulted in misunderstandings about the nature and importance of HPV testing. As a result of this misunderstanding, many women may underestimate their personal risk and decline to participate in screening. If cytology is replaced by HPV testing as the primary cervical cancer screening test in Canada, patient education that focuses on the etiology and risk factors of cervical cancer may improve participation rates. Some of the strongest patient preferences will not be affected by a change in screening modality from cytology testing to HPV. For example, both require an invasive procedure to collect cell sample, and therefore the potential for embarrassment, pain, and logistical inconvenience of that procedure are unchanged. The importance of the relationship between patient and health care provider will also continue to be important.

## Ethical Issues

A systematic review to determine the ethical and legal issues that have been identified for HPV as a primary cervical cancer screening test was performed. Given the paucity of results from a search for research addressing this question directly, we performed a second search to determine the ethical and legal issues that have been identified in cervical cancer screening. This ethical review and analysis focused on equity, non-maleficence, and autonomy issues raised in the existing literature and performed novel analyses of how these issues would be affected by primary screening with HPV testing for persistent infection with high-risk oncogenic HPV strains. It also discussed liability concerns for pathologists and

cytologists that have arisen from cytology. Its analysis is consistent with Parker et al.'s recent argument that "avoiding harm and supporting autonomy are under-prioritized in cancer screening policies and practices."<sup>15</sup>

Cancer screening involves balancing the benefits of disease detection (beneficence) with the harms and burdens of screening attendance, false positives, and overdiagnosis (non-maleficence). This balance of harms and benefits is affected by test characteristics and by the nature of the test, as well as by implementation.

There is no common agreement on the line between an acceptable and an unacceptable balance of harms and benefits in screening. Given that decisions inevitably involve tradeoffs of valid concerns, transparency and fair consideration of diverse concerns are important values.

Screening has traditionally been carried out with a mandate to increase uptake, but screening policy now places greater emphasis on informed choice. This is a response to increased awareness of the low absolute risk reduction screening offers individuals, of screening-related harms, and of the risk of false reassurance.

Under the scenario of HPV as a primary screening test, the implications of a false-positive test result are substantially different for a large proportion of the population: as many as a third of those screened would at some point in their lives receive a diagnosis of a high-risk oncogenic HPV infection, a much larger proportion of the screened population than those who currently might infer their HPV infection status from their true positive cytology results.

Any increase in screening-related harms (increased colposcopy referrals and increased false positives, if HPV testing causes these; the increased burden of STI findings, which is intrinsic to the nature of the test) should be weighed and justified in a transparent manner by minimization of these harms and by an increase in benefits (reduced colposcopy referrals and false positives and reduced cervical cancer mortality, if HPV testing causes these).

Decision-makers should be transparent about the basis for adopting or not adopting HPV testing as a primary screen on a given timeline: is the test being adopted in light of anticipated clinical benefits in the absence of current evidence for mortality outcomes, or on the anticipated cost-effectiveness for the future HPV-vaccinated cohort? Or is it delayed or not adopted because of cytology workforce issues or out of a desire for more definitive evidence?

Decision-makers should also ensure that concrete steps are taken to minimize harms, in specific, addressing possible over-detection and overtreatment, ensuring the evidence base for STI follow-up and the acceptability to screening participants and their partners of this step, and attending to the potential that a test with the purpose of detecting an STI, even if used with the goal of cancer prevention, may have different significance for different communities and individuals.

The balance of harms and benefits depends on patients and providers following guidelines intended to de-intensify screening (start later and extend intervals) and manage the intensity of treatment. Patient information needs — both for informed choice and for mitigating the burden of knowledge of high-risk oncogenic HPV status — and the time and resources for primary or secondary care to manage these needs would change.

There appears to be mixed, speculative views about the effects on equity of HPV as a primary screen. Some underscreened groups may be especially concerned about the HPV-

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

## Implementation Issues

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

To augment the data collected from the literature review, consultations were conducted with targeted experts and stakeholders. Individuals were approached by email and invited to participate in a phone interview or to provide written responses to questions by email, at their convenience. Consultations took place with stakeholders and experts from the Canadian laboratory, pathology, and cancer specialty sectors. Consultations also took place with representatives from countries that are in the process of implementing HPV primary screening, namely England and the Netherlands.

After qualitative coding, the final summary of content was organized by topic-specific categories chosen due to their relevance to health service delivery, with the intent to provide information to policy-makers regarding the operational requirements and supports that could help facilitate effective implementation of the recommendations of the expert committee. The categories were: program administration and change management; effects on laboratory structure and workflow; effects on screening participation rates; health care provider barriers and facilitators; and geographical, socioeconomic, and sociocultural issues.

A number of key issues and themes emerged from the review of implementation issues associated with the potential implementation of HPV testing for primary cervical cancer screening. These key issues can be summarized as follows: a switch to HPV testing would be a large operational and culture shift for clinicians, patients, and laboratories; good planning, funding, and coordination would be needed to make sure implementation runs smoothly; acceptance of a new screening strategy by patients and clinicians has the potential to be a challenge — preventing a drop in screening participation rates could be important; a major change to laboratory configuration, workflow, and human resourcing would be required — this change could present a challenge; there are several facilitators that may help with overcoming these barriers; for example: education, step-wise rollout, organized screening programs, good IT systems, self-sampling.

## References

1. Society of Obstetricians and Gynaecologists of Canada. All about HPV. 2018; <http://hpvinfo.ca/>. Accessed 2018 Apr 2.
2. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017. *Special topic: pancreatic cancer*. Toronto (ON): Canadian Cancer Society; 2017: <http://www.cancer.ca/~media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2017-EN.pdf?la=en>. Accessed 2018 Mar 12.
3. Cervical cancer screening in Canada: Monitoring & evaluation of quality indicators. Toronto (ON): Canadian Partnership Against Cancer; 2016: [https://content.cancerview.ca/download/cv/prevention\\_and\\_screening/cccic\\_microsite/documents/cccicmonitoringevalqualityindicatorspdf](https://content.cancerview.ca/download/cv/prevention_and_screening/cccic_microsite/documents/cccicmonitoringevalqualityindicatorspdf). Accessed 2016 Jun 17.
4. Cervical cancer—patient algorithm. Ottawa (ON): Canadian Task Force on Preventive Health Care; 2016: <https://canadiantaskforce.ca/tools-resources/cervical-cancer-2/cervical-cancer-patient-algorithm/>. Accessed 2016 Sep 2.
5. Health technology assessment of human papillomavirus testing as the primary screening method for prevention of cervical cancer. Mahon (IRE): Health Information and Quality Authority; 2017: <https://www.higa.ie/reports-and-publications/health-technology-assessment/hta-hpv-testing-cervical-cancer-screening>. Accessed 2018 Oct 17.
6. Screening portfolio: HPV testing for cervical cancer screening. *Expert panel: Summary of evidence*. Toronto (ON): Canadian Partnership Against Cancer; 2012: [http://www.cancerview.ca/idc/groups/public/documents/webcontent/hpv\\_testing\\_final.pdf](http://www.cancerview.ca/idc/groups/public/documents/webcontent/hpv_testing_final.pdf). Accessed 2016 Jun 14.
7. Tota JE, Bentley J, Blake J, et al. Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm. Toronto (ON): La Ki Shing Knowledge Institute, St. Michael's Hospital; 2015: <http://healthydebate.ca/wp-content/uploads/2016/04/Report-on-HPV-primary-screening.pdf>. Accessed 2016 Jun 14.
8. Hoste G, Vossaert K, Poppe WA. The clinical role of HPV testing in primary and secondary cervical cancer screening. *Obstet Gynecol Int*. 2013;2013:610373.
9. Jin XW, Lipold L, Foucher J, et al. Cost-effectiveness of primary HPV testing, cytology and co-testing as cervical cancer screening for women above age 30 years. *J Gen Intern Med*. 2016;31(11):1338-1344.
10. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: A systematic review and meta-analysis. *Syst Rev*. 2013;2:35.
11. Kaiser Permanente Research Affiliates Evidence-based Practice Center. Screening for cervical cancer with high-risk human papillomavirus testing: A systematic evidence review for the U.S. Preventive Services Task Force. *Evidence synthesis, no. 158*. Rockville (MD): Agency for Healthcare Research and Quality; 2017: <https://www.uspreventiveservicestaskforce.org/Home/GetFileByID/3279>. Accessed 2017 Oct 18.
12. Health Technology Expert Review Panel deliberative framework. Ottawa (ON): CADTH; 2015: [https://www.cadth.ca/sites/default/files/pdf/hterp/HTERP\\_DFW\\_e.pdf](https://www.cadth.ca/sites/default/files/pdf/hterp/HTERP_DFW_e.pdf). Accessed 2018 Oct 24.
13. Melnikow J, Henderson JT, Burda BU, Senger CA, Durbin S, Weyrich MS. Screening for cervical cancer with high-risk human papillomavirus testing: Updated evidence report and systematic review for the us preventive services task force. *JAMA*. 2018;320(7):687-705.
14. Canadian Task Force on Preventive Health Care, Dickinson J, Tsakonas E, et al. Recommendations on screening for cervical cancer. *CMAJ*. 2013;185(1):35-45.
15. Delays and confusion cloud roll-out of new cervical cancer screening program. Boston (MA): The Conversation; 2017: <http://theconversation.com/delays-and-confusion-cloud-roll-out-of-new-cervical-cancer-screening-program-73605>. Accessed 2017 Jun 7.
16. Flynn H, Lewis P. Rational care or rationing care? The case of cervical screening across the United Kingdom. *Health Policy*. 2013;112(3):197-201.
17. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: Follow-up of four European randomised controlled trials. *Lancet*. 2014;383(9916):524-532.
18. Ogilvie G, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical hpv testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: The hpv focal randomized clinical trial. *JAMA*. 2018;320(1):43-52.
19. Hall MT, Simms KT, Lew JB, et al. The projected timeframe until cervical cancer elimination in Australia: A modelling study. *The Lancet Public health*. 2019;4(1):e19-e27.
20. Franco EL, Mahmud SM, Tota J, Ferenczy A, Coutlee F. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: The need for a paradigm change. *Archives of medical research*. 2009;40(6):478-485.
21. HPV testing for primary cervical cancer screening: A Health Technology Assessment. (*CADTH optimal use report vol. 7, no. 1b*). Ottawa (ON): CADTH; 2019.

## Appendix 1: HTERP

The Health Technology Expert Review Panel (HTERP) consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project three expert members were appointed; their expertise included cervical cancer screening (including HPV and cytology tests) and public health. The core members include health care practitioners and individuals with expertise in evidence-based medicine, critical appraisal, Health Technology Assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest. Further information regarding HTERP is available at: <https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel>

### HTERP Core Members

Brigadier General (Retired) Hilary Jaeger (chair)

Dr. Jenny Basran

Dr. Lawrence Mbuagbaw

Dr. Jeremy Petch

Dr. Lynette Reid

Ms. Tonya Somerton

Dr. Jean-Eric Tarride

### Expert Members

Dr. Valerie Jaeger

Dr. Terence Colgan

Dr. Joan Murphy

### Conflicts of Interest

HTERP core members' declarations are posted on the [CADTH website](#). Dr. Lynette Reid was the author of the ethics report that supported these recommendations, and therefore was a non-voting member for the purpose of recommendations development.

Dr. Colgan is the head of histopathology at LifeLabs. No other members declared conflicts of interest relevant to this project. [Conflicts of interest guidelines](#) are posted on the CADTH website.