

SCREENING PORTFOLIO

## HPV Testing for Cervical Cancer Screening

Expert Panel: Summary of Evidence

March 29<sup>th</sup>, 2012



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## Executive Summary

Cervical screening with the Pap test has been effective in decreasing both the incidence of and the mortality from cervical cancer in Canada over the past five decades, despite the fact that single test sensitivity is quite low at around 55%. These advances were made possible only at the cost of considerable burden for women and the health system.

The causal role of human papilloma virus (HPV) in cervical cancer is now well established and this has led to scientific inquiry into whether there is a role for HPV testing as a primary screening test, potentially replacing the Pap test.

Several large randomized trials comparing Pap testing to HPV testing for primary screening have published results in recent years for one round of screening and for some trials the results are reported after two rounds of screening. The outcomes evaluated by the trials included the detection of pre-cancerous cervical lesions of the cervical intra-epithelial neoplasia (CIN)2 or CIN3 categories or worse (including cancer). No trials carried out in settings similar to Canada have evaluated the impact of HPV testing on cancer mortality outcomes.

While the design and protocols of the trials vary considerably, the overall findings do indicate that screening with the HPV test results in a higher detection rate for pre-cancerous lesions (CIN2 or CIN3) compared to Pap testing after one round of screening. Results from second rounds of screening show a decreased detection rate of these lesions compared to the Pap test arm, presumably because the increased sensitivity of the HPV test resulted in first round detection of some lesions that would have only been detected on subsequent rounds of Pap testing.

Along with the increased detection ability, there is also an increased referral rate to colposcopy for diagnostic evaluation and need for various degrees of intensified monitoring amongst women with a positive HPV test. The frequency of referral and intensified monitoring varied substantially depending on selected triage strategies.

The net balance between the improved detection rate of precursor lesions and the potential downsides of higher referral rates to diagnostic follow-up and need for additional monitoring must be considered when determining whether the evidence is sufficient to move forward on HPV testing as a primary screening option. There are also other planning considerations related to quality control, laboratory practices, availability of established follow-up algorithms and appropriate colposcopy quality standards and guidelines that will need to be addressed in jurisdictions that implement HPV testing.

The introduction of HPV testing should ideally be carried out within a programmatic setting to facilitate ongoing evaluation of screening, follow-up and outcomes. The evaluation is critical to provide answers to questions that remain unanswered by the current published evidence, particularly in the Canadian context. Regardless of the screening test, one of the biggest challenges in cervical screening is the achievement of participation targets. Screening recruitment strategies will remain most important to maximize the impact of screening.

## Purpose

With the discovery of HPV as the causative agent of cervical cancer and the availability of HPV tests to detect the presence of the virus, there has been growing interest in the role of HPV testing in cervical cancer screening.

Several randomized trials comparing HPV to Pap testing for primary screening have been carried out internationally.

The purpose of this document is to provide a summary of the key trials that have published results or are currently underway. This document will also explore potential impacts of HPV testing on screening, follow-up practices and future planning for these services. Only the trials that evaluate the use of HPV testing for primary screening have been considered. HPV testing has been proposed for other purposes, including the follow-up (or triage) of abnormal Pap test (cervical cytology) results and monitoring of patients treated for precancerous lesions. The panel did not address these uses of HPV testing.

The target audience is intended to include clinicians, researchers, policy-makers and other stakeholders in health care who are involved in the planning of cancer screening services for their jurisdictions.

This document is not intended to provide definitive answers or clinical and/or policy recommendations. The views expressed herein represent the views of the HPV Testing for Cervical Cancer Screening Expert Panel.

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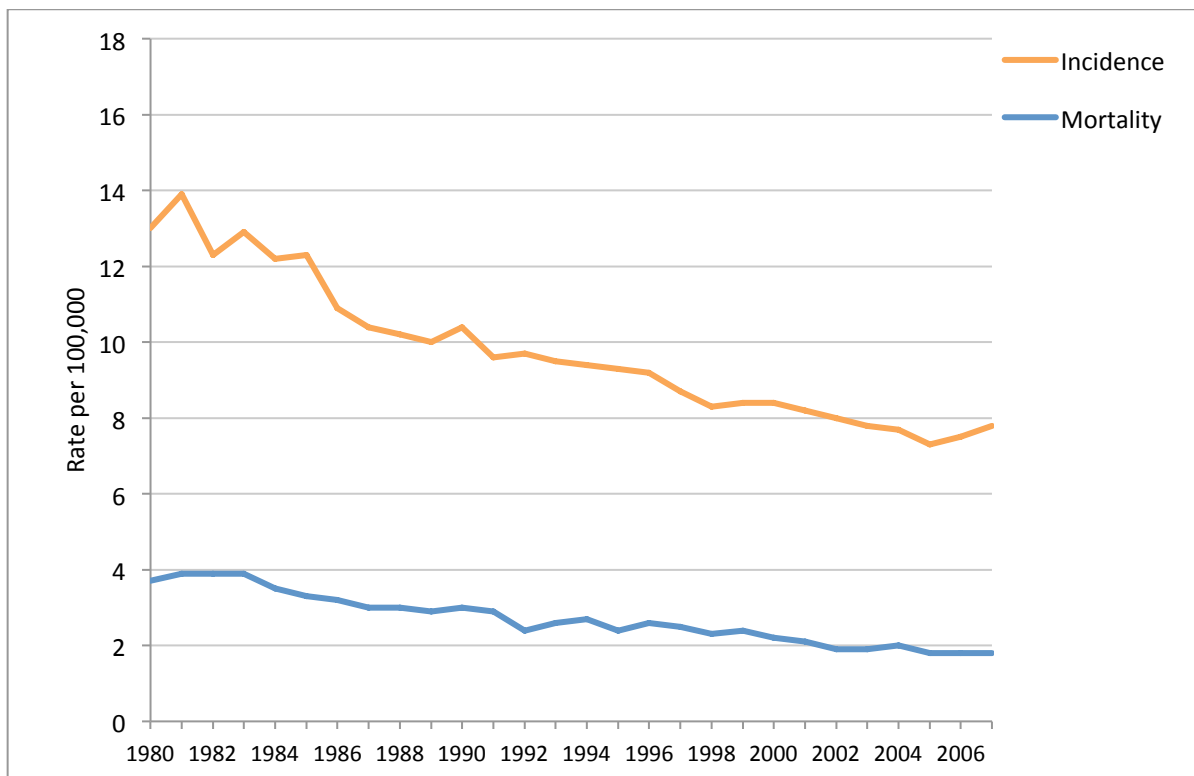
Canadian Partnership Against Cancer, HPV Testing for Cervical Cancer Screening Expert Panel. HPV Testing for Cervical Cancer Screening Expert Panel: Summary of Evidence. Toronto: Canadian Partnership Against Cancer; 2012.

## Background

### Human Papilloma Virus and Cervical Cancer

In Canada, cervical cancer screening has been associated with a steady reduction in cervical cancer incidence and mortality over the past few decades. The incidence rate was estimated at approximately 20 per 100,000 and the mortality rate around 7 per 100,000 in 1970.<sup>1</sup> More recent data available from the Canadian Cancer Registry (CCR) show a continuing decline since 1980 to an incidence rate of 7 per 100,000 in 2007 and a mortality rate of 2 per 100,000 for the same year (rates standardized to the 1991 Canadian population) (Figure 1).

**Figure 1:** Age-standardized mortality and incidence of invasive cervical cancer in Canada<sup>2,3</sup>



The role of human papillomaviruses (HPV) in the pathogenesis of malignant tumours has now been well described.<sup>4,5</sup> HPV is recognized unequivocally as the causal factor for cervical cancer and pre-cancers as well as several other anogenital and oral cancers.<sup>6-9</sup> The identification of a requisite infectious causative agent has led to the development of novel prevention strategies for cervical cancer, including HPV vaccination and HPV testing for cervical cancer screening. Our improved understanding of the natural history of HPV infections and cervical lesions offers an opportunity to review current practices in cervical cancer screening.

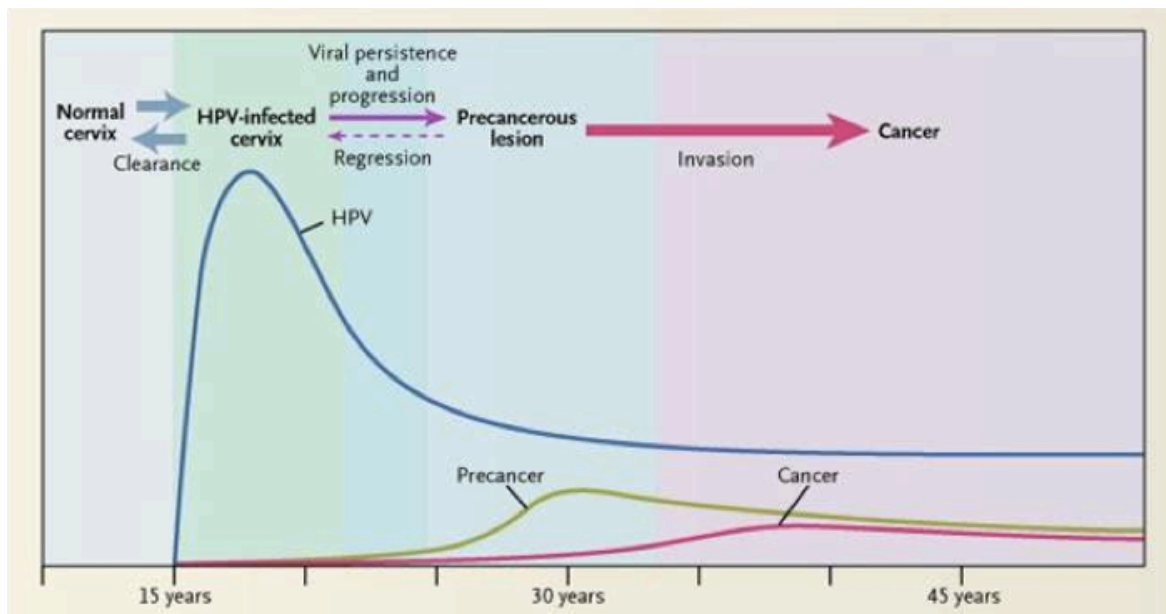
Over 100 types of HPV have been catalogued.<sup>10</sup> These are classified according to their oncogenic potential for cervical cancer into high (HR) or low (LR) oncogenic risk. There are about 40 HPV types that infect the mucosal areas of the body, such as the epithelial lining of the anogenital tract, of which 12 genotypes are officially considered as carcinogenic while 13 others are 'probable' or 'possible' carcinogenic types.<sup>9</sup> The 2009 classification published by the World Health Organization (WHO) International Agency for Research on Cancer referred to HR-HPVs as being types: 16; 18; 31; 33; 35; 39; 45; 51; 52; 55; 56; 58; and probably 68.<sup>9</sup>

It is estimated that over 80% of sexually active women will be infected by a genital HPV at some point in their lifetime, with most of them in the years following initiation of sexual activity.<sup>11</sup> High incidence and prevalence are found in both females and males soon after the onset of sexual activity, but the vast majority of genital HPV infections are asymptomatic and clear within 1-2 years.<sup>12-14</sup> Carcinogenesis of cervical cancer requires not only the acquisition of HR-HPV but also a persistent HR-HPV infection, with transient infections being mostly inconsequential.<sup>15-18</sup> Not all HR-HPV contribute equally to cervical cancer incidence: HPV-16 and HPV-18 alone are responsible for approximately 55-60% and 10-15% respectively, of cervical cancer cases worldwide.<sup>19-21</sup>

Cervical neoplastic development is a slow process of disruption of the normal maturation of the cervical epithelium.<sup>22</sup> The neoplastic development may eventually extend to the full thickness of the cervical epithelium and go through the basement membrane to become invasive. Squamous cervical precancerous lesions (cervical intra-epithelial lesions or CIN) are divided into three categories. CIN1, the less severe category, often regresses without treatment and is not considered a relevant endpoint in epidemiologic or clinical studies related to cervical cancer screening.<sup>23</sup> CIN2 and CIN3 (often referred to as CIN2/3, or high grade CIN (HG-CIN)), make up a more severe category. They carry a higher risk of progression to invasive cancer (up to 30% for CIN3) and their treatment is recommended (although watchful waiting has been suggested by some for CIN2 in young women).<sup>23,24</sup> CIN2 and CIN3 are used as a surrogate endpoint to cervical cancer in clinical studies since it would be unethical to observe women with HG-CIN until they progress to have invasive cancer.



**Figure 2:** The natural history of HPV infection and cervical cancer (adapted)<sup>25</sup>



**Notes** (adapted from original article):

- The peak prevalence of transient infections with carcinogenic types of HPV (blue line) occurs among women during their teens and 20s, after the initiation of sexual activity.
- The peak prevalence of cervical precancerous conditions occurs approximately 10 years later (green line) and the peak prevalence of invasive cancers at 40 to 50 years of age (red line). (The peaks of the curves are not drawn to scale.)

# Screening and Diagnosis of Cervical Cancer

## Principles of Screening

The WHO principles of screening were developed in 1968. They addressed factors related to the disease or condition including the test, the availability of follow-up and treatment for abnormal test results and the diagnosed disease.<sup>26</sup>

Condition:

- The condition should be an important health problem.
- There should be a recognizable latent or early symptomatic stage.
- The natural history of the condition, including the development from latent to declared disease, should be adequately understood.

Screening test:

- There should be an appropriate test or examination.
- The test should be acceptable to the population.

Treatment:

- There should be an effective treatment for patients with recognized disease.
- There should be an agreed policy on whom to treat as patients.
- Facilities for diagnosis and treatment should be available.
- The cost of case-findings (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-findings should be a continuing process and not a 'once and for all' project.

Screening is intended to detect disease at an earlier, more treatable stage than if the disease were to present clinically by means of symptoms. Screening is a process. It requires the use of tests to detect disease to permit timely intervention. For a screening program to demonstrate effectiveness at a population level, the screening tests must be applied systematically on a large scale. A screening test is not intended to be diagnostic. Screening procedures are generally easier to perform and cheaper than diagnostic procedures. They are used to distinguish between those apparently unaffected from those who may have a disease. The test results require confirmation through definitive diagnostic tests, followed by effective treatment of confirmed cases, to reduce the risk of mortality from the disease.

There should be evidence that screening reduces mortality from cancer before being implemented. This evidence is already available for cervical cancer screening, as was detailed in the background section of this document. Given the gains that have already occurred, and the complexity of reducing mortality further, it is unlikely that in Canada any change to the screening test e.g. from Pap test to HPV test will drastically reduce mortality further. However, reduction in incidence and increased efficiency may be worthwhile goals.

## Pap Test

Prevention of cervical cancer is possible through screening as progression from infection to cancer is usually slow, in the order of years, even decades.<sup>24</sup> Traditionally, screening has relied on cytological examination (Pap test) of cervical samples to identify the typical cellular changes of CIN and cancer.

A cervical sample is obtained by scraping the cervix with a spatula and/or a brush-like device. For a “conventional” Pap test, the cervical specimen is then smeared on a glass slide. A cellular fixative is applied. At the cytology laboratory, a cytotechnician creates a stain and looks through a microscope for precancerous or cancerous cellular changes. A newer technology, called “liquid-based cytology” or LBC has emerged for slide preparation. The cervical sample is taken in the same way as for a conventional Pap, but the specimen is transferred in a liquid medium. In the laboratory, the liquid specimen is processed to remove unwanted cells and debris and a thin layer of liquid (containing the cervical cells) is transferred to a glass slide. Coloration and slide reading are then performed.

Cytology-based (Pap test) screening can be credited with curbing incidence and mortality from cervical cancer. Given this success, there is no question that cervical cancer screening works. Although those statistics are encouraging, over 1,300 Canadian women have been diagnosed with cervical cancer in 2011 and 350 have died from the disease.<sup>27</sup> Given the understanding of the natural history of the disease, it appears theoretically possible to eradicate cervical cancer. Meta-analysis of cervical cancer screening failures has underlined the fact that absence of screening or infrequent screening account for the majority of cases of cervical cancer.<sup>28</sup> The Canadian Partnership Against Cancer has already led efforts to foster excellence in strategies to maximize screening attendance.<sup>29</sup> The second most frequent failure of cervical cancer screening is related to false negative screening test.<sup>28</sup> The low sensitivity of the Pap test, as low as 55% in some Canadian settings,<sup>30</sup> and its poor reproducibility are key problems.<sup>31</sup>

Given the above-mentioned limitations of the Pap test, there has been much interest in identifying screening tests that could have better characteristics. In resource-rich setting, the most promising alternative is HPV testing.

## HPV Test

Since there is currently no serological assay clinically useful for the diagnosis of HPV infection and since HPV cannot be isolated in cell culture, the diagnosis of HPV infection relies on the detection of HPV nucleic acids in clinical specimens.<sup>32</sup> Three analytical strategies have been developed for the detection of HPV DNA or RNA in cervical specimens. In the first strategy, HPV generic tests use a cocktail of reagents that detects the presence of high-risk HPV type DNA as a group.<sup>33</sup> In the second strategy, each HPV genotype is detected individually.<sup>33</sup> The third strategy, designated partial genotyping, combines the two latter approaches by detecting some HPV genotypes individually (often genotypes 16 and 18) while several high-risk genotypes are detected as a group.<sup>34,35</sup>

For each of these analytical strategies, three assay formats can be utilized for the detection of HPV nucleic acids in biological fluids: signal amplification assays, nucleic acid amplification techniques (NAAT) and probe amplification or modification assays.<sup>33</sup> In signal amplification assays, processed sample HPV DNA is reacted with single-stranded full-length RNA probes followed by signal amplification of the reaction. In NAAT assays, the initial amount of HPV nucleic acids contained in samples is amplified and the products of this amplification are detected with nucleic acid probes. Probe modification assays are based on the accumulation of modified HPV probes when the probes react with targeted HPV types. The analytical sensitivity of NAAT or probe modification assays can be greater than signal amplification assays but ultra-sensitive assays do not imply necessarily a better performance for clinical use if the added sensitivity is offset by poor specificity.<sup>36</sup>

## HPV Generic Assays

The following two generic assays are currently licensed in Canada for HPV diagnosis.

**The Hybrid Capture system (HC2)** is a signal amplification assay manufactured by Qiagen Inc., where processed sample DNA is detected with a mixture of single-stranded full-length RNA probes against 13 high-risk types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). HC2 is reproducible with an intra-assay coefficient of variation below 5%.<sup>37</sup> HC2 does not control for the quality of sample by measuring cell DNA content.<sup>35</sup> A good agreement between HC2 and NAAT has been reported in several studies.<sup>38,39</sup> There is some cross-reactivity between the high-risk probe cocktail and HPV types not included in the probe mix such as types 6, 34, 42, 53, 54, 62, 66, 67, 70, 73, and 82; some of which are low-risk types.<sup>33,34,39,40</sup> This cross-reactivity increases the overall sensitivity of the assay but contributes to lowering its specificity. HC2-positive samples containing only low-risk genotypes are usually weakly reactive.<sup>34,40</sup> Since HC2 is the most evaluated assay and since the clinical sensitivity of HC2 to detect CIN2 or CIN3 in various studies was above 90%, HC2 was considered by an international panel of experts as the gold standard for accepting novel generic HPV tests.<sup>41</sup> The value of HC2 has been established for the triage of women with atypical cells of undetermined significance (ASC-US) Pap tests and for cervical cancer screening.<sup>34,35,42-44</sup>

**The Amplicor HPV test**, a NAAT assay manufactured by Roche Diagnostics, is based on the polymerase chain reaction (PCR) amplification of HPV DNA from the same 13 high-risk genotypes that are detected by HC2.<sup>35</sup>  $\beta$ -globin is co-amplified with HPV to assess the integrity of sample. An agreement of 97.5% was reached in one study between Amplicor HPV and Inno-LIPA, a full-spectrum genotyping assay.<sup>45</sup> Several groups have reported levels of agreement within 78% to 89% Amplicor HPV test and HC2 for high-risk HPV detection.<sup>46-49</sup> A higher cut-off for positivity might increase specificity without affecting sensitivity.<sup>48-50</sup> Cross-reactivity of Amplicor HPV was demonstrated with low-risk type 6, 11, 54, 70, 61, 67, 72, 73 and with high-risk genotypes not included in the probe cocktail such as types 53, 66 and 82.<sup>40,49</sup> Reactivity with low-risk types was often weak.<sup>40</sup> The clinical sensitivity of Amplicor HPV for the detection of CIN2 or CIN3 in women with ASC-US of Amplicor HPV is similar to that of HC2 but the specificity is lower.<sup>48,49</sup> The clinical sensitivity and specificity for detection of CIN2 or CIN3 in women with ASC-US in a study conducted in Canada of Amplicor HPV and HC2 were 89.7% (95% CI 72.8-97.2) and 62.5% (95% CI 57.5-52.4), and 93.1% (95% CI 77.0-99.2) and 72.2% (95% CI 67.4-76.5), respectively.<sup>49</sup> The value of Amplicor HPV has not been established for primary cervical cancer screening.

The reader should be aware that this field is evolving rapidly. The APTIMA HPV (Gen-Probe Inc.) assay, a genomic amplification test, is currently under evaluation by Health Canada. APTIMA HPV detects the presence of 15 high-risk genotypes by selective amplification of HPV messenger RNA, using a transcription mediated amplification protocol.<sup>51</sup>

## Partial Genotyping Assays

Three partial genotyping assays are currently licensed in Canada for HPV diagnosis. They allow for the detection of several high-risk HPV genotypes as a group (generic test), but also detect the presence of HPV16 or HPV18 DNA separately from the high-risk group.

**The Cobas 4800 HPV test** is a NAAT assay manufactured by Roche Diagnostics. The assay is based on the TaqMan technology in which 14 genotypes are amplified and detected: HPV16 and HPV18 are detected separately, and 12 high-risk genotypes (HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) are detected as a group.<sup>35</sup> One report found that cross-reactivity with low-risk genotypes was more frequently encountered with HC2 than the Cobas 4800 HPV test.<sup>52</sup> The assay integrates an automated platform for sample processing with nucleic acid extraction, HPV DNA amplification and HPV detection. There are only three publications on the value of the Cobas 4800 HPV test. One study reported an agreement between the Cobas 4800 HPV test and the Linear array, a PCR-based full spectrum genotyping assay, of 94.7%.<sup>53</sup> The clinical sensitivity and specificity for detection of CIN2 or CIN3 in women with ASC-US of the Cobas 4800

HPV test was reported to be similar to that of HC2 in the ATHENA study conducted in the US.<sup>54</sup> In ATHENA, the sensitivity and specificity of Cobas 4800 HPV on samples from 1,578 women were respectively 90% (95% CI 81.5 to 94.8) and 70.5% (95% CI 68.1 to 72.7).

In another study, the Cobas 4800 HPV test demonstrated comparable analytical performance to HC2 for the detection of HR HPV infection.<sup>52</sup> In an evaluation in press conducted in Canada on 392 women with ASC-US, the clinical sensitivity and specificity to detect CIN2+ was 89.7 % (95 % CI 72.8 - 97.2) and 66.7 % (95% CI 61.7 - 71.3), 93.1 % (95 % CI 77.0 - 99.2) and 72.2 % (95 % CI 67.4 - 76.5) with Cobas 4800 HPV and HC2 respectively.<sup>55</sup> The Cobas 4800 HPV test was also shown to be more sensitive than liquid-based cytology for detection of CIN2 or CIN3 for primary screening of cervical cancer, but was not compared to HC2.<sup>56</sup> In a recent report of the ATHENA study, 4,219 women with positive results for HR-HPV plus 886 HR-HPV-negative women were referred for colposcopy and biopsy.<sup>57</sup> The estimated absolute risk of CIN2+ in HPV-16+ and/or HPV-18+ women was 11.4% (95% CI, 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) in HR-HPV+ and 0.8% (95% CI, 0.3%- 1.5%) in HR-HPV-negative women.

**The Cervista HR HPV and Cervista 16/18 HPV tests**, manufactured by Hologic Inc., are probe amplification or modification assays.<sup>35</sup> The assays are based on the the Invader technology, initially developed by Third Wave Technologies.<sup>58,59</sup> Cervista HR HPV detects 14 HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) using three separate oligonucleotide probe sets. The results are reported as positive or negative for each probe set. A histone cellular control is included to assess sample integrity. The assay did not show cross-reactivity with low-risk genotypes.<sup>35</sup> Various versions of Cervista HR HPV show 82% to 95% agreement with HC2.<sup>35,58,60-62</sup> The sensitivity of Cervista HR HPV to detect CIN2 or CIN3 among women with ASC-US cytology was 92.8% in one study.<sup>63</sup> In a study conducted on 8,556 women between the ages of 25 and 59 years, the sensitivity for detecting CIN3 with HC2 and Cervista HR HPV was 97.9% and 95.1% respectively, a difference that was not statistically significant.<sup>64</sup> Concerns have been raised on a higher rate of positivity for high-risk HPV DNA with Cervista HR HPV compared to HC2 in women without CIN.<sup>34,65</sup> Recent reports do not support a higher detection rate of HR HPV DNA with Cervista HR HPV compared to HC2 in women without lesion.<sup>60,64</sup> The Cervista 16/18 HPV test detects the presence of these genotypes separately in samples positive with the Cervista HR HPV test.<sup>35</sup> Large-scale studies on the use of this partial genotyping assay in screening are still needed.

**The Abbott Realtime High Risk HPV test (Abbott Molecular)**, based on genomic amplification with real time PCR, was also currently under review by Health Canada when this document was written, but is now accepted for clinical use by Health Canada.<sup>35,66</sup> The assay is based on the TaqMan technology in which 14 genotypes are amplified and detected: HPV16 and HPV18 are detected separately, and 12 high-risk genotypes (HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) are detected as a group.<sup>35,66-68</sup> The assay integrates an automated platform for sample processing with nucleic acid extraction, HPV DNA amplification and HPV detection. In one study performed in Europe, in a screening setting, the sensitivity of HC2 and Abbott RealTime HR HPV test to detect CIN2+ lesions was 97.6% and 96.4% respectively, while the specificity obtained with both assays was similar.<sup>67</sup> The overall agreement in that study between these two assays was 96.5%. The intralaboratory reproducibility of the RealTime HR HPV assay by Abbott was also excellent at 98.5%. In another study, the sensitivity and specificity of the Abbott RealTime HR HPV test for detection of CIN2+ was 100% and 93.3%, respectively; results were comparable to those obtained with HC2.<sup>68</sup> The performance of the Abbott RealTime HR HPV assay to detect the presence of CIN2+ or CIN3 was also similar to that of HC2 in a population of women referred to colposcopy because of an abnormal smear.<sup>69</sup> Agreement between the Abbott RealTime HR HPV test and HC2 for the detection of HR HPV was high at  $\pm 94\%$  in stored samples from women with cervical cancer or CIN3.<sup>70</sup> More studies are needed to assess the utility of using partial genotyping in screening programs.

## Full Genotyping Assays

Only one full-spectrum genotyping assay is currently licensed in Canada for HPV diagnosis. The assay allows for the detection and typing of 36 genital genotypes including the high-risk genotypes detected by the assays above.

**The Linear array** is a NAAT assay manufactured by Roche Diagnostics. The assay is based on the consensus amplification with PCR of 36 HPV genotypes: HPV6, 11, 16, 18, 26, 31, 33, 34 (formerly known as type 64), 35, 39, 40, 42, 44 (formerly known as type 55), 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82 (including subtype IS39), 83, 84, and 89 (formerly known as CP6108) that are individually detected with type-specific probes fixed on an array.<sup>34,35,71</sup> Detection of high-risk HPV types with the Linear array had a sensitivity of 92.3% for detecting CIN3 and cancer in women with ASC-US in one study.<sup>72</sup> The risk for progressing to CIN3 and cancer was the greatest for women positive with the Linear array for HPV-16.<sup>72</sup> For the time being, clinical guidelines do not include full spectrum HPV genotyping for patient management. HPV typing is useful as a research tool to evaluate type-specific HPV prevalence and assess the geographic heterogeneity in HPV genotype distribution, assess the type-specific concordance between partners, monitor persistent infection in consecutive HPV-positive samples, monitor HPV infection in clinical trials, evaluate cross-reactivity in generic assays, and monitor the duration of protection in vaccinated populations and the potential shift in type distribution.<sup>37</sup> The Linear array is for the time being a research tool useful for HPV genotyping.

## Diagnostic Evaluation after Screening

Women with abnormal cervical cancer screening tests results undergo diagnostic evaluation, which consists of examining the cervix through a magnifying lens with proper illumination (colposcopy) after the application of acetic acid and/or iodine solution(s). Specific patterns of epithelium change can be identified as possible CIN. Histological examination of colposcopy-directed biopsies of such lesions confirms the diagnosis.

# Randomized Controlled Trials of HPV Screening

## Key Aspect of Valid HPV Testing Screening Studies

Before summarizing the actual studies, some factors that may impact the validity of such studies are described.

**Population:** Because screening targets a healthy, asymptomatic population, studies evaluating a new screening test should recruit from the general population. Bias may be introduced when recruitment for a cervical cancer screening study takes place in a colposcopy clinic, essentially focusing on women at high-risk and most of whom already have abnormal screening test results. HPV infections and related diseases tend to run a more aggressive course in immuno-suppressed individuals. For this reason, results from cervical cancer screening studies conducted in certain regions of the world with high rates of HIV/AIDS may not be easily translated in our own setting. Moreover, the spectrum of disease identified by screening will be completely different in settings where women have never undergone screening (over representation of later stage disease) compared to settings where women have undergone multiple rounds of screening in their lifetime (identification of mostly pre-invasive disease). As such, when looking for evidence to change screening strategies in settings where screening is already widespread (cervical cancer screening in Canada) it is preferable to focus on studies including a population of women who have previously undergone screening.

**Interventions and group allocation:** Given that Pap testing is currently the standard in Canada, relevant studies should compare HPV testing to Pap testing. The cut-off for referral to diagnostic testing should be clearly stated. The screening tests compared should be suitable for clinical use. Randomization should determine group allocation.

**Outcome definition/diagnostic procedure (gold standard):** As summarized in the background section the natural history of pre-cancers and cancers of the cervix has been well characterized. CIN3 carries a 30% risk of progression to invasive disease over 30 years.<sup>24</sup> Consequently, cervical cancer screening activities have focused primarily on the identification of pre-invasive disease to allow for the treatment of such lesions in order to prevent cancer. It is thus very difficult (not to mention unethical) to have cancer as the primary outcome in cervical cancer screening studies.

Cervical intraepithelial neoplasia grade 1 (CIN1) is very frequent, especially in younger women, and most often regresses without treatment. It is not considered a relevant endpoint in cervical cancer screening studies. The endpoint of choice includes a combination of biopsy-proven CIN2, CIN3/CIS and cancer. The validity of CIN2 as an endpoint has been put into question mainly because of the poor reproducibility of this diagnosis, but also because it probably regresses spontaneously more frequently than previously thought.<sup>73,74</sup> Pathologists in many settings do not report CIN2 and CIN3/CIS separately since the recommended management is identical. For research purposes, "CIN3 and worse lesion" should be reported separately from "CIN2 and worse lesions", when this diagnosis is available. However, program planners should be aware that in Canada the treatment threshold remains CIN2.

## Summary of Trials

### HPV Testing in Primary Screening of Cervical Cancer

Key trials that meet the criteria detailed in the previous section are summarized. These criteria include the following:

- Targeted population of women with previous access to screening
- Compared Pap testing to HPV testing (using an HPV test suitable for clinical practice)
- Randomized participants
- Biopsy-proven “CIN2 or worse” or “CIN3 or worse” as their disease definition

We have identified seven large, randomized studies of which several were imbedded in population-based cervical cancer screening programs. Tables 1-4 summarize key methodological aspects and main findings. Six of those trials took place within organized programs in Europe (Swedescreen,<sup>75,76</sup> POBASCAM,<sup>77-79</sup> ARTISTIC,<sup>80-82</sup> NTCC,<sup>83-86</sup> FPHT,<sup>87-91</sup>) and Canada (FOCAL<sup>92</sup>), and one trial targeted a population where opportunistic screening occurs (CCCaST<sup>30,44</sup>). The trials were initiated between 1997 and 2007, and accrued between 10,000 and over 70,000 women (Table 1). The Italian trial (NTCC) accrued women in two phases that actually represent two different trials (different screening strategies were compared). Phase 1 and Phase 2 results are thus presented separately in all tables. In both phases NTCC included women as young as 25 years of age. Most results were different for women below and over 35 years, presented separately in publications. We have thus decided to separate findings for the NTCC according to age group.

**Table 1:** Identification of randomized controlled trials of HPV testing compared to Pap testing in primary screening in industrialized countries

Study Name	Country	Recruitment period	Sample Size	Age	Main Objective
Swedescreen <sup>76</sup>	Sweden	1997-2000	12,527	32-38	Compare incidence of CIN2 and CIN3 found AFTER the enrolment screen
POBASCAM <sup>78,79</sup>	Netherlands	1999-2002	44,938	29-61	Evaluate if adding HPV testing to Pap testing improves effectiveness/ efficiency of cervical cancer screening: assess whether HPV testing in the 1 <sup>st</sup> screen decreases CIN3+ at 2 <sup>nd</sup> screen
ARTISTIC <sup>80</sup>	U.K.	2001-2003	24,510	20-64	Evaluate effectiveness of HPV testing/ detection rate of CIN3+ at the second screening round
CCCaST <sup>30</sup>	Canada	2002-2005	10,154	30-69	Compare absolute sensitivities of Pap and HPV testing
NTCC Phase 1: 34 and younger <sup>85</sup>	Italy	2002-2003	12,410	20-34	Compare effectiveness, acceptability, and cost of HPV testing and cytology
NTCC Phase 1: 35 and older <sup>85</sup>			33,364	35-60	
NTCC Phase 2: 34 and younger <sup>85</sup>		2003-2004	13,725	20-34	



Study Name	Country	Recruitment period	Sample Size	Age	Main Objective
NTCC Phase 2: 35 and older <sup>85</sup>			35,471	35-60	
FPHT <sup>87,90,91</sup>	Finland	2003-2008 (planned) 2003-2005 (focus of publications)	493,200* 71,337	25-65	Assess screening effectiveness/validity/performance of HPV testing with cytology triage
FOCAL <sup>92</sup>	Canada	2007-2012	33,000**	25-65	Compare efficacy of HPV testing with cytology triage to efficacy of cytology with HPV of ASC-US

\* Projected number of women randomized to either conventional cytology or HPV testing, which would actually attend screening.<sup>87</sup> Estimates in following tables are based on interim analyses and as such sample sizes are much smaller.

\*\*Target sample size

The performance of a screening test is directly dependent on the threshold used for referral to diagnostic testing. Hence, it is essential to report the algorithms that were used. The definition of abnormality (outcome) is equally essential and reported in Table 2. Each trial included a control group of cytology testing. The control group relied on liquid-based cytology for two trials (ARTISITC and FOCAL) and conventional cytology for the other five trials. Only FOCAL used HPV triage of ASC-US results in the control arm. CCCaST referred all women with an ASC-US result or worse to colposcopy. In the other trials, two or three abnormal smears were necessary if the initial result was ASC-US or LSIL (low-grade squamous intra-epithelial lesion). It should be noted that most European programs do not use the Bethesda terminology. Though the Class I abnormality category is translated to ASC-US for simplicity, it, in fact, included some smears that would be labelled normal by Bethesda (benign reactive cellular changes).<sup>93</sup>

Each trial included some type of HPV testing in the intervention arm. GP5/GP6 PCR was used in Swedescreen and POBASCAM while Hybrid Capture 2 was used in the other trials. The performance of those two tests is thought to be similar in the context of clinical use for screening.<sup>36</sup> Four trials included cytology at the same time as HPV testing (co-testing) in the intervention arm, and assessed a screening strategy based on co-testing as their primary analysis (Swedescreen, POBASCAM, ARTISTIC, NTCC phase 1). Of the four, three referred women with normal cytology only after two or three positive HPV tests, up to 24 months apart (Swedescreen, POBASCAM, ARTISTIC). Two trials assessed HPV testing as a stand-alone test (CCCaST, NTCC Phase 2). Two trials assessed the performance of a screening strategy based on HPV testing done as a primary test, with cytology done for women with a positive HPV test, initially referring only women with abnormal cytology (FPHT, FOCAL).

**Table 2:** Study interventions and outcomes

Study acronym (reference to table data)	Control intervention	Control arm threshold for referral to colposcopy <sup>^</sup>	Study intervention	Intervention arm threshold for referral to colposcopy	Cervical lesion definition*
Swedescreen <sup>76</sup>	Conventional cytology (CC)	ASC-US in Stockholm; HSIL/Repeat ASC-US or LSIL (2) in other centers <sup>~</sup>	CC and GP5/GP6 PCR	Same as control arm; In case of normal CC but HC2+, 2 HPV + tests for same HPV type, 12 months apart	CIN2+ CIN3+
POBASCAM <sup>77,78</sup>	CC	HSIL/Repeat ASC-US or LSIL (2)	CC and GP5/GP6 PCR	HSIL; Repeat HPV + tests (2 or 3); Repeat ASC-US/ LSIL (2 or 3) <sup>†</sup>	CIN3+
ARTISTIC <sup>80</sup>	Liquid-based cytology (LBC)	HSIL Repeat LSIL 2) Repeat ASC-US (3)	LBC and HC2 <sup>‡</sup>	Same as control arm; In case of normal LBC but HC2+, 2 <sup>nd</sup> HC2 If again HC2+, women could choose between colposcopy or a 3 <sup>rd</sup> HC2 12 months later	CIN3+
CCCaST <sup>44</sup>	CC	ASC-US	HC2	1pg/ml	CIN2+
NTCC Phase 1: 34 and younger <sup>85</sup>	CC	ASC-US* in 7 centers LSIL/repeat ASC-US (2) in 2 centers	LBC and HC2	ASC-US If normal LBC and HC2+, repeat LBC and HC2 at 12 months, colposcopy if either positive (2)	CIN2+
NTCC Phase 1: 35 and older <sup>85</sup>			HC2	ASC-US or HC2+	
NTCC Phase 2 <sup>85</sup>			HC2	1pg/ml	
FPHT <sup>89</sup>	CC	LSIL/repeat ASC-US (2)	HC2/ CC triage of HC2+	HC2+ AND LSIL /Repeat ASC-US; If normal CC, 3 HC2+ tests each 12 months apart	CIN1+ CIN2+ CIN3+
FOCAL <sup>92</sup>	LBC/HC2 triage of ASC-US	LSIL ASC-US/HPV+	HC2/LBC triage of HC2+	HC2+ AND ASC-US or worse If LBC normal, 3 HC2+ at 0.6 and 12 months	CIN3+

<sup>^</sup> See Appendix for summary of Bethesda 2001 cytological terminology abbreviations

\* Main outcome(s) of interest, as reported in publication(s)

<sup>~</sup> Number in parenthesis refers to number of abnormal tests required for referral to colposcopy

<sup>†</sup> Summarized referral algorithm for POBASCAM.

<sup>‡</sup> HC2: Hybrid Capture 2 test, threshold of 1pg/ml used in included trials

\* Bethesda 1991 terminology

## Main Study Results

Despite different screening and referral protocols, and different outcome definitions, all trials except one showed very similar findings from the initial screening round: HPV-based strategies pick up more cancer precursors (CIN2/CIN3 or CIN3) compared to Pap-based strategies (Table 3).

**Table 3:** Main study results (initial round of screening)

Study	Main results	Immediate colposcopy referrals	Intensified follow-up*
Swedescreen <sup>76</sup>	DR <sup>^</sup> CIN2+ intervention arm: 1.82% DR CIN2+ in control arm: 1.21% RDR CIN2+: 1.51 (1.13-2.02) RDR CIN3+: 1.31 (0.92-1.87)	-	-
POBASCAM <sup>79</sup>	DR CIN3+ intervention arm: 0.86% DR CIN3+ in control arm: 0.75% RDR CIN3+: 1.15 (0.92-1.43) RDR CIN2+: 1.25 (1.05-1.50)	Intervention arm: 0.83% Control arm: 0.89%	Intervention arm: 6.20% Control arm: 2.62%
ARTISTIC <sup>81</sup>	DR CIN3+ intervention arm: 1.27% DR CIN3+ in control arm: 1.31% RDR CIN3+: 0.97 (0.75-1.25)	Intervention arm: 1.95% Control arm: 1.71%	Intervention arm: 19.91 % Control arm: 11.1%
CCCaST <sup>30</sup>	Sensitivity of HPV testing: 94.6% (84.2%-100%) Sensitivity of Pap testing: 55.4% (33.6%-77.2%)	Intervention arm: 6.1% Control arm: 2.9%	Intervention arm: 0 % Control arm: 0%
NTCC Phase 1: 34 and younger <sup>85,86</sup>	DR CIN2+ ** in intervention arm: 1.30% DR CIN2+ in control arm: 0.64% RDR CIN2+: 2.00 (1.38-3.01)	Intervention arm: 8.76% Control arm: 3.96%	Intervention arm: 8.50% Control arm: 0.58%
NTCC Phase 1: 35 and older <sup>84,85</sup>	DR CIN2+ intervention arm: 0.64% DR CIN2+ in control arm: 0.33% RDR: 1.94 (1.40-2.68)	Intervention arm: 10.34% Control arm: 2.92%	Intervention arm: 0% Control arm: 0.64%
NTCC Phase 2: 34 and younger <sup>83,85</sup>	DR CIN2+ intervention arm: 1.66% DR CIN2+ in control arm: 0.37% RDR CIN2+: 4.50 (2.92-6.93)	Intervention arm: 13.07% Control arm: 3.98%	0%
NTCC Phase 2: 35 and older <sup>83,85</sup>	DR CIN2+ intervention arm: 0.55% DR CIN2+ in control arm: 0.26% RDR CIN2+: 2.13 (1.50-3.03)	Intervention arm: 5.80% Control arm: 3.13%	0%
FPHT <sup>90,91</sup>	RDR of CIN3+: 1.77 (1.16-2.74) RDR of cancer: 1.98 (0.52-9.38)	Intervention arm: 1.18% Control arm: 1.18%	Intervention arm: 6.40% Control arm: 5.48%

\*Not including women needing intensified follow-up after initial colposcopy

<sup>^</sup>RDR: relative detection ratio as labeled in articles. RDR relates to ratio of cumulative detection of outcome: cumulative detection of outcome in intervention group/ cumulative detection of outcome in control group

\*\*CIN2+ refers to CIN2-CIN3-AIS for data of the NTCC<sup>86</sup>

The only trial that found a relative detection rate (RDR) below 1 at the initial round of screening was the UK-based ARTISTIC trial. It should be noted that LBC had been introduced in the UK shortly before the start of the ARTISTIC trial.<sup>80</sup> This required an adjustment of cytological readings, which translated in unexpectedly high rates of abnormal tests in the control arm (12.8%).<sup>80,94,95</sup> The authors also had difficulty explaining the drop in CIN3+ between rounds 1 and 2 (from 1.27-1.31% to 0.25-0.47%), putting into question the validity of the endpoint diagnostic accuracy.<sup>81,94</sup> Finally most women in the intervention arm who were HPV positive but Pap normal were never followed up,<sup>95</sup> making the screening strategies in the two arms very similar.

## Other Results from the Initial Screening Round

From the first screening round of the trials, we also learned that HPV-based strategies increased referrals to colposcopy and the proportion of women in the “intensified follow-up” category (Table 3). Using triage tests and/or requiring repeat abnormalities to warrant referral decreased the number of immediate referrals to colposcopy. However this is at the cost of increasing the number of women who will be put in an “intermediate category”, often referred to as “intensified screening”. These women do not have entirely normal screening tests and thus cannot be placed back to regular screening. However, they are not deemed sufficiently at risk to be investigated immediately by colposcopy. If the majority of these women quickly revert to normal and can then be placed back to regular screening, the strategy can be worthwhile as it would limit the number of colposcopies. If, however, most of these women ultimately require colposcopy, then the strategy has increased the cost and burden on the health care system compared to immediate colposcopy. Unfortunately the trials provide very little data on the number of women in the intensified screening category (there is no data on women who were initially referred to colposcopy though not requiring treatment, but rather in need of continued intensified follow-up), on the median duration of such episodes and on the proportion of women who ultimately require colposcopy.

## Results from Trials including a Second Round of Screening

Four trials have published results from a second round of screening (Swedescreen, POBASCAM, ARTISTIC, NTCC). Table 4 summarizes the findings. None used the same screening/referral protocol in the first and second rounds. The trials found that women in the intervention arm were less likely to be diagnosed with a cancer precursor or a cancer at the second round of screening. This can be explained by the fact that the precursors found at the initial round were “true” precursors and their treatment led to a decreased prevalence in round 2. The most important implication from this finding is that a screening interval could be safely lengthened if HPV-based screening strategies were used. Intervals of five to six years have been deemed as safe as the current intervals used for Pap testing.<sup>82,96</sup>

**Table 4:** Results from the second screening round, and additional analysis

Study	Interval between screening rounds	2 <sup>nd</sup> round screening protocol <sup>a</sup>	Main results of second screening round	Other results/comments
Swedescreen <sup>75,76</sup>	3 years	CC	RDR CIN2+: 0.58 (0.36-0.96) RDR CIN3+: 0.53 (0.29-0.98)	Re-analysis identified HPV testing followed by cytology triage and repeat HPV testing in case of normal cytology as the most “feasible” among 11 strategies

Study	Interval between screening rounds	2 <sup>nd</sup> round screening protocol <sup>^</sup>	Main results of second screening round	Other results/comments
POBASCAM <sup>79</sup>	5 years	CC and GP5/GP6 PCR	DR CIN3+ intervention arm: 0.45% DR CIN3+ in control arm: 0.62% RDR CIN3+: 0.73 (0.55-0.96)	Significantly fewer cancers were detected at the second screening round, RR 0.29 (0.10-0.87)
ARTISTIC <sup>81,82,97</sup>	3 years	LBC and HC2	DR CIN3+ intervention arm: 0.25% DR CIN3+ in control arm: 0.47% RDR: 0.53 (0.30-0.96)	No evidence of significant psychological distress associated with HPV testing  Analysis of a third round (LBC only, 73 months median follow-up) concludes that a negative HPV test is more protective than a negative cytology and that the screening interval could be safely extended to 6 years if switching to HPV based screening
NTCC phase 1: 34 and younger <sup>85</sup>	3 years	CC	DR CIN2+ intervention arm: 0.19% DR CIN2+ in control arm: 0.23% RDR CIN2+: 0.85 (0.38-1.89)	No cancers were found after the initial round of screening in women in the intervention (HC2) group  Little advantage of LBC+HC2 compared to HC2 alone
NTCC phase 2: 34 and younger <sup>85</sup>			DR CIN2+ intervention arm: 0.11% DR CIN2+ in control arm: 0.27% RDR CIN2+: 0.40 (0.17-0.95)	Little advantage of LBC compared to CC, except decrease in unsatisfactory smears <sup>98</sup>
NTCC phases 1 and 2: 35 and older <sup>85</sup>			DR CIN2+ intervention arm: 0.05% DR CIN2+ in control arm: 0.09% RDR CIN2+: 0.51 (0.28-0.93)	Possibility of over-diagnosis and overtreatment of regressive lesions in women younger than 35 when HPV testing is used

<sup>^</sup>Same protocol for both study arms at 2<sup>nd</sup> round

<sup>\*\*</sup>CIN2+ refers to CIN2-CIN3-AIS for data of the NTCC<sup>86</sup>

## Knowledge Gaps and Research Needs

### Parameters of HPV-based Screening

**When to start:** Evidence clearly shows that HPV testing in young women (younger than 30 or 35 years of age) would lead to unnecessary procedures.<sup>85</sup> Programs looking to phase in HPV-based screening may want to consider starting with older age groups because of lower rates of HPV positivity. It will also be possible to start an HPV-based screening program and change parameters as more data becomes available.

**Interval:** Because cervical cancer usually progresses slowly, and because the negative predictive value of HPV testing is over 99%, there is a consensus that the interval between rounds of screening could be much longer if HPV-based screening was used. Current evidence supports intervals of five to six years.<sup>82,96</sup>

**Optimal age to stop:** No research has specifically addressed this question for HPV-based screening (it is a question which is also difficult to answer for Pap testing). Given the fact that a negative HPV result provides a longer “protection” than a negative Pap result, it may be safe to stop screening a few years earlier when switching to HPV-based screening. However, the risk of clinically relevant disease following a new infection acquired later in life has not been well characterized and for this reason caution is required when devising new algorithms for older women.

**Optimal triage strategy of a positive HPV test result:** Across a population more women have a positive screening test result when HPV testing is used as a primary screening test compared to a Pap-based screening strategy. Moreover, HPV testing is less specific than Pap testing.<sup>30</sup> Considering those drawbacks there is much interest in identifying triage options that could flag, among HPV positive women, those most at risk of HG-CIN or cancer thereby restricting diagnostic evaluation to them. Experts have proposed the use cytology as the triage test for HPV positive women: after a positive HPV test women would have a Pap test, and only those with a positive result would go for colposcopy.<sup>43</sup>

Program planners should be aware that the performance of Pap triage for HPV positive test results would vary according to the performance of Pap testing. There is no evidence that the detection rate of HG-CIN by Pap testing will significantly improve when the Pap test is used as a triage test compared to when it was used as a primary screening test.<sup>99</sup> In settings with low Pap sensitivity, solid cytology quality assurance programs should be implemented or alternative triage strategies such as genotyping or other molecular tests should be considered. It may also be possible to identify groups of women who would not need triage. For example, triage strategies may be of limited value in women over 40 or 50 years of age with no prior HPV test as most infections in that age group will tend to be of longer duration and thus, less likely to regress during follow-up and more likely to cause HG-CIN/cancer.

### Overall Burden of Screening

When switching to HPV-based screening, attention should be given to minimizing the number of women for whom intensified screening is suggested. Having abnormal screening tests with no definite answer on the presence or absence of disease would cause a lot of anxiety. This situation also complicates the screening strategy, increasing the risk of error in follow-up. Finally as the number of visits needed increases, so does the risk of poor compliance. Given that different screening and/or referral protocols were used by the trials, some useful comparison could be made through data that is already collected.

As cohorts of HPV vaccinated young women become eligible for participation in cervical screening, an additional issue will emerge. Women protected from acquiring HPV-16 and HPV-18 infection will have a

much lower risk of high-grade cervical disease and this will affect the performance of screening tests, particularly the positive predictive value of Pap testing or generic HPV testing.

## Planning Considerations

**Laboratory organization and performance:** A switch to HPV-based screening will have a considerable impact on cytology laboratories. Volumes will fall drastically and re-orientation of technical staff would need to be planned in advance, along with possible reorganization of services. For example, some centralization of cytology (if used as a triage tool) may help the implementation of rigorous quality assurance measures. The choice of which HPV test to use should be among Health Canada approved generic tests. Quality assurance measures for HPV testing should be planned.

**Diagnostic Colposcopy services and standards:** Guidelines for the follow-up of abnormal screening tests are an important tool to maximize benefits and minimize harms from screening. Some provinces have implemented guidelines for the follow-up of abnormal screening test results including procedures to monitor adherence to those guidelines. A switch to HPV-based testing will require new guidelines and provide all provinces with an opportunity to develop, implement and monitor such guidelines. It is anticipated that there could be an increase in demand for colposcopy services in the immediate and longer-term following the implementation of HPV-based screening. Program planners should ensure that resources are available in a timely manner.

**Health care provider information/education:** Although the knowledge about HPV and HPV-related diseases has probably increased among health-care professionals in recent years, some confusion remains.<sup>97,100,101</sup>

Information campaigns addressing the specifics of HPV-based screening (including natural history, HPV tests, meaning of test results, referral recommendations, etc.) will need to be carried out to support any policy changes that introduce or implement HPV testing for primary screening. Practitioners will need to be able to explain HPV testing to women, as well as the meaning of positive results and the steps required for follow-up. There may be a need to educate or provide communication tools to support practitioners (physician training).

**General public information/education:** Similar information will be necessary for the general population. Studies have shown that when women are provided with appropriate information about HPV and HPV testing, they readily consent to HPV testing; abnormal results do not cause more anxiety or stress compared to an abnormal Pap test result.<sup>97</sup> Explaining the reasons behind the switch to HPV-based screening may also help decrease the risk that women perceive the measure as essentially a cut in services (because of the lengthened interval).

## Other Planning Considerations

Before considering changes to a successful screening strategy by switching screening tests, a multi-faceted evaluation is necessary and should take into account the principles of screening described earlier in this document. The application of a screening test in usual practice is not a “one-time” event, but repeated testing at regular screening intervals. Although a single HPV testing round may be more costly than Pap testing, routine screening based on HPV testing may be more cost-effective if there can be longer intervals between screening rounds and if cancers are prevented.

Apart from a reduction in cervical cancer mortality, program planners may be interested in a screening test that could reduce cancer incidence. Still in 2011, a cervical cancer diagnosis most often entails invasive and mutilating procedures, often ending childbearing capacity for young women. A screening test that could improve on the benefits and minimize the harms or inconveniences of a screening strategy may be worth considering.

Coverage should remain a key focus of all cervical cancer screening programs. In order for women to benefit from the best screening technology they need to receive cervical cancer screening. However, changing the screening test will not address challenges related to screening program population coverage, diagnostic and/or treatment issues. As part of the performance monitoring recommendations from the Public Health Agency of Canada, screening programs are advised to monitor coverage rates. Participation rate is defined as the percentage of eligible women in the target population (20-69) with at least one Pap test in a three-year period. Using data from the Canadian Community Health Survey of 2008, overall, 79% of women in Canada reported having a Pap smear in the past three years. This is an increase from 2000-1, where 75% of women reported having a Pap smear. In 2008, there was a range of self-reported uptake rates from 74% in Nunavut to 88% in the North West Territories.<sup>102</sup> The most recent screening participation rates (not adjusted for hysterectomy status) from cervical screening programs in Canada indicate that on average 70% of women aged 20-69 have had a Pap test within three years. Participation rates from this 2011 report are based on actual screening data and may explain why rates are lower than those published in the 2010 report (contained self-reported rates).<sup>102</sup>

There are economic implications associated with the fact that HPV testing has higher sensitivity and lower specificity. On the one hand overall costs could increase since HPV testing is more expensive than cytology screening (although costs are expected to drop if it becomes the primary screening test). The additional follow-up exams would also bring costs up. On the other hand overall costs could decrease due to the fewer number of cases of invasive cancer and the longer interval between screening rounds.

The clinical and economic trade-off of introducing HPV screening is best assessed by cost-effectiveness analysis in comparison to the established policy. So far, several economic analyses of HPV testing, either in combination with cytology or as a stand-alone test, have been published. These studies differ by their methodological approach, parameter estimates and local costing, making comparisons across jurisdictions difficult and a full analysis beyond the scope of this report. A common finding is that locations with the most frequent cytology testing may achieve the most efficiency gains by adopting a less frequent screening interval or by incorporating HPV testing.<sup>103,104</sup> Among the three economic analyses based on Canadian data, two showed that HPV testing was an attractive strategy.<sup>105,106</sup> However the third analysis, three-year cytology testing with HPV triage for women aged 30 and over, appears to be the most cost-effective solution (assuming the sensitivity of cytology at 0.74).<sup>107</sup>

As vaccinated cohorts will reach soon the age to be screened, the incidence of severe cytological abnormalities is expected to drop significantly, in parallel to a decrease in infection by vaccine targeted HPV types. The performance, specifically positive predictive value, of cytological screening is likely to diminish even more. That should make HPV testing more attractive for screening and surveillance.

The most efficient way to transition to HPV testing for primary screening of cervical cancer will need to be evaluated in each province and territory, considering the different cervical cancer screening practices. Such a change should be part of a comprehensive plan for moving forward to improve cervical cancer control and should include: strategies to maximize participation, ensuring appropriate follow-up of abnormal test results, analysis of relative gains and costs, close monitoring of test utilization, and monitoring outcomes of testing. These data will help to inform future screening guidelines and algorithms by providing information on key parameters of screening success.



## Appendix

**Table 5:** Cytological classification abbreviations according to the 2001 Bethesda System terminology<sup>108</sup>

Cellular type	Abbreviation	Terminology
Squamous	ASC	Atypical squamous cells
	ASC-US	Atypical squamous cells of undetermined significance
	ASC-H	Atypical squamous cells, cannot exclude a high-grade lesion
	LSIL	Low-grade squamous intra-epithelial lesion (encompassing papillomavirus infection, CIN1)
	HSIL	High-grade squamous intra-epithelial lesion (moderate and severe dysplasia, carcinoma in situ; CIN2 and CIN3)
	Squamous cell carcinoma	Squamous cell carcinoma
Glandular	AGC	Atypical glandular cells
	AIS	Adenocarcinoma in situ
	Adenocarcinoma	Adenocarcinoma

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