Executive Summary

Introduction of molecular HPV testing as the primary technology in cervical cancer screening:

Acting on evidence to change the current paradigm
Evidence to Change the Cervical Cancer Screening Paradigm in Canada

EVIDENCE REVIEW AND REPORT

Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm

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EXECUTIVE SUMMARY

It is well established that persistent infection with human papillomavirus (HPV) is a requirement for cervical cancer. While Pap cytology (or the Pap test) has had unequivocal success in reducing the cervical cancer burden since its introduction in the 1940s, this technology has many limitations in comparison with tests that screen for HPV.

Rationale for shifting from the Pap test to testing for HPV in cervical cancer screening

Evidence from over a decade of large-scale clinical trials, feasibility studies and real-world experience in countries that have adopted testing for HPV as the primary cervical screening method overwhelmingly prove that the benefits for shifting to HPV primary screening far outweigh potential or perceived harms. HPV testing has proven to be clinically superior to the Pap test in cervical cancer screening, without increasing the costs.

• **HPV testing is much more sensitive in detecting high-grade precancerous lesions than the Pap test.**
  
  o Numerous clinical trials including the Canadian Cervical Cancer Screening Trial (CCCaST)\(^2\) have shown that HPV screening is much more sensitive, demonstrating sensitivity as high as 95% for HPV primary screening versus 55% for conventional Pap cytology (based on alcohol fixed direct smears).
  
  o Results from the HPV FOCAL RCT in B.C.\(^3\) and the VASCAR (community based) demonstration project in Montreal\(^4\) indicate that HPV testing followed by Pap triage leads to greater detection of precancerous lesions.

• **A negative HPV test provides greater and longer reassurance to women that they are at very low risk of developing cervical cancer.**
  
  o In a recent US study (n=1,011,092; representing the largest and longest experience with routine HPV testing in clinical practice), investigators reported much lower risks associated with a negative HPV test compared with a negative cytology test result.\(^5\) The five-year risk of high-grade cervical precancer associated with a negative HPV test is lower than the three-year risk associated with a negative cytology test.

• **HPV testing with Pap triage has been shown in Canadian and international studies to be much more effective and less expensive compared with primary screening using the Pap test.**

• **HPV testing has efficiency and quality benefits** - HPV testing is objective, highly consistent, can be automated and centralized, and allows for rapid quality assurance of a high volume of tests.

• **HPV testing offers the opportunity for self-sampling, which could help reduce disparities and increase screening rates among some populations.**

• **HPV testing offers greater protection against cervical adenocarcinoma.**

• **HPV testing is a more logical technology for screening women in the HPV vaccination era.**

The need for the most effective prevention and screening strategy
In Canada, there were an estimated 1,450 cases of cervical cancer and 380 deaths in 2014. Cervical cancer takes a heavy toll on Aboriginal Canadians and recent immigrants. Fortunately, most cervical HPV infections clear spontaneously and only a small proportion of infections (10-30%) persist beyond two years. However, because precancerous lesions are asymptomatic, screening is essential to detect and treat high-grade lesions.

Current HPV vaccines do not protect against all HPV genotypes. Cervical screening will continue to be recommended for vaccinated and unvaccinated populations for the foreseeable future.

The urgency to shift to HPV primary screening is increased by the fact that, by 2015, the first cohort of Canadian girls vaccinated against HPV 16 and 18 will be 21 years old - the age when routine cervical screening typically begins. As an increasing number of vaccinated females move into the screening target population, ensuring the most appropriate screening protocol that maximizes benefits and minimizes potential harms for both vaccinated and unvaccinated women becomes even more pressing.

**Cost-effectiveness**

In Canadian and international cost-effectiveness analyses, HPV primary testing was much more effective and less expensive compared with cytology primary screening. 

The fact that women will require fewer lifetime screens will also contribute to the cost-effectiveness of HPV primary screening. Investigators for B.C.’s FOCAL study found that, although HPV testing may initially increase referrals for colposcopy (compared with Pap cytology primary screening), cumulative colposcopy rates over the long-term would be similar for women 30 years of age and above.

HPV self-testing may be an acceptable option to women who do not participate in regular screening programs. In an Argentinian study, offering women the opportunity to self-collect a specimen for cervical screening led to a four-fold increase in screening uptake within six months.

**HPV test accepted as a superior primary screening method**

Health Canada approved the first HPV test for primary cervical cancer screening in 2011; others have been approved subsequently.

The Ontario Cervical Screening Guideline Working Group (in conjunction with the Program in Evidence-based Care; an initiative of Cancer Care Ontario) now recommends stand-alone HPV primary testing every five years for women aged 30 to 65 years, with Pap cytology triage. These new guidelines for Ontario were published in 2012. Cancer Care Ontario’s Ontario Cancer Plan 2015-2019 identifies that one of the initiatives is to “pilot the human papillomavirus (HPV) test as the primary screening mechanism for the Ontario Cervical Screening Program”. However, the Plan does not specify in which year this pilot will be initiated.

In November 2014, the Canadian Partnership Against Cancer (CPAC) hosted a Pan-Canadian Cervical Cancer Screening Network (PCCSN) Expert meeting to formulate options for optimal cervical cancer screening. Cancer prevention and control experts from across Canada reached “a general consensus that a change in screening protocols is necessary and that the primary screening modality should be the HPV test.”
Despite the weight of evidence in support of HPV primary screening and showing that Pap cytology is an inadequate mainstay of cervical cancer screening, HPV testing has not become a frontline strategy in cervical cancer screening in Canada. Some of the hesitation comes from the mistaken perception that cervical cancer screening must first be fully organized before technological changes can be made. In fact, the opportunity for changing the core technology is a major incentive for implementing organized screening in Canada. This has certainly been the case in other jurisdictions that are implementing HPV primary screening.

International experience with Implementing HPV Primary Screening
Other countries have moved more quickly than Canada to adopt HPV primary screening. Mexico recently became the first country to introduce stand-alone HPV primary testing. The program has been implemented in all 32 states and targets women 35 to 65 years of age. To date, over six million women have been screened for HPV.\textsuperscript{14,15}

Turkey also recently introduced HPV primary screening. Its goal is to screen 13.5 million women in the next five years. All HPV testing is being consolidated and centralized into two major laboratories, which should improve the quality of testing, ensure standardized processing, and reduce costs.

To date, HPV primary screening programs have been introduced in nine provinces in Italy, with >175,000 women tested each year. The Netherlands, Sweden and Scotland are also currently planning to introduce primary HPV screening within the next few years.

Implementation in Canada is imperative and highly feasible
With the rapid pace of technological changes and new discoveries, uncertainty will almost always exist in cervical cancer screening. However, questions surrounding the best triage strategy for referring HPV positive women to colposcopy, or the most appropriate age groups and interval to screen women should not be viewed as obstacles to the implementation of HPV primary screening in Canada. Moreover, policymakers should not postpone decisions assuming that randomized controlled trials will answer all of these questions. In a recent report, separate from this current evidence review, the PCCSN describes in detail a number of concrete steps that can be taken in Canadian provinces now to implement primary HPV screening.
References