



## Evidence-based Series 15-9 IN REVIEW

A Quality Initiative of the  
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

### Cervical Screening

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Original Report Date: May 20, 2005  
Current Report Date: October 5, 2011

An assessment conducted in April 2016 placed Evidence-based Series (EBS) 15-9 IN REVIEW. This means that it is undergoing a review for currency and relevance. The PEBC has determined that it is still appropriate for this document to continue to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

The full Evidence-based Series (EBS) 15-9 is comprised of 3 sections and is available on the [CCO website](#) on the [PEBC Cancer Screening page](#)

- Section 1: Guideline Recommendations
- Section 2: Evidentiary Base
- Section 3: EBS Development Methods and External Review Process

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In Review



## Evidence-based Series 15-9: Section 1

# Cervical Screening: Guideline Recommendations

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### QUESTIONS

In Ontario, in the context of an organized cervical screening program:

1. What is the optimal primary cervical screening method (i.e., human papillomavirus [HPV] DNA testing and/or cytology testing)?

In average risk, asymptomatic women:

2. What is the most appropriate age for the initiation of cervical screening?
3. What is the optimal interval between cervical screenings?
4. What is the most appropriate age for the cessation of cervical screening?

### TARGET POPULATION

Average risk asymptomatic women in Ontario, Canada.

### INTENDED USERS

This guideline is intended for family physicians, other primary care providers, and gynecology specialists involved in screening women for cervical cancer and its precursors.

### INTRODUCTION

The Ontario Cervical Screening Program (OCSP) is currently being relaunched to incorporate an organized call and recall component. This relaunch has necessitated a review of evidence related to the research questions listed above and an update of the relevant portions of the Program in Evidence-based Care (PEBC) May 2005 guideline *Cervical Screening* (1). The updated guideline will help the OCSP to realize its long-term goals of reducing the incidence of and mortality from cervical cancer through an organized screening program and improving the capacity of providers to engage in organized cervical screening. It will also

address the 2011-2014 Ontario Cancer Plan (2) goal of creating evidence-based guidelines for cervical cancer screening.

Evidence clearly indicates that there is a role for HPV testing in primary screening, and, thus, the primary recommendations presented in Part 1 of this guideline are for HPV-based testing for women 30 years of age and over. The proposed algorithm (Figure 1) assumes the existence of an organized province-wide screening program.

There is lesser quality evidence at this time for the appropriate screening algorithm for women under 30. For this reason, and because HPV testing is not currently funded in the province and the components of an organized screening program are in the process of being put in place, a set of interim recommendations (Section 1, Part 2) are also provided that include the younger age group and acknowledge the current standard of cytology-based testing. The goal of the interim recommendations is to provide a bridge to the time when HPV testing for primary screening is funded in Ontario. Because screening for cervical cancer is a quickly evolving field, the HPV testing-based algorithm, the optimal age for screening initiation, and a method of screening for women younger than 30 years should be reviewed prior to implementation. A comparison of recommendations contained in this guideline and in the previous version published in 2005 is presented in Table 1. A table of screening test results terminology and a glossary of terms are provided in Appendices 1 and 2, respectively. For more information on HPV and the development of cervical cancer, details of the systematic review, and discussion of the impact of adoption of HPV testing for primary screening, please see Section 2 of this report.

**Table 1. Summary of PEBC screening recommendations for Ontario: 2005-2013.**

Year (Section)	Evidence base	Implementation timeframe	Primary screening test	Age of screening initiation	Screening interval	Age of screening cessation*
2011 (Part 1)	Evidence- and consensus-based (up to 2011)	2013 (anticipated implementation of HPV testing in the Province of Ontario)	Women 30+: HPV testing; women <30: to be determined	To be determined at the time that HPV is implemented	Every 5 years with a negative HPV test result	65
2011 (Interim) (Part 2)	Evidence and Consensus-based	2011-2012	Cytology testing	21 years of age	Every three years	70
2005 (1)	Evidence-based (up to 2005)	2005-2010	Cytology testing	Within 3 years of initiation of sexual activity	Annually until three negative tests, then every 2-3 years	70

**Abbreviation:** HPV = human papillomavirus. \*Provided that an adequate negative screening history has been established.

## PART 1: RECOMMENDATIONS FOR CERVICAL SCREENING WITH HPV DNA TESTING

### RECOMMENDATION

#### Primary Screening Test

HPV DNA testing of cells collected from the cervix is recommended for primary cervical screening. Cytology screening, which was recommended for primary screening in the previous version of this guideline, is now recommended only in the event of a positive HPV DNA test result (see HPV screening algorithm, Figure 1). Interim recommendations are provided in Section 1, Part 2 (Interim Recommendations), because HPV testing is not funded at this time for primary screening in Ontario.

### KEY EVIDENCE

#### HPV testing

Seven randomized controlled trials (RCTs) (3-8) have been conducted to assess the performance of HPV testing in primary screening. The trials assessed the rates of cervical intraepithelial neoplasia grade 2 or grade 3 (CIN2 or CIN3), either at a baseline screening round or over two screening rounds. CIN2 is a useful indicator because it is often the threshold for clinical management. CIN3 is less likely than lower grades of CIN to regress or resolve without treatment and so is a useful predictor of the risk for cervical cancer. The results showed that:

- HPV testing consistently detected significantly more CIN2 and CIN3 in the baseline screening round than did cytology-based testing. HPV testing detected fewer CIN2 or more severe (CIN2+) cases in the subsequent screening round, indicating a lead time gain with HPV testing.
- The one trial that had sufficient sample size to report incidence and mortality due to cervical cancer found a significant reduction with HPV testing but not with cytology testing, compared to standard care (9).
- There was no significant difference in the number of invasive cancers detected in the baseline screening round in the New Technologies in Cervical Cancer trial (8) comparing HPV testing and cytology testing. In the subsequent screening round, no cases of cancer were found in the HPV-testing group, while nine cases were found in the cytology-testing group. A high number of the cancers detected in the second round in the cytology group were adenocarcinomas (10). This is consistent with previous reports that cytology is less effective in preventing adenocarcinomas than squamous cell carcinomas (approximately 20% of cervical cancers in Ontario are adenocarcinomas) (11).

#### Cytology Triage of HPV Positive Results

- Due to the higher sensitivity of HPV testing compared to conventional cytology, the rate of colposcopy referral with HPV testing alone is higher than the rate with conventional cytology. For example, in the Canadian Cervical Cancer Screening Trial (CCCaST) RCT, the rate of referral to colposcopy after a positive HPV test alone was 6.1%, compared to a referral rate of 2.6% for conventional cytology results of atypical squamous cells of undetermined significance (ASCUS) (3).
- A triage test can reduce the number of colposcopy referrals and increase the specificity of the screening algorithm. In CCCaST, HPV with Pap triage resulted in a 1.1% rate of referral based on ASCUS (3). The Finnish Public Health Trial found the frequency of colposcopy referrals was 1.2% in both the conventional cytology arm at a threshold of low-grade squamous intraepithelial lesions (LSIL) and the HPV with cytology triage arm of their trial

(12).

#### **QUALIFYING STATEMENT**

- The recommendation for HPV testing is applicable only in the context of an organized screening program with an adequate database infrastructure that allows for an invitation to screening at recommended intervals, and a follow-up of women with abnormal test results.
- HPV testing has been shown to be more effective for women 30 years of age and older (see Age of Screening Initiation below).
- Women who have never been sexually active<sup>1</sup> do not require cervical screening.

#### **RECOMMENDATION**

##### **Age of Screening Initiation**

It is the opinion of the Cervical Screening Guideline Working Group (the Working Group) that there is insufficient evidence at this time to make a recommendation for the age at which to begin cervical screening using HPV testing as the primary screen. HPV testing performs better for women 30 and over compared to younger women because the rate of transient infections is higher in the younger age group; therefore, the screening algorithm in the following recommendation is presented for women 30-65 years of age.

#### **RECOMMENDATION**

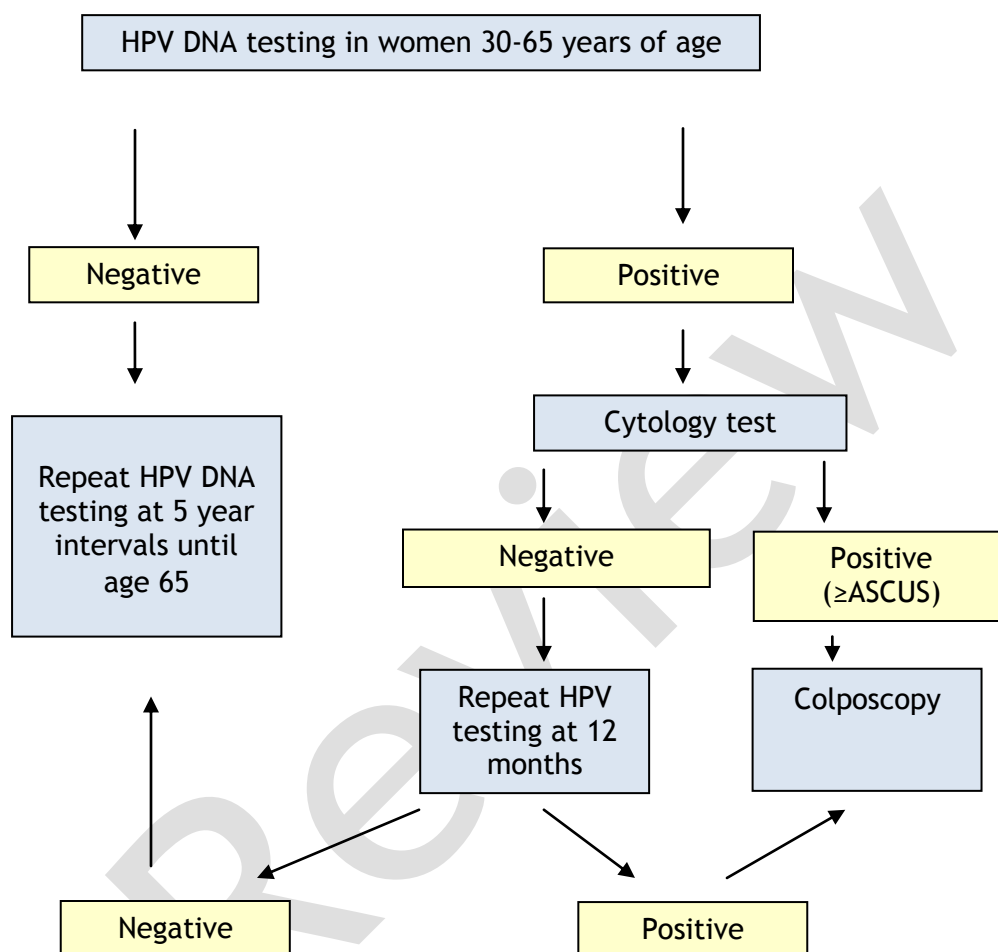
##### **Screening Interval (Women 30-65)**

Screening interval recommendations are according to the algorithm presented in Figure 1. For women aged 30-65, HPV DNA testing is to occur at five-year intervals after an initial negative result, which is a change from the recommendation for repeat cytology testing every two to three years contained in the 2005 version of this guideline. HPV-positive tests should be assessed with cytology testing and not referred directly to colposcopy. Repeat HPV testing for results of HPV positive/cytology negative should be conducted after one year.

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<sup>1</sup> Sexually active is defined as vaginal intercourse and vaginal/oral and/or vaginal/digital sexual activity.

Figure 1: Primary cervical screening with HPV testing (women 30-65)<sup>2</sup> (adapted from Cuzick et al. 2008 (13)).



#### KEY EVIDENCE

The proposed HPV testing algorithm is based on a combination of evidence from cohort studies, the natural history of HPV infections, and the consensus of the Working Group.

#### Five-Year Interval after HPV Negative Results

- Six years after a negative HPV test, pooled cohort data found a cumulative incidence rate for CIN3+ of 0.27% (95% CI, 0.12 to 0.45), which was lower than the rate after three years with a negative cytology test (0.51%; 95% CI, 0.23 to 0.77) (14). This indicates that retesting at five-year intervals would entail a low level of risk.
- The risk of CIN3+ after a negative HPV test is low: in a Danish cohort study the 12-year absolute risk of CIN3+ after a negative HPV DNA test in women with normal cytology was 3.0% (95% CI, 2.5 to 3.5%) (15).

<sup>2</sup> This screening algorithm should be reviewed for currency prior to its implementation as results from subsequent screening rounds of the HPV RCTs are expected in the next one to two years.

**One-Year Interval with HPV Positive/Cytology Negative Results**

The short-term persistence of HPV infection for at least one year is an important predictor of CIN2+ (16). In women who tested HPV positive at enrolment and negative after about one year (nine-21 months), the cumulative incidence of CIN2+ after three years was 1.2% (95% CI, -0.2 to 2.5). The three-year cumulative incidence of CIN2+ in women who tested positive for carcinogenic HPV at study enrolment and again after approximately one year was 17.0% (95% CI, 12.1 to 22.0) (16). Consequently, referral to colposcopy after two consecutive positive HPV tests occurring a year apart is recommended, even in the event of initially negative cytology results.

**QUALIFYING STATEMENTS**

The screening algorithm (Figure 1) should be reviewed for currency prior to implementation.

A variation on this algorithm includes genotyping for HPV 16 and/or HPV 18 immediately after a positive HPV test and cytology results of normal, ASCUS or LSIL, based on the rationale that HPV 16 has been shown to be more persistent and more often associated with high-grade lesions, and HPV 18 is more often associated with difficult to detect lesions in the endocervical canal (13). Positivity for either of these types may require immediate colposcopy.

**RECOMMENDATION****Age of Screening Cessation**

Screening may be discontinued after the age of 65 provided there is an adequate negative screening history in the previous 10 years (i.e., two or more negative tests) and a final negative HPV test at age 65. Women who do not meet these requirements should continue with screening at recommended intervals. This is a change from the previous recommendation of cessation at age 70 (1).

**KEY EVIDENCE**

This recommendation is the consensus of the authors, taking into account the low rate of cervical cancer in this age group among women who have previously been adequately screened, the potential discomfort of the procedure, and difficulties with visualization of the squamocolumnar junction in older women.



## **PART 2: INTERIM RECOMMENDATIONS (TO BE FOLLOWED UNTIL HPV TESTING IS FUNDED)**

### **INTERIM RECOMMENDATION**

#### **Primary Screening Test**

On an interim basis, the authors endorse the recommendation contained in the 2005 version of this guideline: primary screening with cytology testing (1).

#### **KEY EVIDENCE**

This recommendation is the opinion of the authors based on the systematic review conducted for the previous version of this guideline (1).

#### **QUALIFYING STATEMENTS**

- Women with Pap tests that lack transformation zone components (i.e., endocervical and/or metaplastic cells) may continue screening at the regular intervals recommended by the guideline. Repeated samples lacking transformation zone may require further investigation.
- The above statement does not include women with test results of “unsatisfactory”, who should undergo repeat screening in three months. This qualifying statement is the opinion of the Working Group based on the clinical experience that a shorter waiting period may result in the detection of reactive changes as a result of the first screening test.
- The Working Group maintains the recommendations for screening of special populations contained in the 2005 guideline:
  - Immunocompromised women (e.g., those currently taking long-term immunosuppressants, those who are HIV positive) should receive annual screening.
  - Screening can be discontinued in women who have undergone a total hysterectomy for benign causes with no history of cervical dysplasia or HPV. Women who have undergone subtotal hysterectomy (with an intact cervix) should continue screening according to the guidelines.
  - Indications for screening frequency for pregnant women should be the same as for women who are not pregnant. Manufacturers’ recommendations for the use of individual screening tools in pregnancy should be considered.
  - Women who have sex with women should follow the same cervical screening regimen as women who have sex with men.

### **INTERIM RECOMMENDATION**

#### **Age of Screening Initiation**

Cytology testing should commence at 21 years of age for sexually active women.

#### **KEY EVIDENCE**

Lower quality evidence was available for the questions regarding the age of initiation of cervical screening. Three case-control studies were found that addressed the questions of initiation (17-19). The results of these studies were mixed, with a trend towards higher efficacy of screening for older women. There were no studies found that directly assessed the optimal age of initiation of cervical screening with HPV testing as the primary screen.

#### **RATIONALE**

- After weighing the available evidence, the authors of this guideline have concluded that the harms of screening women under 21 years of age significantly outweigh the benefits. In the opinion of the authors, the potential for adverse reproductive outcomes with treatment, anxiety related to the testing procedure, and the anxiety and potential stigma

associated with positive test results considerably outweigh the benefits of screening in women younger than 21 years of age (20-23), given the relatively high rate of HPV infection (24), rarity of cervical cancer in women under 25 years, and the up to decades-long time period of progression from HPV infection to cervical cancer (25).

- In the opinion of the Working Group, evidence regarding the necessity, utility, and/or effectiveness of screening in women 21 to 24 years is not as clear; the authors of this guideline are not convinced that the harms outweigh the benefits of screening for these women. Therefore, the consensus is that lesions in these women should be detected and treated where appropriate in order to minimize the potential for their progression to cervical cancer.
- The guideline authors do recognize that there is also a potential for harm with screening. The potential harms related to treatment of CIN are adverse reproductive outcomes, including premature rupture of membranes, low birth weight, and preterm delivery (22). The early detection and treatment of CIN3 in young women, however, might prevent some cancers developing to a stage where treatment could result in compromised fertility. Based on the information available at this time, the authors of this guideline consider that the benefit of eliminating potential cases of invasive cervical cancer in women 21-24 years of age outweighs the reproduction-related harms, as well as the potential anxiety, fear, and uncertainty related to abnormal screening tests, intensified screening, colposcopy, biopsy, and treatment for CIN.

#### QUALIFYING STATEMENTS

- Women who are not sexually active<sup>3</sup> by age 21 may delay cervical screening.
- Women who have never been sexually active do not require cervical screening.
- The interim recommendation to begin screening at 21 years of age should be reviewed within 24 months of the publication of this guideline.
- As HPV-vaccinated women reach the age of screening initiation, there may be impact on the screening recommendations.

#### KEY EVIDENCE

The key evidence for this recommendation is presented in Section 2 (systematic review section) of the 2005 PEBC guideline *Cervical Screening* (1).

#### INTERIM RECOMMENDATION

##### Screening Interval

Women should be screened every three years.

#### KEY EVIDENCE

The previous guideline recommended three annual negative screens before lengthening the screening interval to two to three years. Evidence presented in the previous version of this guideline showed that the excess risk with screening every three years compared to annually was approximately three additional cases of cervical cancer per 100,000 women (26).

A modelling study conducted in Australia found that increasing the recommended screening interval from two years to three years with cytology-based testing would result in no substantial change to incidence and mortality due to cervical cancer (27).

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<sup>3</sup> Sexually active is defined as vaginal intercourse and vaginal/oral and/or vaginal/digital sexual activity.

## INTERIM RECOMMENDATION

### Age of Screening Cessation

The authors endorse the age of cessation of cytology-based testing presented in the 2005 version of this guideline:

- Screening may be discontinued after the age of 70 if there is an adequate negative cytology screening history in the previous 10 years (i.e., three to four negative cytology tests).

### KEY EVIDENCE

Key evidence for this recommendation is presented in Section 2 (systematic review section) of the 2005 PEBC guideline *Cervical Screening* (1).

### Recommended Management for Women with Abnormal Cytology

Management recommendations were not included in the scope of the current guideline. The algorithm for the management of abnormal results from the previous version of this guideline has been appended, however, as its recommendations still apply to the interim cytology-based guidelines provided here. Please see Appendix 3 (Section 1, page 19). If the evidence base for these recommendations is required, please email [ccopgi@mcmaster.ca](mailto:ccopgi@mcmaster.ca).

### FUTURE RESEARCH

Results from further screening rounds of several of the RCTs included in the evidence base for this guideline are anticipated (Table 2). These results should further inform the optimal screening algorithm for women 30 years of age and older and the optimal age for commencing cervical screening. An international agreement has been reached to conduct future meta-analyses of the HPV screening trials and to synthesize evidence on new methods for cervical cancer prevention (28).

**Table 2. Anticipated results from randomized trials.**

Study acronym (ID number)	Study initiation date	Study end date	Further results anticipated?
CCCaST (ISRCTN57612064)	September 2002	July 2007	Yes; long-term efficacy data (personal communication, Eduardo Franco, January 2011).
NTCC (ISRCTN81678807)	February 2002	December 2004	Yes; A cost-benefit analysis is underway (10). Also, the group is updating the follow-up of a third screening round (personal communication, Guglielmo Ronco, May 2011).
ARTISTIC (ISRCTN25417821)	June 2001	November 2009	Yes; the ARTISTIC trial is continuing to follow women while maintaining the randomised concealment of HPV testing results for a further three-year round of screening (29).
FPHT (ISRCTN 23885553)	January 1999	December 2020	Yes; the group intends to rescreen women according to the same allocation at least twice; publications based on this ongoing follow-up are anticipated (30).
POBASCAM (ISRCTN20781131)	January 1999	September 2007	No
Sankaranarayanan	October 1999	2007	No
Swedescreen (NCT00479375)	May 1997	May 2007	No

**Abbreviations:** ARTISTIC = A Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Screening (UK = United Kingdom), CCCaST = Canadian Cervical Cancer Screening Trial, FPHT = Finnish Public Health Trial, NTCC = New Technologies in Cervical Cancer (Italy), POBASCAM = Population Based Screening Study Amsterdam (the Netherlands).

The HPV FOCAL study (Trial Registration No. ISRCTN79347302) is being conducted by the BC (British Columbia) Cancer Agency, in collaboration with the BC Centre for Disease Control, the University of British Columbia, McGill University, and healthcare providers in Metro Vancouver and Greater Victoria. In a Canadian context, this study aims to establish the efficacy of human HPV testing as a stand-alone screening test with cytology triage of HPV positive women, establish an appropriate screening interval for HPV negative women, and determine cost-effectiveness of HPV testing as a primary screening test.

Other HPV testing strategies under study are based on molecular markers and include viral load, genotyping, testing for the RNA of the viral oncogenes E6 and E7, and testing for the overexpression of the p16-INK4A protein (31).

As research continues into the risk factors for cervical cancers and the different type-specific and other tests evolve, screening algorithms will become increasingly more complex. In response to this, a group is developing a tool to predict the risk for a woman of having or developing cervical precancer. These risk estimates could be used to make referral and screening interval decisions (32) and may be considered for implementation in future update of this guideline.

#### RELATED GUIDELINES

- Fung-Kee-Fung M, Howlett R, Oliver T, Murphy J, Elit L, Strychowsky J, et al. The optimum organization for the delivery of colposcopy service in Ontario. *J Low Genit Tract Dis.* 2010 Jan;14 (1):1-21. doi: 10.1097/LGT.0b013e3181a911b8.
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In Review

Appendix 1. Screening test results terminology.

Cytology Diagnosis	Histology Diagnosis	Other terms
<b>Atypical squamous cells (ASC):</b>		
Atypical squamous cells of uncertain significance (ASCUS)		Borderline changes
Atypical squamous cells: cannot exclude high grade squamous (ASC-H)		
Low-grade squamous intraepithelial lesion (LSIL)	Cervical intraepithelial neoplasia grade 1 (CIN1)	Mild dysplasia
High-grade squamous intraepithelial lesion (HSIL)	CIN2	Moderate dysplasia
	CIN3, carcinoma in situ	Severe dysplasia
Squamous cell carcinoma (SCC)		
Atypical glandular cells - not otherwise specified (AGC-NOS)		
Atypical glandular cells (AGC-neoplastic)		
Adenocarcinoma in situ (AIS)		



## Appendix 2. Glossary of terms.

*Adenocarcinoma* - a malignant tumour originating in glandular epithelium (33).

*AGREE II* - the Appraisal of Guidelines for Research and Evaluation, an international tool to assess the quality and reporting of practice guidelines (34).

*Case-control study* - a study design that examines a group of people who have experienced an event (usually an adverse event) and a group of people who have not experienced the same event, and looks at how exposure to suspect (usually noxious) agents differed between the two groups. This type of study design is most useful for trying to ascertain the cause of rare events, such as rare cancers (35).

*Cervical dysplasia* - the abnormal microscopic appearance of cells on the surface of the cervix. Although it is not cancer, dysplasia is considered a precancerous condition (33).

*Cervical intraepithelial neoplasia* - dysplasia that is seen on a cervical biopsy is called cervical intraepithelial neoplasia (CIN) and is grouped into three categories:

- CIN I -- mild dysplasia
- CIN II -- moderate to marked dysplasia
- CIN III -- severe dysplasia to carcinoma in situ (33)
- 

*Cohort study* - a non-experimental study design that follows a group of people (a cohort) and then looks at how events differ among people within that group. A study that examines a cohort, which differs in respect to exposure to some suspected risk factor (e.g., smoking), is useful for ascertaining whether exposure is likely to cause specified events (e.g., lung cancer). Prospective cohort studies (which track participants forward in time) are more reliable than retrospective cohort studies (35).

*Colposcopy* - a magnifying instrument designed to facilitate visual inspection of the vagina and cervix (33).

*Conventional cytology* - see Pap smear.

*Cotesting* - for the purposes of this guideline, cotesting refers to cervical screening using the combination of cytology plus HPV testing concurrently.

*Cytology* - a branch of biology dealing with the structure, function, multiplication, pathology, and life history of cells (33).

*Dysplasia* - abnormal growth or development (as of organs or cells) (33).

*Epithelium* - a membranous cellular tissue that covers a free surface or lines a tube or cavity of an animal body and that serves especially to enclose and protect the other parts of the body, to produce secretions and excretions, and to function in assimilation (33).

*Genotype* - all or part of the genetic constitution of an individual or group (33).

*Hazard ratio (HR)* - broadly equivalent to relative risk (RR); useful when the risk is not

constant with respect to time. The HR uses information collected at different times and is typically used in the context of survival over time. If the HR is 0.5 then the RR of dying in one group is half the risk of dying in the other group (35).

*Histology* - a branch of anatomy that deals with the minute structure of animal and plant tissues as discernible with the microscope (33).

*Human papillomavirus (HPV)* - a double-stranded DNA virus of the genus *Papillomavirus* (species *Human papillomavirus*) that has numerous genotypes causing various human warts (e.g., common warts of the extremities, plantar warts, genital warts), including some associated with the production of cervical cancer (33).

*Intraepithelial* - occurring in or situated among the cells of the epithelium (33).

*Invasive cervical cancer* - cancer cells tending to spread, especially tending to invade healthy tissue (33).

*Lesion* - an abnormal change in the structure of an organ or a body part due to injury or disease, especially a change that is circumscribed and well defined (33).

*Natural history* - natural development of something (e.g., organism, disease) over a period of time (33).

*Negative predictive value (NPV)* - the chance of not having a disease given a negative test result (not to be confused with *specificity*, which is the other way round) (35).

*Oncogene* - gene having the potential to cause a normal cell to become cancerous, e.g. viral oncogenes E6 and E7 (33).

*Opportunistic screening program* - a screening program that lacks the features of an organized screening program (see below).

*Organized screening program* - a screening program that is characterized by information systems linked to population databases to facilitate the recruitment of target populations, invitation and recall at appropriate intervals, communication of abnormal results, and follow-up and monitoring of program quality (36).

*Pap smear* - a method, or a test based on it, for the early detection of cancer, especially of the uterine cervix, that involves staining exfoliated cells by a special technique that differentiates between diseased and healthy tissue—also called a Papanicolaou smear, Papanicolaou test, or Pap test (33) and referred to in this guideline as ‘conventional cytology’.

*Positive predictive value (PPV)* - the chance of having a disease given a positive test result (not to be confused with *sensitivity*, which is the other way round) (35).

*Precancerous lesions* - lesions that are tending to become cancerous (33).

*Randomized controlled trials (RCTs)* - a trial in which participants are randomly assigned to two or more groups: at least one (the experimental group) receiving an intervention that is

being tested and the other (the comparison or control group) receiving an alternative treatment or placebo. This design allows an assessment of the relative effects of interventions (35).

*Relative detection rate* - the ratio of two detection rates.

*Screen* - to test or examine for the presence of something (a disease, for instance) (33).

*Sensitivity* - the chance of having a positive test result given that you have a disease (not to be confused with *positive predictive value [PPV]*, which is the other way around) (35).

*Specificity* - the chance of having a negative test result given that you do not have a disease (not to be confused with *negative predictive value [NPV]*, which is the other way around) (35).

*Squamous cell carcinoma* - a carcinoma that is made up of or arises from squamous cells. Squamous cells are made up of or derived from squamous epithelium (33).

*Squamous intraepithelial lesion (SIL)* - dysplasia that is seen on a Pap smear. These changes may be graded as:

- Low-grade (LSIL)
- High-grade (HSIL)
- Possibly cancerous (malignant) (33)

*Systematic review* - a review in which specified and appropriate methods have been used to identify, appraise, and summarize studies addressing a defined question. It can, but need not, involve meta-analysis (35).

*Triage* - the sorting of patients (as in an emergency room) according to the urgency of their need for care (33).

#### Commonly used Acronyms

PEBC	Program in Evidence-based Care
CIN	Cervical Intraepithelial Neoplasia
CCO	Cancer Care Ontario
HPV	Human Papillomavirus
LBC	Liquid-based Cytology
OCSP	Ontario Cervical Screening Program
SIL	Squamous Intraepithelial Lesion

### **Appendix 3. Recommended management for women with abnormal cytology (i.e., appendix to the Interim Recommendations).**

#### *ASCUS (Atypical squamous cells of uncertain significance)*

- HPV DNA testing with cytology is recommended for women aged 30 or older with ASCUS (C-III).
  - If the HPV DNA test is positive, women should be referred for colposcopy. If the HPV DNA test is negative, women should have repeat cytology in 12 months. Once a woman has had two negative cytology test results, she should return to routine screening.
  - In the absence of HPV DNA testing, a repeat Pap test in six months is acceptable. If the Pap test is abnormal, women should be referred for colposcopy. If the Pap test is negative, women should have repeat cytology in another six months. Once a woman has had two negative Pap tests results, she should return to routine screening.
- In women under the age of 30, a repeat Pap test in six months is recommended (C-III).
  - If the Pap test is abnormal, women should be referred for colposcopy. If the Pap test is negative, women should have repeat cytology in another six months. Once a woman has had two negative Pap tests results, she should return to routine screening.
- Referral to colposcopy, without HPV DNA testing or repeat cytology, is only recommended in situations where there is a high probability of patient loss to follow up, or if there are other symptoms suggesting cervical abnormality (e.g., abnormal bleeding) (A-I).

#### *ASC-H (Atypical squamous cells: cannot exclude high grade squamous)*

- Colposcopy is recommended for women with ASC-H (A-II).

#### *LSIL (Low-grade squamous intraepithelial lesion)*

- Either colposcopy or repeat cytology in six months is recommended for women with LSIL (B-II).
  - If repeat cytology is used and the Pap test is abnormal, women should be referred for colposcopy. If the Pap test is negative, women should have repeat cytology in another six months. Once a woman has had two negative Pap test results, she should return to routine screening.
  - There is limited evidence to support the use of intravaginal estrogen to reverse the cytologic changes in postmenopausal women with LSIL. A course of intravaginal estrogen followed by repeat cytology approximately a week after completing the regimen is acceptable for women with LSIL who have clinical or cytological evidence of atrophy and no contraindications to using intravaginal estrogen. Referral for colposcopy is recommended if a result of ASC-US or greater is obtained (CIII).

#### *HSIL (High-grade squamous intraepithelial lesion),*

- Colposcopy is recommended for women with HSIL (A-II).

#### *AGC (Atypical glandular cells)*

- Colposcopy is recommended for women with AGC (A-II).
- Women with AGC should also receive endocervical and endometrial sampling, where appropriate (A-II).

### Qualifying Statements

- These are minimum guidelines only. Certain clinical situations may require earlier follow-up/referral for colposcopy.
- Repeat Pap test should not be performed earlier than three months following the original.
- Pap test should not be used as the sole assessment of a visible cervical lesion. These patients require biopsy for accurate diagnosis.

### Key Evidence

Seven practice guidelines, six technology assessments, one meeting press release, one systematic review, three randomized controlled trials, one meta-analysis, eight cross-sectional studies, one prospective cohort study, four case-control studies, seven retrospective studies, and one conference report form the evidence for this practice guideline. If the evidence-base for these recommendations is required, please email [ccopgi@mcmaster.ca](mailto:ccopgi@mcmaster.ca).

In Review



cancer care  
ontario  
program in  
evidence-based care

action cancer  
ontario  
programme de soins  
fondé sur des preuves

## Evidence-Based Series 15-9: Section 2

### Cervical Screening: Evidentiary Base

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A Quality Initiative of the  
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

**Original Report Date: May 20, 2005**  
**Current Report Date: October 5, 2011**

#### QUESTION

In Ontario, in the context of an organized cervical screening program:

1. What is the optimal primary cervical screening method (i.e., human papillomavirus [HPV] DNA testing and/or cytology testing)?

In average risk, asymptomatic women:

2. What is the most appropriate age for the initiation of cervical screening?
3. What is the optimal interval between cervical screenings?
4. What is the most appropriate age for the cessation of cervical screening?

#### INTRODUCTION

The incidence of cervical cancer has declined dramatically over the past several decades in developed countries, largely due to the widespread implementation of the Papanicolaou (Pap) smear cervical screening test. While the dramatic decline in cervical cancer is remarkable, there were still an estimated 500 new cases and 140 deaths from the disease in Ontario in 2011 and, as in many other jurisdictions, the decline in incidence and mortality has plateaued <sup>1</sup>.

The purpose of cervical screening is to reduce the risk of cervical cancer through the detection of lesions that have the potential to become invasive cervical cancer. A secondary aim is to reduce the risk of advanced cancer through the detection of asymptomatic or early-stage cancer <sup>2</sup>. The natural history and epidemiology of HPV and cervical cancer can inform decisions about cervical screening age ranges and intervals <sup>3</sup>. However, additional factors that can influence these decisions include whether or not an organized screening program is in place, the nature of the program, and the availability of financial and human resources. Even in the absence of an organized system, the screening rate between 2006 and 2008 in Ontario was 72% for women 20 to 69 years of age. Recently, concerns about the sensitivity and

accuracy of cervical cytology screening and advancements in the understanding of the natural history of HPV have spurred research into alternatives to the conventional Pap screening paradigm.

New research in this area is timely because the Ontario Cervical Screening Program (OCSP) is currently being relaunched as an organized program with invitations to women in the target population. Until now, screening has largely been delivered opportunistically in Ontario. The features of an organized program are information systems linked to population databases to facilitate the recruitment of target populations, invitations to and the recall of women at appropriate intervals, communication of abnormal results to participants, and follow-up and monitoring of the program quality<sup>4</sup>. The OCSP relaunch has necessitated a review of evidence related to the research questions listed above and an update of the relevant portions of the PEBC 2005 guideline *Cervical Screening*<sup>5</sup>. The updated guideline will help the OCSP to realize its long-term goals of reducing the incidence of and mortality from cervical cancer through an organized screening program, and improving the capacity of providers to engage in organized cervical screening. It will also address the 2011-2014 Ontario Cancer Plan<sup>6</sup> goal of creating evidence-based guidelines for cervical cancer screening.

## **BACKGROUND**

### **Cervical Cancer**

The incidence and mortality rates for cervical cancer in Ontario are projected to be 7 in 100,000 (7/100,000) and 2/100,000 respectively in 2011, which is consistent with the national average<sup>1</sup>. By comparison, the rates are somewhat lower in other jurisdictions with highly functioning organized screening systems such as Finland and the Netherlands. Squamous cell carcinomas account for 80% of cervix cancers in Ontario, while the remainder are adenocarcinomas or adenosquamous carcinomas<sup>7</sup>.

The median age at diagnosis of cervical cancer is 47 years. The hysterectomy-corrected incidence rate rises continuously with age, reaching approximately 23/100,000 at age 65, after which it declines. The incidence for women in Ontario between 1998 and 2002 was very low among women 20 to 24 years of age (1.5/100,000)<sup>7</sup>. In the United States (US), the risk of being diagnosed with cervical cancer in the next 10 years was 0.04% at age 20<sup>8</sup>. The decline in incidence and mortality rates for cervical cancer over the past few decades has occurred in women 35 and older, while the rates for women 20 to 34 were low in 1971 and had declined relatively little by 2002<sup>9</sup>.

### **Cervical Screening**

Despite the low incidence of cervical cancer in young women, the decision to start screening at a relatively young age in Canada was prompted by results from the British Columbia (BC) cohort study (1949-1985) that showed the incidence of carcinoma in situ (CIS) was appreciable in women aged 20 to 24<sup>3</sup>. Other factors include an incomplete knowledge of the role of HPV in the development of cervical cancer, the perception that low-grade squamous intraepithelial lesions (LSIL) are an important precursor of cancer, and the link between cervical screening and other women's health concerns such as contraceptive prescriptions and sexually transmitted infection or disease (STI or STD) screening. For example, in describing the history of the British Columbia (BC) cervical screening program, which began in 1949, Boyes et al. say that the original age distribution of women attending for cervical screening was altered between 1960 and 1970 with the acceptance of the suggestion that patients utilizing oral and intrauterine contraceptives should have annual smears<sup>10</sup>. As a result, the highest screening coverage was shifted to the 20 to 29 years age group, whereas the rate had previously been highest in the 40 to 49 years age group.

Additionally, in the absence of nationally or provincially organized screening programs,

a “safety net” of more intense screening has been built into screening recommendations in Canada and the US <sup>3, 11</sup>.

Ontario introduced an HPV vaccination program for Grade 8 girls in 2007 <sup>12</sup>. At this time, because the vaccine does not cover all types of oncogenic HPV, screening is still required. A new challenge in years to come will be integrating the vaccination and screening programs. As successive cohorts of young women are vaccinated, the probability of a positive screening test will decline, and as these rates decline, heightened quality assurance and the positive predictive value of the tests will become increasingly important.

### **Human Papillomavirus and the Development of Cervical Cancer**

The Nobel prize-winning discovery that HPV causes cervical cancer was made in the mid-1970s and gained gradual acceptance over the years. Results from a large international study published in 1999 showed that HPV DNA is present in 99.7% of cases of cervical squamous carcinomas <sup>13</sup>, thus establishing HPV as the *necessary* (though not sufficient) cause of cervical cancer. Twelve HPV types have been identified by the International Agency for Research on Cancer as group 1 carcinogens <sup>14</sup>, including HPV types 16 and 18, which cause about 77% of cervical cancers. Others have been identified as probably or possible carcinogens <sup>13</sup>. A meta-analysis showed that the prevalence of HPV 16 and HPV 18 in high-grade squamous intraepithelial lesion (HSIL) cases was 45.0% and 7.1%, respectively. The prevalence of HPV 16 and HPV 18 was 54.3% and 12.6% in squamous cervical cancer, respectively <sup>15</sup>. Other HPV types were less prevalent. HPV infection is very common, especially in younger age groups <sup>16</sup>. For example, in a study of women undergoing routine cytology screening at family practices across Ontario, the prevalence of HPV infection in women aged 20 to 24 years was 24.0%, decreasing in successive five-year age groups to 3.4% in women 45 to 49 years of age <sup>17</sup>.

Research in recent years has advanced our understanding of the characteristics of HPV. We now know that, although HPV infection is very common, most infections, especially in young women, are transient and cleared by the host's immune system without intervention, even after one to three years <sup>11, 18</sup>. HPV infection can cause squamous intraepithelial lesions (SIL). Once present, these lesions do not necessarily progress in a linear fashion to higher grade SIL and cervical cancer <sup>19, 20</sup>. Winer et al., using a shorter screening interval, found that the time between the first detection of HPV and the first detection of cytologic abnormalities was similar for all grades of cervical intraepithelial neoplasia (CIN), and that HSIL is often an early manifestation of HPV infection in young women <sup>20</sup>. Low-grade SIL (LSIL) in young women is likely to regress; one study showed a regression rate of 94% for LSIL in 13- to 22-year olds <sup>11</sup>.

The cytology classification of HSIL includes the histology diagnoses of CIN grade 2 (CIN2) and CIN3, also known respectively as moderate and severe dysplasia. Determining what percentage of CIN3 would naturally progress to cancer is difficult because CIN3 is usually treated. A study, based on data collected before screening began in BC, estimated that the rate of progression of CIS to cervical cancer was probably between 26% and 53% and between 19% and 38% for dysplasia and CIS, respectively <sup>10</sup>. An unethical study conducted in New Zealand found that 13% (95% CI, 8% to 20%) of CIS progressed to invasive cervical cancer after five years and 31% (95% CI, 23% to 42%) progressed over a 30-year time period when treatment was withheld <sup>21</sup>. Sasieni et al. hypothesized, based on an extrapolation of CIN3 cases in England, that the progression rate is lower in young women and that approximately 3% of CIN3 in women aged 20 to 24 years would progress to cervical cancer by age 25 <sup>22</sup>. In general, the prevalence data show that the peak of CIN3 occurs in women in their late 20s, approximately five to seven years after the peak in incidence of HPV infection and about a decade before the peak of cancer incidence rates <sup>23, 24</sup>.



Because most lesions, especially those of a low-grade nature found in younger women, tend to regress, their detection and treatment can cause unnecessary anxiety<sup>25</sup>. There is also an increased risk of adverse reproductive outcomes such as preterm labour and premature rupture of membranes after the treatment of lesions<sup>26, 27</sup>. An optimal approach entails starting, ending, and rescreening at appropriate ages and intervals in order to strike a balance that prevents invasive cervical cancer, while minimizing adverse psychosocial and reproductive outcomes and unnecessary invasive procedures.

### **Cervical Screening Tests**

Ideally, a screening test should have a high sensitivity to detect disease (low false-negative rate), a high specificity (low false-positive rate), and high positive and negative predictive values (PPV, NPV)<sup>28</sup>. In conventional cytology, cervical cells are smeared on a glass slide and examined under a microscope for abnormalities. With liquid-based cytology (LBC), the cervical sample is rinsed immediately in an aliquot of fixative and sent to the laboratory where the final slide is produced. LBC provides a uniformly fixed and distributed sample of cells. Both conventional and LBC samples are evaluated by cytotechnologists in a similar fashion. The sensitivity of conventional cytology testing is variable because it requires adequate infrastructure and stringent training and quality control<sup>24</sup>.

Testing for HPV requires detecting HPV DNA within cervical cells. The Hybrid Capture 2 (HC2) HPV DNA test (Qiagen, Hilden, Germany) has been approved by Health Canada and the US Food and Drug Administration (FDA) for HPV testing. It uses a modified enzyme-linked immunoabsorbant assay (ELISA) to detect positivity for one or more of 13 carcinogenic types. Cervista™ HPV HR, which detects 14 high-risk types, and Cervista™ HPV 16/18, which detects HPV high-risk types 16 and/or 18 have been approved more recently. The Roche Amplicor HPV DNA test (Roche Diagnostics, Basel, Switzerland) is also approved by Health Canada. This test uses polymerase chain reaction, allowing amplification of DNA from 13 oncogenic HPV types, even with very low levels of infection or poor sample collection. HPV testing is automated and objective, which allows for better quality control compared to cytology testing. Results from studies conducted in Europe and North America show that HPV testing with HC2 has a sensitivity for high-grade intraepithelial neoplasia of 98.1% (95% CI: 96.8-99.4%) and a specificity of 91.7% (95% CI: 90.3-93.1%). HPV testing has a higher sensitivity and slightly lower specificity than cytology testing<sup>24</sup>.

### **METHODS**

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle<sup>29</sup>. For this project, the core methodology used was the systematic review. Evidence was selected and reviewed by a Research Coordinator from the PEBC and the Cervical Cancer Screening Guideline Working Group (the Working Group) (Appendix 1).

The systematic review is a convenient and up-to-date source of the best available evidence on the research questions listed above. The recommendations developed by the Working Group are published in Section 1 of this evidence-based series. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding source.

### **Literature Search Strategy**

Web sites of international guideline developers, Canadian provincial and national cancer agencies, and CancerViewCanada ([www.cancerguidelines.ca](http://www.cancerguidelines.ca)) were searched for existing evidence-based practice guidelines. As an initial screen, guidelines were assessed

with item seven from the AGREE II tool, which is part of the Rigour of Development domain<sup>30</sup>, an assessment of whether guideline development included a systematic search for evidence. If guidelines rated highly on this item, they were then to be assessed with the remainder of the questions from the AGREE II Rigour of Development domain (8 items in total). MEDLINE and EMBASE were searched (2005 to November 2010) using the same text words and medical subject headings (MeSH) as were used for the 2005 version of this guideline: cervix, cervical, cancer, carcinoma, screening, and mass screening (as an exploded MeSH term). Search terms related to study design and publication type included clinical trial (text word and publication type), clinical trials (as an exploded MeSH term), meta-analysis (text word and publication type), and systematic review. Reference lists of papers and review articles were scanned for additional citations. Cochrane Library was searched for topic-specific reviews from 2005 to 2010. The current controlled trials registry ([www.controlled-trials.com](http://www.controlled-trials.com)) was searched to ensure that the most recently published results for the randomized controlled trials (RCTs) were included. For the full literature search, please see Appendix 2.

As the development of the guideline neared completion, an additional search of MEDLINE using the key words listed above was conducted to bring the evidence base current to October 2011.

### **Inclusion Criteria**

Eligible sources for the method of primary screening question included the following: practice guidelines, systematic reviews with or without a meta-analysis, and randomized trials. For the questions of age of initiation, age of cessation, and screening interval, cohort and case-control studies were also considered for inclusion in the evidence base. Descriptive studies of the natural history of HPV were also used to inform the recommendations.

### **Exclusion Criteria**

1. Abstracts, letters and editorials.
2. Papers published in a language other than English, because of a lack of funding for translation.
3. Studies that were designed to assess outcomes in special populations, e.g., high-risk populations.

## **RESULTS**

### **Literature Search Results**

The systematic review identified nine published guidelines from other Canadian provinces and eight additional guidelines from other countries or organizations that contained recommendations based on a combination of evidence and consensus. In addition, 13 papers reporting results from seven randomized trials either recently completed or underway to assess the use of HPV testing in primary screening were identified. A further seven studies (three case-control, one pooled cohort, two single cohort, and one review article) were identified that address the research questions relating to screening age range and interval. The results of the literature search for primary studies are outlined in Appendix 3. The updated search (November 2010 to October 2011) found one study related to screening interval<sup>31</sup> and one study that provided further results for one of the RCTs that had previously been identified<sup>32</sup>.

### **Existing Guideline Documents**

The search for guidelines published since 2005 found guidelines from all Canadian provinces. Recent guidelines in the US have been published by the American College of Obstetricians and Gynecologists (ACOG), the National Cancer Institute, and the American

Cancer Society. Internationally, guidelines for the Europe Against Cancer Programme, Australia, the United Kingdom (UK), New Zealand, and the World Health Organization were identified. None of the guidelines from these groups or agencies rated highly on AGREE II item seven, i.e., they did not report a systematic search of the literature, and so they were not assessed with the remaining questions from the Rigour of Development domain or considered for adaptation. In general, North American, Australian, and New Zealand guidelines were more likely to recommend commencement of screening at a younger age, whereas the guidelines for European-based programs were more likely to recommend screening initiation at an older age, e.g., 25 years.

## **Primary Studies**

### **Primary Screening Test**

The study of HPV testing for primary cervical screening has benefited from the initiation of a number of RCTs<sup>33-39</sup>. Most of these RCTs are based in countries in Europe that have established, organized screening programs<sup>33-37</sup>. A Canadian RCT included women who sought screening under an opportunistic model<sup>38</sup>. Sankaranarayanan et al. studied outcomes with a one-time screen of a population that did not previously have access to screening<sup>39</sup>. All RCTs used conventional cytology testing in the control group, with the exception of one study that used LBC<sup>37</sup> and one that used standard care<sup>39</sup>. The intervention group usually consisted of screening with HPV testing with the Hybrid Capture II test (Qiagen, Hilden, Germany), and a polymerase chain reaction-based test was employed in two of the studies<sup>33, 34</sup>. The follow-up periods ranged from just over two years<sup>37</sup> to eight years<sup>39</sup>. Of the seven RCTs, four included women 29 years of age and older<sup>33, 34, 38, 39</sup>, two included women 25 and older<sup>35, 36</sup>, and one included women from 20 years of age<sup>37</sup>. Baseline data from these RCTs have been published, and second screening round results are in some cases available. Due to significant differences in study characteristics, a meta-analysis was not considered appropriate. Further information on the characteristics of these RCTs and their management strategies can be found in Appendix 5 and Appendix 6, respectively.

One strength of the RCTs located in the systematic review is that, with the exception of the RCT conducted in India, they were conducted within established screening programs, and thus were designed to evaluate outcomes in a real-world setting. In addition, relative detection rates were similar across studies, reinforcing the validity of the findings. On the other hand, because it is difficult to accrue a sample size large enough to assess the incidence of cervical cancer, most of the RCTs used the intermediate endpoints of CIN2 or CIN3 rates rather than incidence or mortality. Whether a reduction in CIN2/3 is sufficient evidence upon which to make policy decisions is a matter that has been debated<sup>40</sup>. Another limitation of these RCTs is that, in some cases, final results have not been published. The conclusions based on the outcomes reported to date could be strengthened by the inclusion of these final data.

In general, the RCTs have corroborated the findings of previous cross-sectional and cohort studies showing that HPV testing is more sensitive and slightly less specific for detecting CIN than cytology testing. In order to improve the specificity of the HPV test, some studies attempted to triage positive HPV test results. Triage with cytology testing was found to improve specificity and reduce referrals to colposcopy. One study that examined triage with HPV genotyping for HPV types 16 and 18 found that it did not improve the specificity of HPV testing. A summary of these outcomes can be found in Table 1.

**Table 1. Sensitivity, specificity, PPV, and NPV for RCTs of HPV testing in primary screening.**

Testing Method	Study	CIN3+				CIN2+			
		Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
CC	Swedescreen <sup>a 41</sup>	74.0 (59.7- 85.4)	98.2 (97.9- 98.5)	25.3 (18.5- 33.2)	99.79 (99.63 - 99.89)	71.3 (60.6 - 80.5)	98.6 (98.3 - 98.9)	42.5 (34.3 - 50.9)	99.59 (99.39 - 99.73)
	FPHT <sup>b 42</sup>	NA	98.9 (98.8- 99.0)	8.1 (5.7- 11.1)	NA	NA	99.1 (99.0- 99.2)	25.7 (21.6- 30.2)	NA
	CCCaST <sup>c 38</sup>	NA	NA	NA	NA	55.4 (33.6- 77.2)	96.8 (96.3- 97.3)	7.1 (4.8- 10.3)	99.8 (99.7- 100.0)
LBC	ARTISTIC <sup>d 37</sup>	95.7 (93.2- 97.9)	NA	LSIL: 4.7 (2.4-8.2)	NA	92.9 (90.2- 95.1)	89.3 (88.8- 89.7)	LSIL: 11.9 (8.1-16.8)	NA
HPV DNA	Swedescreen	96.0 (86.3- 99.5)	93.6 (93.0 - 94.2)	11.1 (8.3 - 14.4)	99.96 (99.87 - 100.0)	95.4 (88.6 - 98.7)	94.2 (93.5 - 94.7)	19.2 (15.6 - 23.2)	99.93 (99.82 - 99.98)
	FPHT (all women)	NA	92.7 (92.4- 93.0)	1.6 (1.1 to 2.2)	NA	NA	93.0 (92.7 to 93.2)	5.6 (4.7 - 6.5)	NA
	FPHT (women 25-34)	NA	83.3 (82.3 - 84.2)	1.0 (0.5- 1.9)	NA	NA	84.0 (83.1- 85.0)	6.2 (4.8-7.9)	NA
	CCCaST	NA	NA	NA	NA	94.6 (84.2- 100)	94.1 (93.4- 94.8)	6.4 (5.0-8.0)	100.0 (98.6- 100.0)
	ARTISTIC	NA	NA	7.9 (6.9- 9.0)	NA	NA	NA	14.8 (13.5- 16.1)	NA
HPV DNA targeting types 16 and 18	Swedescreen	56.0 (41.3- 70.0)	NA	16.0 (10.9 - 22.3)	NA	50.6 (39.6 - 61.5)	NA	25.1 (18.9 - 32.2)	NA
	ARTISTIC	97.0 (93.9- 98.8)	NA	NA	NA	93.4 (90.7- 95.5)	86.4 (85.9- 86.9)	NA	NA
HPV DNA with CC triage	FPHT	NA	98.9 (98.8- 99.0)	9.9 (7.2- 13.2)	NA	NA	99.2 (99.1- 99.3)	NA	NA
	CCCaST (pooled study arms)	NA	NA	NA	NA	53.8	99.1	21.4	99.8
	ARTISTIC	92.7 ( 88.6- 95.7)	NA	NA	NA	86.3 (82.8- 89.3)	95.6 (95.3- 95.9)	NA	NA
HPV DNA and CC or LBC (co- testing)	NTCC	NA	NA	NA	NA	NA	NA	NA	NA

**Abbreviations:** ARTISTIC = A Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Screening (UK), CC = conventional cytology, CCCaST = Canadian Cervical Cancer Screening Trial, CIN = cervical intraepithelial neoplasia, CIN2+ = cervical intraepithelial neoplasia grade 2 or more severe, CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe, FPHT = Finnish Public Health Trial, HPV = human papillomavirus, LBC = liquid-based cytology, LSIL = Low grade squamous intraepithelial lesion, NA = not available, NPV = Negative Predictive Value, NTCC = New Technologies in Cervical Cancer (Italy), PPV = positive predictive value.

**a** intervention arm only; **b** baseline data; **c** CCCaST data for HPV with cytology triage are pooled data from both study arms; **d** round 1

Relative detection rates are presented in Table 2 for studies that reported rates of CIN2+ over more than one screening round. Intervals between screening rounds ranged from as little as two years (ARTISTIC)<sup>37</sup>, to at least 6.5 years (POBASCAM)<sup>34</sup>. The consistent finding was an increased relative detection rate in the first screening round for CIN2, CIN2+, and CIN3+, followed by a decrease at the subsequent screening round (Table 2).

In addition, the Finnish Public Health trial conducted an initial screen and then followed women for up to five years. An analysis among those who attended screening (excluding those who were invited but did not attend), showed that there was an increase in overall detection of CIN3+, with a relative rate of 1.77 (95% CI, 1.16 to 2.74)<sup>43</sup>.

Sankaranarayanan et al.<sup>39</sup> followed participants for eight years after an initial screen. This RCT was conducted in a lower-resource population without an established history of cervical screening. Clusters of women were randomized to three intervention arms: HPV testing, cytology testing, and visual inspection with acetic acid (VIA). The control group was randomized to standard care (i.e., not offered screening). The hazard ratio (HR) for the incidence of stage II+ cervical cancer with HPV testing compared to standard care was 0.47 (0.32-0.69), while the HR for cytology testing compared to standard care was 0.75 (0.51-1.10). The study found a reduction in mortality from invasive cervical cancer with a single HPV test but not with the other forms of intervention, although HPV testing did not produce a significant reduction in high-grade CIN, which would be expected as these lesions are the precursors of invasive cervical cancer.

Results from the first screening round of the Canadian Cervical Cancer Screening Trial (CCCaST) were published in 2007<sup>38</sup>. CCCaST is investigating how HPV testing performs as a stand-alone screening test in a population of women who seek cervical screening on their own initiative. The setting of this trial most closely approximates the Ontario context, as it takes place within an opportunistic screening program in a high resource location. Both HPV testing and conventional cytology testing were performed in each of the study groups of women 30 to 69 years of age, but each index test was analyzed as if it had been done alone. The study corrected for verification bias by referring a sample of women with negative test results for colposcopy. The percentage of positive tests in the cytology arm was 3.0% (based on  $\geq$ ASCUS) compared to 6.3% with HPV testing. Further results from another screening round of this trial are anticipated.

Table 3 includes referral rates to colposcopy reported for RCTs carried out in higher resource settings. Rates of referral for colposcopy reflected detection rates and, therefore, were higher with HPV testing in baseline screening rounds and correspondingly lower in subsequent rounds. Again as a reflection of the detection rate, younger women were referred more often for colposcopy. A triage test of HPV positive results reduced the referral rate. ARTISTIC was not included in this comparison because of the high percentage of participants who were not fully assessed to determine whether or not they should receive colposcopy.

A summary of recently published meta-analyses and systematic reviews suggested a screening algorithm that employs HPV testing as the primary screen and uses cytology to triage HPV positive women. This proposal is based on the principle that the more sensitive screening test should be applied first and that the more specific test should be used for women who test HPV positive in order to determine management<sup>24</sup>.

**Table 2. Relative detection rates of CIN (HPV group (intervention)/cytology group (control)) (95% confidence interval) for RCTs with results for a screening round beyond baseline.**

	NTCC (aged 25-34) * † <sup>36</sup>	NTCC (aged 35-60) * † <sup>36</sup>	POBASCAM ‡ <sup>34</sup>	Swedescreen <sup>33</sup>	ARTISTIC <sup>37</sup>
<b>CIN3+</b>					
Baseline	NA	2.08 (1.47-2.95)	1.70 (1.15-2.51)	1.31 (0.92-1.87)	0.97 (0.75-1.25)
Round two	NA	0.48 (0.21-1.11)	0.45 (0.28-0.72)	0.53 (0.29-0.98)	0.53 (0.30-0.96)
Both rounds	NA	1.65 (1.21-2.26)	0.98 (0.74, 1.30)	1.04 (0.77-1.40)	1.18 (0.90-1.55)
<b>CIN2</b>					
Baseline	4.09 (2.24-7.48)	2.00 (1.44-2.77)	1.31 (0.76-2.25)	2.01 (1.19-3.4)	1.39 (1.03-1.88)
Round two	0.64 (0.23-1.27)	0.54 (0.23-1.28)	0.75 (0.39-1.47)	0.85 (0.38-1.90)	0.74 (0.41-1.34)
Both rounds	3.11 (2.20-4.39)	1.68 (1.25-2.26)	1.05 (0.69-1.59)	1.56 (1.02-2.40)	1.18 (0.90-1.55)
<b>CIN2+</b>					
Baseline	3.03 (2.28-4.03)	2.03 (1.60-2.57)	1.56 (1.14-2.13)	1.51 (1.13-2.02)	1.14 (0.94-1.38)
Round two	0.59 (0.33-1.05)	0.51 (0.28-0.93)	0.53 (0.36-0.78)	0.58 (0.36-0.96)	0.63 (0.42-0.96)
Both rounds	2.21 (1.73-2.81)	1.66 (1.34-2.06)	1.00 (0.79-1.27)	1.17 (0.92-1.49)	0.99 (0.83-1.19)

**Abbreviations:** CIN = cervical intraepithelial neoplasia, CIN2+ = cervical intraepithelial neoplasia grade 2 or more severe, CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe, HPV = human papillomavirus, NA = not available, NTCC = New Technologies in Cervical Cancer, POBASCAM = Population Based Screening Study Amsterdam, ARTISTIC = A Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Screening, \*Both phases combined, † CIN3+ = CIN3 and AIS, CIN2+ = CIN2, CIN3, and AIS, ‡ 95% confidence intervals calculated using OpenEpi software.

**Table 3: Colposcopy referral rates (%) for RCTs.**

Test	Positivity Threshold	Screening round	Age Group (yr)	FPHT 42-43	NTCC Phase 1 36, 44-46	NTCC Phase 2	POBASCAM 34	CCCaST 38
CC	≥ASCUS	Baseline	25-34	NA	4.1	3.1	NA	NA
			25-60	NA		2.5	NA	NA
			35-60	NA	2.2		NA	NA
			35-60	NA	NA	2.3	NA	NA
			30-69	NA	NA	NA	NA	2.9
	≥LSIL	Baseline	30-69	NA	NA	NA	NA	1.0
			3 year follow-up	25-29	3.5	NA	NA	NA
		3 year follow-up	30-34	1.7	NA	NA	NA	NA
			25-65	1.2	NA	NA	NA	NA
	≥HSIL	Baseline	29-56	NA	NA	NA	1.3	
HPV only	1pg/ml	Baseline	25-34	NA	NA	12.3	NA	
			25-60	NA	NA	7.3	NA	
			30-69	NA	NA		NA	6.1
			35-60	NA	NA	5.4	NA	
HPV with CC triage	1pg/ml/ASCUS	Baseline	30-69	NA	NA	NA	NA	1.1
	1pg/ml/LSIL	3 year follow-up	25-29	3.5	NA	NA	NA	NA
			30-34	2.5	NA	NA	NA	NA
			25-65	1.2	NA	NA	NA	NA
CC and HPV cotesting	ASCUS or 1pg/ml	Baseline	30-69	NA	NA	NA	NA	7.9
			25-34	NA	11.7 <sup>a</sup>	NA	NA	NA
			35-60	NA	7.6*	NA	NA	NA
CC and HPV cotesting after intensified follow-up	HSIL or 1pg/ml	Baseline	29-56	NA	NA	NA	2.3	NA
		Round 2	29-56	NA	NA	NA	Intervention: 1.3 Control: 1.9	NA

**Abbreviations:** ASCUS = Atypical Squamous Cells of Undetermined Significance, CC = conventional cytology, CCCaST = Canadian Cervical Cancer Screening Trial, FPHT = Finnish Public Health Trial, HPV = human papillomavirus, HSIL = high grade squamous intraepithelial lesion, LSIL = low grade squamous intraepithelial lesion, NA = not available, NTCC = New Technologies in Cervical Cancer (Italy), pg = picogram, POBASCAM = Population Based Screening Study Amsterdam  
a Liquid-based cytology

### *Age of Screening Initiation*

A case-control study conducted in the UK <sup>47</sup> assessed the odds ratio (OR) for developing cervical cancer in the next five-year interval in those screened in a given three-year age band, compared with those not screened in that age band or within the previous two years. They found no protective effect of screening at ages 22 to 24; the OR of developing cancer (all stages) at 25 to 29 years was 1.11 (95% CI, 0.83 to 1.50) for those screened at 22 to 24 years, compared to those not screened at 20 to 24. There was a significantly lowered OR in the older age groups reported, indicating a benefit of screening within the previous six years for those in the age groups 35 to 39, 45 to 49, and 55 to 59.

Another case-control study <sup>48</sup> found that adequate screening had a protective effect for women under the age of 30 (OR, 0.49; 95% CI, 0.24 to 0.98). Adequate screening in this study was defined as every three years for ages 23 to 50 and every five years from 51 to 60 (i.e., the recommended screening ages and intervals in Sweden). The OR for developing cervical cancer in the Swedish study was 2.37 in age group 21-29 (95% CI, 1.36 to 4.13), 2.51 (95% CI, 2.14 to 2.94 ) in the 30-65 age group, and 2.79 (95% CI, 1.89 to 4.11) in the 66+ age group for the unscreened group compared to those with adequate screening. The risk of cervical cancer for women without, compared to with, a Pap smear was similarly increased for all age groups (p=0.96). In a further analysis, the investigators specified that there were significantly reduced odds of the development of stage 1B+ cervical cancer for women aged 27 years and older who had participated in three-yearly screening, but that there was no benefit to having participated in three-yearly screening for women aged 23 to 26.

A smaller case-control study of women 25 to 74 years of age in Trento, Italy <sup>49</sup> included 61 cases, with 12 in the under-40 age group. The study found that the Pap test offers less protection for younger age groups; the OR of developing cervical cancer in women less than 40 who had undergone at least one Pap test compared to no Pap test was 1.00 (95% CI, 0.18 to 5.65).

### *Screening Interval*

Data from seven European studies were pooled to examine the long-term predictive values of cytology and HPV testing <sup>50</sup>. NPVs are useful for determining appropriate screening intervals, and the critical factor is the cumulative incidence of CIN3+ among women who had negative results at baseline screening. Because low and moderate grades of CIN often regress, CIN3+ was considered the more appropriate endpoint. After three years of follow-up, the rate of CIN3+ was 0.51% (95% CI, 0.23 to 0.77) for women with negative cytology results and 0.12% (95% CI, 0.03 to 0.24) for women with negative HPV results. The rate of CIN3+ after six years with a negative HPV test was 0.27% (95% CI, 0.12 to 0.45) <sup>50</sup>. Another cohort study showed that the risk of CIN3+ after a negative HPV test is low: the 12-year absolute risk of CIN3+ after a negative HPV DNA test in women with normal cytology was 3.0% (95% CI, 2.5 to 3.5%) <sup>51</sup>.

Persistent lesions have a higher likelihood of progressing to cervical cancer. The short-term persistence of HPV infection for at least one year is an important predictor of CIN2+: Women who tested HPV positive at enrolment and negative after about one year had a cumulative incidence of CIN2+ after three years of 1.2% (95% CI, -0.2 to 2.5). The three-year cumulative incidence of CIN2+ in women who tested positive for carcinogenic HPV at study enrolment and again after approximately one year was 17.0% (95% CI, 12.1 to 22.0) <sup>52</sup>.

The ARTISTIC trial found that over three rounds of screening, the rate of CIN2+ was 1.41% (95% CI, 1.19 to 1.65%) in women with negative baseline cytology and 0.87% (95% CI, 0.70 to 1.06%) in women with a negative baseline HPV test. Based on these findings, they suggest that the screening interval could be extended to six years with HPV testing as the primary screen <sup>53</sup>.

Results from a cohort study in BC <sup>54</sup> showed that multiple consecutive negative



cytology tests approximately one year apart were not associated with a reduced risk of invasive cervical cancer in women with no history of moderate atypia on previous screens. With those with three or more negative screens being the referent group, the relative risk was 0.73 (95% CI, 0.45 to 1.19) for women with two consecutive negative screens and 0.95 (95% CI, 0.65 to 1.4) for one previous negative screen. By contrast, the risk was of invasive cervical cancer was reduced with multiple negative screens for women with a history of moderate atypia.

A modelling study conducted in Australia found that increasing the recommended screening interval from two years to three years with cytology-based testing would result in no substantial change to incidence and mortality due to cervical cancer<sup>31</sup>.

#### *Age of Screening Cessation*

No studies were found that addressed age of cessation and met the inclusion criteria.

## **DISCUSSION**

Balancing the benefits and harms of cervical screening is an ongoing challenge. When reviewing the evidence and making recommendations, we must keep in mind that the primary goal of screening is to reduce the incidence of and mortality from cervical cancer by detecting precancerous lesions before they progress to cancer, while avoiding the detection of lesions that are destined to regress. It is not possible to know for certain which lesions are destined to progress or regress, but studies of the characteristics of HPV, the necessary cause of cervical cancer, have provided some guidance. For example, we know that persistent infection with a high-risk HPV type is an important predictor of progression and that the vast majority of lesions detected in young women are destined to regress.

To achieve optimal effectiveness, a screening program must be organized, with a call and recall system that facilitates a high level of coverage in the population at risk. Indeed, increasing the coverage rate has more potential for lowering cervical cancer rates than making changes to the screening ages or intervals or a more sensitive screening test<sup>55</sup>. Currently, relevant population databases are in the process of being given prescribed registry status in Ontario, which will allow for implementation of the organized program. Ontario's imminent adoption of an organized screening program for cervical cancer and the move away from opportunistic screening are positive steps, especially because the longer screening intervals indicated by HPV negative tests will need to be implemented in an organized program with ongoing process and outcome evaluations<sup>24, 56</sup>. Organized screening will also mean that the OCSP will be better positioned to reach out to groups that have demonstrated lower rates of screening, such as immigrant women, older women, and women of lower socioeconomic status<sup>57</sup>.

Despite the awareness that organized screening programs are more effective<sup>3</sup>, Ontario has historically delivered cervical screening opportunistically due to legislative and regulatory restrictions on the use of population databases and concerns that women would not accept the use of these databases for this purpose<sup>4</sup>. Screening recommendations have been consensus-based in order to allow for this context, and the theory that a "safety net" approach based on shortening screening intervals and beginning at a younger age would compensate for an inadequately organized screening program was widely accepted. The consequences of formulating such recommendations have been the overscreening of younger women and the inadequate screening of older women who are most at risk. The negative outcomes of overscreening young women include the anxiety related to positive test results and future adverse pregnancy outcomes as a consequence of the treatment of lesions.

In light of these considerations, the Working Group has recommended an interim screening initiation age of 21, a recommendation that would curtail the screening of

teenagers who are at extremely low risk of cervical cancer. This is a change from the previous guideline recommendation, which called for screening within three years of the initiation of sexual activity, thus including many women 20 years of age and under in the population to be screened. The new recommendation was the consensus of the Working Group, based on a number of factors, including the traditionally high rate of attendance among women under 30 years of age<sup>58</sup>, the potential reduction in cancer risk associated with the treatment of high-grade lesions, and the general desire to be conservative with the management of women in this age group given overall trends towards decreasing screening rates among younger women in developed countries<sup>59</sup>. This recommendation should be reviewed if the HPV screening algorithm is funded in the province.

The advent of HPV testing in primary screening and the accumulation of high-quality evidence favouring its adoption have forced a shift in the way that women are screened for precursors of cervical cancer. Previously, cytology screening was administered to screen for lesions that were caused by HPV infection. With the increased sensitivity for detecting CIN of HPV testing, it is possible to gain valuable lead-time. The somewhat lower specificity of HPV testing compared to conventional cytology can be mitigated by a triage step before a referral to colposcopy. The recommended algorithm uses the best available evidence to date and recommends cytology testing for the triage of positive HPV test results. While co-testing with HPV testing and cytology has been adopted for women 30 years and older in some jurisdictions, this strategy is not recommended here because the gain in sensitivity is offset by higher costs and reduced specificity<sup>60</sup>. As the literature regarding HPV testing is evolving with new results anticipated from ongoing RCTs, it would be prudent to revisit the recommended algorithm to ensure its currency before implementation.

With HPV testing as the primary screening test, a recommendation for the HPV triage of ASCUS/LSIL cytology results in women 30 years and older would no longer be necessary. As well, the HPV test is automated, which will be more important as an increasing proportion of the population is vaccinated against HPV and the percentage of women who are infected decreases, accompanied by a decline in the probability of a cytotechnologist viewing a positive cytology test. In this scenario, the PPV of cytology testing will likely suffer more than the PPV of HPV testing. HPV testing with cytology triage would protect the effectiveness of cytology testing because cytology testing would be performed in those in whom the prevalence of lesions is high<sup>61</sup>. Furthermore, an economic model found that, in Canada, screening women every three years beginning at age 25 with HPV testing as the primary screen, the cytology triage of positive results, and the referral to colposcopy for ASCUS or worse to be more cost effective and result in fewer cases of cervical cancer than was the typical practice in many parts of Canada of screening with cytology testing every year beginning at age 18, then every three years from age 21, and the referral to colposcopy for results of LSIL or worse<sup>62</sup>.

The Working Group for this guideline is aware that recommendations for an overall reduction in the number of recommended screens over women's lifetimes may be controversial<sup>63</sup>. There is also evidence to suggest that frequent Pap tests provide women with peace of mind regarding their reproductive health and that physicians may reinforce these perceptions<sup>64, 65</sup>. For these reasons, education regarding the purposes of the Pap test and the HPV test is needed so that women understand their risk of cervical cancer, the risks associated with treatment, and the frequency with which they should be screened. These recommendations should ideally be implemented in a holistic manner, taking into account the related facets of women's health care. Preventive care bonuses for physicians who achieve a targeted screening rate need to be aligned to provincial guidelines and responsive to changes in guideline recommendations.

These guidelines should also be put into the wider Canadian context. The Canadian

Task Force on Preventive Health Care has highlighted the need to address these questions from a national perspective, and they are currently facilitating an evidence review at the national level.

## CONCLUSION

Sufficient evidence has accumulated from RCTs to indicate that HPV testing for primary screening for cervical cancer prevention is advisable for women aged 30 and older. A screening algorithm has been presented that incorporates the most current evidence to date. Given that HPV testing for primary screening is not funded at this time in the Province of Ontario, the authors provide interim recommendations until HPV testing is in place and more evidence is available, particularly with respect to the age of initial screening.

## FUTURE RESEARCH

Results from further screening rounds of several of the RCTs that are included in the evidence base for this guideline are anticipated in the next one to three years (Table 4). These results should further inform the optimal screening algorithm for women 30 years of age and older and the optimal age to commence cervical screening. An international agreement has been reached to join forces to conduct future meta-analyses of the HPV screening trials and to synthesize evidence on new methods for cervical cancer prevention <sup>66</sup>.

**Table 4. Anticipated results from randomized trials.**

Study name (ID number)	Study Initiation date	Study End date	Further results anticipated?
CCCaST (ISRCTN57612064)	September 2002	July 2007	Yes; long-term efficacy data (personal comm. Eduardo Franco).
NTCC (ISRCTN81678807) <sup>36</sup>	February 2002	December 2004	Yes; A cost-benefit analysis is underway <sup>36</sup> . Also, an update with data from the third screening round and analysis on the longitudinal accuracy of different screening methods, such as genotyping, are underway. (personal comm. Guglielmo Ronco).
ARTISTIC (ISRCTN25417821)	June 2001	November 2009	Yes; the ARTISTIC trial is continuing to follow women while maintaining the randomised concealment of HPV testing results for a further 3-year round of screening <sup>53</sup> .
FPHT (ISRCTN 23885553)	January 1999	December 2020	Yes; the group intends to rescreen women according to the same allocation at least twice; publications based on this ongoing follow-up are anticipated <sup>43</sup> .
POBASCAM (ISRCTN20781131)	January 1999	September 2007	No
Sankaranarayanan	October 1999	2007	No
Swedescreen (NCT00479375)	May 1997	May 2007	No

**Abbreviations:** ARTISTIC = A Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Screening (UK), CCCaST = Canadian Cervical Cancer Screening Trial, FPHT = Finnish Public Health Trial, NTCC = New Technologies in Cervical Cancer (Italy), POBASCAM = Population Based Screening Study Amsterdam (The Netherlands).

The HPV FOCAL study (Trial Registration No. ISRCTN79347302) is being conducted by the BC Cancer Agency, in collaboration with the BC Centre for Disease Control, the University of British Columbia, McGill University, and healthcare providers in Metro Vancouver and Greater Victoria. In a Canadian context, this study aims to establish the efficacy of human

papillomavirus (HPV) testing as a stand-alone screening test with cytology triage of HPV positive women, establish an appropriate screening interval for HPV negative women, and determine cost-effectiveness of HPV testing as a primary screening test.

Other HPV testing strategies under study are based on molecular markers and include viral load, genotyping, testing for the RNA of the viral oncogenes E6 and E7, and testing for the overexpression of the p16-INK4A protein (37).

As research continues into the risk factors for cervical cancers and the different type-specific and other tests evolve, screening algorithms will become increasingly more complex. In response to this, a group is developing a tool to predict risk for a woman of having or developing cervical precancer. These risk estimates could be used to make referral and screening interval decisions (38), and may be considered for implementation in future versions of this guideline.

### CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Expert Panel members, internal reviewers, and external targeted peer reviewers were asked to disclose potential conflicts of interest.

Four authors declared they had no conflicts. Three others (SD, MFKF, and MS) declared conflicts. SD reported involvement in a clinical trial on this topic. MFKF reported a potential decrease in colposcopy referrals as a result of this guideline. MS reported receiving more than \$5000 in a single year from consulting fees, honoraria, and/or other support from GlaxoSmithKline and Graceway Pharmaceuticals, as well as several publications on this topic in the past five years.

For the Expert Panel, six members declared they had no conflicts of interest, and five (LE, AC, MP, JF, TC) declared conflicts. LE reported receiving more than \$5000 in a single year from consulting fees, honoraria, and/or other support from the Canadian Partnership Against Cancer for the creation of an economic model from primary prevention to palliation in cervical cancer and publishing on this topic in the past five years. AC and MP have received honoraria for HPV vaccine-related speaking engagements. JF and TC have published on this topic in the past five years or have related publications in press.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at [ccopgi.mcmaster.ca](mailto:ccopgi.mcmaster.ca)

### JOURNAL REFERENCE

A systematic review article and a clinical practice guideline article have been published in the *Journal of Obstetrics and Gynaecology Canada* (© JOGC 2012; <http://www.jogc.com/>):

- Murphy J, Kennedy EB, Dunn S, McLachlin M, Fung Kee Fung M, Gzik D, et al. HPV testing in primary cervical screening: a systematic review and meta-analysis. *J Obstet Gynaecol Can.* 2012;34(5):443-52.
- Murphy J, Kennedy EB, Dunn S, McLachlin M, Fung Kee Fung M, Gzik D, et al. Cervical screening: a guideline for clinical practice in Ontario. *J Obstet Gynaecol Can.* 2012;34(5):453-58.

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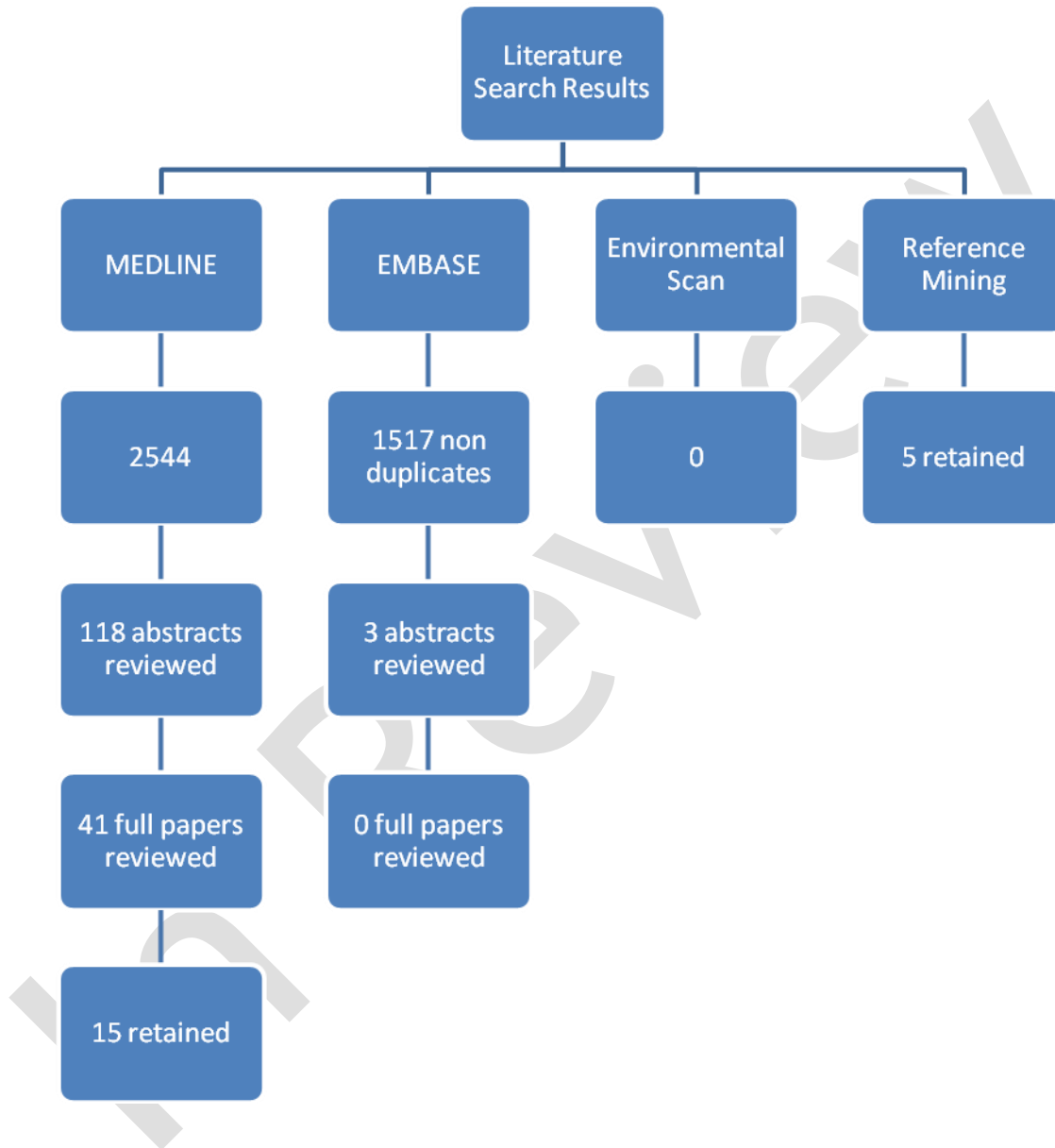
## Appendix 1. Cervical Cancer Screening Working Group and Expert Panel members.

<b>Working Group</b>	
Dr. Joan Murphy (Chair) Gynecologic Oncologist Division of Gynecologic Oncology, University Health Network 610 University Avenue, M-700 Toronto	Erin Kennedy, Research Coordinator Program in Evidence-based Care, Cancer Care Ontario McMaster University, Juravinski Site 711 Concession Street, Hamilton
Dr. Sheila Dunn Family Practitioner Family Practice Unit, Women's College Hospital 76 Grenville Street Toronto	Dr. Meg McLachlin Deputy Chief, Pathology London Health Sciences Centre 339 Windemere Road, A3-150 University Campus London
Dr. Michael Fung Kee Fung Director of Gynecologic Oncology Program Ottawa General Hospital 501 Smyth Road Ottawa	Dr. Lawrence Paszat Senior Scientist Institute for Clinical Evaluative Sciences 2075 Bayview Avenue Toronto
Dr. Danusia Gzik Family Practitioner Regional Primary Care Lead - Cancer Care Ontario North Simcoe Muskoka Local Health Integration Network	Dr. Michael Shier Director - Colposcopy Unit - Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Toronto
<b>Expert Panel: Members of the Cancer Care Ontario Cervical Clinical Advisory Committee and/or the Gynecologic Cancer Disease Site Group</b>	
Dr. Terence Colgan Pathologist Pathology & Laboratory Medicine, Mount Sinai 600 University Avenue Toronto	Ms. Carol McDowell Nurse practitioner Women's Health Centre, Group Health Centre Sault Ste. Marie
Dr. Alan Covens Gynecologic Oncologist Associate Scientist Sunnybrook Health Sciences Centre 2075 Bayview Ave Toronto	Dr. Michel Prefontaine Gynecologic Oncologist London Health Sciences Centre - Victoria Hospital 800 Commissioners Road East London
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## Appendix 2. Literature search details

1. cervix.tw.
2. cervical.tw.
3. cancer.tw.
4. carcinoma.tw.
5. screening.tw.
6. mass screening.tw.
7. clinical trial.tw.
8. meta-analysis.tw.
9. Cervix Uteri/
10. Cervical Intraepithelial Neoplasia/
11. Neoplasms/
12. Carcinoma/
13. Mass Screening/
14. clinical-trial.pt.
15. exp Clinical Trial/
16. meta-analysis.pt.
17. 1 or 2 or 9 (cervix)
18. 3 or 4 or 11 or 12
19. 5 or 6 or 13
20. 17 and 18 and 19
21. 20 and (7 or 14 or 15)
22. 20 and (8 or 16)
23. 20
24. 21 or 22 or 23
25. 25
26. limit 26 to (english language and yr="2004 - 2010")

Appendix 3. Flow diagram of systematic review results.



## Evidence-Based Series 15-9: Section 3

### Cervical Screening: EBS Development Methods and External Review Process

*J. Murphy, E. Kennedy, S. Dunn, M. Fung Kee Fung, D. Gzik, C.M. McLachlin, M. Shier,  
and L. Paszat*

A Quality Initiative of the  
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

**Original Report Date: May 20, 2005**  
**Current Report Date: October 5, 2011**

#### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels, termed Guideline Development Groups, called together for a specific topic and all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

#### The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in

Ontario by review participants.

- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

## DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

### Development and Internal Review

This EBS was developed by the Cervical Screening Guideline Working Group (the Working Group) and review and internal approval were provided by the Cervical Screening Expert Panel of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on cervical screening, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario and elsewhere.

### Expert Panel Review and Approval of the Draft Guideline

The Expert Panel comprised members of the PEBC Gynecologic Cancer Disease Site Group (Gyne DSG), and the CCO Cervical Clinical Advisory Committee (CCAC) who were not already on the Working Group. The Expert Panel was invited to review the draft guideline. Six of 12 members of the CCAC agreed to review the document, and five of these six completed the review. Of the 11 Gyne DSG members who were asked to participate, six agreed, and five completed the review. Not including relatively minor formatting or wording changes, the comments fell into the broad categories listed below. The Working Group's responses are presented after each comment. A member of CCO's Molecular Oncology Advisory Committee (MOAC) also reviewed the document.

- Terms needing definition:
  - high risk human papillomavirus
  - adequate negative screening history
  - organized screening program

### *Modifications/Action/Response*

The Working Group added the definitions or further explanations for these terms and also decided to include a glossary of terms.

- Needs more explanation:
  - meaning of persistent positivity for high risk HPV
  - “no longer a need for ASCUS/LSIL triage”
  - the guideline is very focused on HPV testing, and it is not clear that the screening recommendations are to commence at age 21 (or later)
  - rationale for some recommendations not obvious, specifically:
    - colposcopy in HR HPV+, negative cytology, and repeated in 1 yr with same results
    - repeating HPV testing at 5 yr intervals if HR HPV-

### *Modifications/Action/Response*

Further explanation was provided for the first two statements. More detail was added to the rationale for colposcopy, and the heading of the third paragraph in same section was changed to reflect the addition. As well, the heading of the fourth paragraph under Key Evidence for the HPV testing algorithm was changed to read: *Repeat HPV Testing at Five-Year Intervals after HPV Negative Results*.

- Should be added to the document:
  - Mention of underscreened populations.
  - Roche Amplicor HPV test & genotyping and other tests: i.e., P16INK4a, E6, also cotesting.
  - Headings to clearly indicate Part 1 and Part 2 of the recommendations.
  - Specify what do in the case of results of inadequate specimens, or no endocervical cells.
  - Explicit statement of the differences between the new recommendations and current standard practice in Section 1.
  - More description of the randomized controlled trials, in particular a description of their limitations in the results, Section 2.
  - A new version of what to do for each variety of abnormal report.

*Modifications/Action/Response*

The Working Group agreed that all the suggested items should be added to the guideline document, with the exception of recommendations related to each variety of abnormal report, because this topic was determined at the outset to be beyond the scope of the systematic review. A table was added to the beginning of Section 1 to summarize the recommendations and clearly indicate which are interim and which are evidence-based.

- Should be removed from the document:
  - extensive discussion of other guidelines

*Modifications/Action/Response*

The original document had an extensive description of guidelines from other jurisdictions. The Working Group agreed that much of this text was unnecessary; therefore, it was removed from the main body of the report and added to an appendix.

- Missing evidence:
  - “Awaiting mature results of the contributing randomized controlled studies which could facilitate a meta-analysis would strengthen this guideline.”
  - Note that follow up RCT data from subsequent screening rounds is not available.

*Modifications/Action/Response*

A table has been added (Table 4) that outlines which RCTs are expected to provide data from further screening rounds. While a meta-analysis may not be appropriate due to difference in study designs, the Working Group agreed that data from further screening rounds would be useful in informing the recommendations at the time that HPV testing is implemented in the Province of Ontario.

- Implementation concerns:
  - Where cotesting with HPV and cytology testing has been implemented, a proportion of HPV+/cyto- women have been unwilling to wait one year for re-testing, and often demand colposcopy. Has there been an analysis of what the Working Group’s recommendations will mean for colposcopy services in Ontario (will they be overwhelmed)?
  - It does seem premature to fully recommend an entirely new screening paradigm without first acknowledging the necessity for thorough impact analysis and delineation of system prerequisites for success.

- ...incentive programs, while excellent in supporting providers to think preventively, need to be quickly responsive to the changing prevention guidelines
- As the qualifying statement suggests the infrastructure for this recommendation does not exist. It was not clear to me that this strategy would result in lower rates of cervical cancer since there is still apparently a 3% false negative rate, and presumably none of those women would have a repeat smear for 5 years. Therefore, if there is a significant associated cost there would be some concerns. Do we have any estimates on # of cervical cancer cases prevented?

#### *Modifications/Action/Response*

The purpose of this systematic review was to provide recommendations based on health-related outcomes of interest, i.e., incidence of cervical intraepithelial neoplasia and invasive cervical cancer. An analysis of the cost and system-related implications would be the next step, completed by specialists in this type of analysis.

Although it was beyond the scope of this project to include costing estimates in the evidence base for the recommendations, a costing study that was mentioned in the Discussion found that, in Canada, screening women every three years beginning at age 25 with HPV testing as the primary screen, cytology triage of positive results, and referral to colposcopy for ASCUS or worse to be more cost effective and resulted in fewer cases of cervical cancer than the typical practice in many parts of Canada of screening with cytology testing every year beginning at age 18, then every three years from age 21, and referral to colposcopy for results of LSIL or worse (2).

Periodic co-collection using both HPV and cytology testing was raised by one group member as a method of dealing with the false-negative rate; however, this was not adopted as a recommendation at this time. Kulasingam et al. have provided an estimate of the number of cases of cervical cancer prevented (2).

- Recommendation for cessation:
  - Note that the SEER database in the USA suggests that 10% of cases are found between ages 65 and 74. I would argue that 10% strikes me as still a significant minority, although the arguments raised by the committee were reasonable.

#### *Modifications/Action/Response*

The group wanted to emphasize that screening should only be discontinued if women had an adequate screening history and a final negative HPV test. A sentence was added to emphasize that women who did not meet these requirements should not cease cervical screening.

- Questions:
  1. It is inappropriate to recommend a screening age of initiation of 30. Without screening how many of these women will develop cancer, and only have it detected after age 30, and subsequently be rendered infertile or subfertile by treatment?
  2. Do we have any economic modeling to support a recommendation like this one?
  3. Why did we not state that screening is required within 3 years of initiation of sexual activities?
  4. One reviewer noted that the UK is not moving to HPV testing based on the results of the ARTISTIC trial and asked why we have come to a different conclusion for Ontario, given the similarities between our two jurisdictions, e.g. the use of liquid-based cytology.

## Responses

1. The Working Group recognized that, as drafted, our recommendation for HPV testing to begin at 30 years of age could be interpreted as a recommendation not to screen women younger than 30. In response, the interim recommendation for cytology screening for 21 to 29 year olds is mentioned with the recommendation for HPV testing. In addition, in answer to the question posed by the reviewer, the OCSP Report (2001-2005) indicates that between 0.002% and 0.003% of cytology results for women in Ontario in 2001, 2002, and 2003 were “carcinoma”, which equates to between six cases (2003) and nine cases (2002) per year. This is the number of cases that would be missed if women younger than 30 were not screened and that would be detected on or after age 30.
2. Kulasingam et al. have published an economic model that was mentioned in the Discussion.
3. The Working Group discussed this wording and decided that, because there was no evidence base for the recommendation to screen within three years of initiation of sexual activity, it would be preferable to recommend that “*women who are not sexually active by age 21 may delay cervical screening.*”
4. Results from the ARTISTIC trial were evaluated along with data from several other RCTs. Our report weighed the evidence from all seven trials that were found as a result of the systematic review, including CCCaST, which was conducted in Canada, and came to a different conclusion than did the UK study, which was based on data from ARTISTIC alone. In terms of trial quality, ARTISTIC had several limitations, including the incomplete ascertainment of cases of CIN2+ (3). As well, the implementation of the trial at the same time that LBC was being implemented in the UK might have affected the estimates of CIN2 and CIN3. ARTISTIC plans to follow participants for another round of screening. The results of this analysis are awaited with interest and will likely help to inform future guideline recommendations.

## Report Approval Panel

Prior to the submission of this EBS draft report for External Review, the report was reviewed by the PEBC Report Approval Panel (RAP), a three-person panel whose members have clinical, methodological, and oncology expertise. The key issues raised by the Report Approval Panel included the following:

- In order for the document to be approved, the authors need to provide a stronger rationale for recommendations to commence screening at age 21 and for the requirement for three annual negative cytology tests. This comment pertains to the following draft recommendations and supporting evidence (BOX 1):

### BOX 1:

DRAFT RECOMMENDATIONS and KEY EVIDENCE (circulated for internal review April 2011)

INTERIM RECOMMENDATION (to be followed until HPV testing is in place)

*Age of screening initiation*

Cytology testing should commence at 21 years of age for sexually active women.

### KEY EVIDENCE

Three case-control studies were the highest level of research evidence found in the systematic review. One case-control study found no protective effect of screening at ages 22-24; the odds ratio of developing cancer (all stages) at 25-29 years was 1.11 (95% CI 0.83-1.50) for those screened at 22-24 compared to those not screened at 20-24. (4). Another case control study found a protective effect of screening from age 24 and up (5). A third smaller



study found screening to be less effective in younger women.

While the authors of this guideline acknowledge that there is no specific evidence to indicate that age 21 is the optimal age to begin screening, they would like to take the opportunity provided by the update of this guideline to recommend that screening of adolescents be curtailed. Evidence of the potential for adverse reproductive outcomes with treatment, anxiety related to the testing procedure and the anxiety and potential stigma associated with positive test results considerably outweigh the benefits of screening in women younger than 21 years of age (6-9), given the high rate of transient HPV infections (10) (11), and the extreme rarity of cervical cancer in this age group. Although there is also little evidence for screening women between 21 and 25 years of age (below age 25, cervical cancer is also extremely rare, transient cytological abnormalities are quite common, and over 90% of low grade squamous intraepithelial lesions regress (11)), the authors anticipate that there will be evidence within the next 24 months to provide a more solid evidence base for a screening age recommendation. Therefore, an incremental increase in screening initiation age to 21 from the previous recommendation to begin screening within 3 years of initiation of sexual activity is provided as an interim recommendation.

#### **INTERIM RECOMMENDATION (to be followed until HPV testing is in place)**

##### ***Screening interval***

The authors endorse the screening intervals presented in the 2005 version of this guideline:

- Screening annually until there are three consecutive negative Pap tests.
- Screening should continue every two to three years after three annual negative Pap tests
- Women who have not been screened in more than five years should be screened annually until there are three consecutive negative Pap tests.

##### **KEY EVIDENCE**

- Although the evidence for annual screening until there are three consecutive negative Pap tests is not substantial and a cohort study published since the previous guideline did not find a benefit with annual screening (12), the consensus of the authors is to maintain this recommendation until the HPV-based screening algorithms have been adopted and organized screening has been established in the province.
- Further evidence for this recommendation is presented in the 2005 PEBC guideline *Cervical Screening: A Systematic Review*.

- The guideline appears to have been written by specialists for specialists; and assumes knowledge of cytology and histology classifications. More information on screening tests should be added to the introductory notes in Section 1.
- The authors should explain why they only used AGREE II instrument item 7 to assess the guidelines that were located in the systematic review.
- Impact of HPV vaccination on screening should be added to the Introduction before the section on cervical screening tests
- The authors have not made it clear why cervical screening has to be detached from other women's health issues.
- The goal of the interim recommendation is unclear. The authors should state the purpose of these recommendations. Is the goal to include appropriate recommendations for women younger than 30 since they are currently being screened, with the goal that screening these women would stop when HPV testing is adopted?

### *Modifications/Actions/Response*

Upon receiving the RAP feedback, the authoring group discussed the rationale for the two recommendations that had not been approved and came to the following consensus:

- The group had originally decided to endorse the recommendation from the previous guideline for three annual negative screens before the extension of the screening interval in order to maintain consistency with the 2005 guideline, in light of very little new evidence being published in the interim. However, upon further discussion, the Working Group agreed that there was limited evidence for this position, and thus, the group decided to eliminate the requirement for three annual negative screens before extending the screening interval.
- The recommendation for the age of initiation was also discussed, and the group felt strongly that beginning at age 21 in the interim until HPV testing is in place in Ontario should be recommended. The Working Group members recognized, however, that a stronger rationale would be needed to support this position and thus drafted a revised RATIONALE section for this recommendation, which more fully describes the values of the group, and the harms and benefits that were weighed in coming to consensus on this recommendation. The revised rationale is presented in BOX 2.

#### **BOX 2:**

**Interim recommendation for age of screening initiation with Rationale updated in response to RAP comments**

**INTERIM RECOMMENDATION (to be followed until HPV testing is in place)**

#### ***Age of screening initiation***

**Cytology testing should commence at 21 years of age for sexually active women.**

After weighing the available evidence, the authors of this guideline have concluded that the harms of screening women under 21 years of age significantly outweigh the benefits. In the opinion of the authors, the potential for adverse reproductive outcomes with treatment, anxiety related to the testing procedure and the anxiety and potential stigma associated with positive test results considerably outweigh the benefits of screening in women younger than 21 years of age (6-9), given the relatively high rate of HPV infection (10) (11), rarity of cervical cancer in women under 25, and the up to decades-long time period of progression from HPV infection to cervical cancer(13).

In the opinion of the Working Group, evidence regarding the necessity, utility and/or effectiveness of screening in women 21-24 is not as clear; the authors of this guideline are not convinced that the harms outweigh the benefits of screening for these women. Therefore, the consensus is that lesions in these women should be detected and treated where appropriate in order to minimize the potential for their progression to cervical cancer. The reasons for this are:

- The authors of this guideline consider that rates of high grade lesions may be used as a surrogate for cancer risk. The rate of HSIL (CIN2 or CIN3) in women 20-29 who underwent screening in Ontario in 2003 was 0.5%, which is equivalent to diagnosis in approximately 1,500 women (14). Treatment of these women, where appropriate, reduces the risk of microinvasive or invasive cancer for the estimated 3% of 21-24 year olds with CIN3 who could be expected to develop cervical cancer by age 25 (15).
- Although the gap has more recently narrowed, the rate of attendance for cervical screening has traditionally been highest among women under 30 years of age (16). Screening women in their early 20s has provided an opportunity to establish a patient-physician relationship and it is hoped that this would facilitate ongoing screening at appropriate intervals throughout the age range for which screening is recommended. Furthermore, the interaction provides an opportunity to give accurate information about

LSIL, and other health promotion topics (17).

- The screening participation rate fell by 1.1% in women 20-29 years of age in Ontario between 2000-2002 and 2006-2008 (16). Greater decreases have been recorded in other developed countries (18). This trend points towards being conservative in the absence of good mechanisms to invite and recall women for screening. These mechanisms are under development in Ontario at the time of this writing.
- The incidence of cervical cancer has declined by about 2.0%-2.5% per year since 1981 in all age groups from 20-34 years and over, suggesting that cervical screening has had a positive impact at all age groups. That is, the age standardized rate declined for women 20-34 in Ontario from approximately 11/100,000 in 1981 to 9/100,000 in 2002 (19).
- Screening young women is established practice and accepted by patients and clinicians as a beneficial activity that reduces the risk of cervical cancer and provides peace of mind regarding reproductive health (20).

The authors of this guideline recognize that there is also potential for harm with screening in this age group. The potential harms related to treatment of CIN are adverse reproductive outcomes including premature rupture of membranes, low-birth weight births and pre-term delivery (8). However, detecting and treating CIN3 in young women may prevent some cancers from developing and attaining a level of severity for which treatment could result in compromised fertility. The reproductive-related harms as well as potential anxiety, fear and uncertainty related to abnormal Pap tests, intensified screening, colposcopy, biopsy and treatment for CIN are considered by the authors of this guideline to be outweighed by the benefit of eliminating potential cases of invasive cervical cancer in this age group.

- An appendix was added with the classification system nomenclature for cytology and histology testing. The Working Group also agreed to include a glossary of terms, including the word “triage”, which was specifically mentioned as needing further explanation, and the definitions of the screening tests being considered.
- Further explanation was provided for why AGREE Item 7 was used and not the entire AGREE tool or at least the entire Rigour of Development domain. Briefly, Item 7 was used as an initial screen to see whether the guidelines used systematic methods. We would then have proceeded to use the entire Rigour of Development domain had any of the guidelines passed this initial screen, but none had passed.
- A note about the impact of HPV vaccination on screening was added to the Introduction.
- The Working Group decided to eliminate the recommendation to detach women’s health issues as it was found to not be consistent with the rationale provided for cervical screening of women 21 to 24 years of age.
- The goal of the interim recommendations is to provide guidance in the interim period between the publication of this guideline and the provincial implementation of HPV testing.

## External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Working Group circulated Sections 1 and 2 to external review participants for review and feedback. Box 2 summarizes the draft recommendations and supporting evidence developed by the Working Group.

### **BOX 2:**

**DRAFT RECOMMENDATIONS** (approved for external review July 7, 2011)

#### **QUESTIONS**

In Ontario, in the context of an organized cervical screening program:

5. What is the optimal primary cervical screening method (i.e., human papillomavirus [HPV] DNA testing and/or cytology testing)?

In average risk, asymptomatic women:

2. What are the most appropriate ages for the initiation and cessation of cervical screening?
3. At what interval should women be recalled for cervical screening?

#### **PART 1: RECOMMENDATIONS FOR CERVICAL SCREENING WITH HPV DNA TESTING**

##### **RECOMMENDATION**

###### **Primary Screening Test**

High-risk HPV DNA testing is recommended for the primary screening of women 30 years of age and older. Cytology screening, which was recommended for primary screening in the previous version of this guideline, is now recommended only in the event of a positive HPV DNA test result (see HPV screening algorithm, Figure 1). Screening recommendations for women 21 to 29 years of age are outlined in Section 1, Part 2 (Interim Recommendations).

##### **KEY EVIDENCE**

Seven randomized controlled trials (RCTs) (2-8) have been conducted to assess the performance of HPV testing in primary screening. Five of these RCTs compared HPV testing with conventional cytology testing (i.e., the Papanicolaou [Pap] smear test) (2-5,7), and two compared HPV testing with liquid-based cytology (LBC) (6,8). Five studies took place in European countries with established, organized screening programs, while the others were conducted in Quebec and Newfoundland, Canada and Osmanabad Province, India. All of the trials assessed rates of cervical intraepithelial neoplasia grade 2 or grade 3 (CIN2 or CIN3), either at a baseline screening round or over two screening rounds. CIN2 is a useful indicator because it is often the threshold for clinical management. CIN3 is less likely than lower grades of CIN to regress or resolve without treatment and so is a useful predictor of the risk for cervical cancer. Consistently across studies, HPV testing detected significantly more CIN2 and CIN3 in the baseline screening round than did cytology-based testing. HPV testing detected fewer CIN2 or more severe (CIN2+) cases in the subsequent screening round, indicating a lead time gain with HPV testing.

The endpoint of invasive cervical cancer is relatively rare and was only assessed by three

of the trials. One of these had limited statistical power to analyse any impact on invasive cervical cancer (9). The two studies that were powered to detect differences in rates of invasive cervical cancer found the following:

- A hazard ratio (HR) for the detection of advanced cancer of 0.47 (95% confidence interval [CI], 0.32 to 0.69) in the HPV testing group, and 0.75 (95% CI, 0.51 to 1.10) in the cytology testing group compared to a control group of women who were not offered screening but were advised on how to seek screening (standard care). This trial had sufficient numbers to report mortality due to cervical cancer and found a significant reduction with HPV testing, but not with cytology testing, compared to standard care (4).
- There was no significant difference in the number of invasive cancers detected in the baseline screening round in the New Technologies in Cervical Cancer trial (8) comparing HPV testing and cytology testing. In the subsequent screening round, no cases of cancer were found in the HPV-testing group, while nine cases were found in the cytology-testing group ( $p=0.028$ ). A high number of the cancers detected in the second round in the cytology group were adenocarcinomas.

#### **QUALIFYING STATEMENT**

- The recommendation for HPV testing is applicable only in the context of an organized screening program with an adequate database infrastructure that allows for an invitation to screening at recommended intervals, and a follow-up of women with abnormal test results.
- Women who have never been sexually active<sup>4</sup> do not require cervical screening.

#### **RECOMMENDATION**

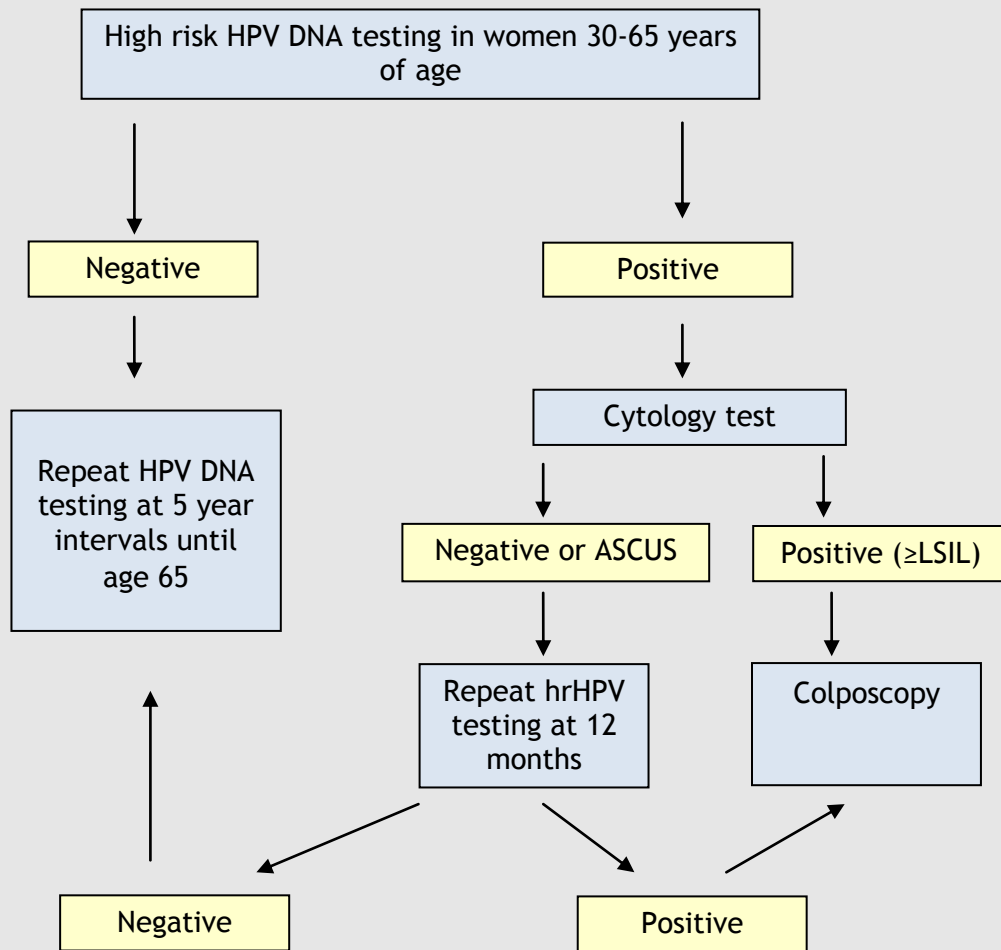
##### **Screening Interval for Women 30-65**

Screening interval recommendations are according to the algorithm presented in Figure 1. For women aged 30-65, HPV DNA testing is to occur at five-year intervals with a negative result, which is a change from the recommendation for repeat cytology testing every two to three years contained in the 2005 version of this guideline. HPV-positive tests should be assessed with cytology testing and not referred directly to colposcopy. Repeat HPV testing for results of HPV positive/cytology negative or atypical squamous cells of undetermined significance (ASCUS) should be conducted after one year.

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<sup>4</sup> Sexually active is defined as vaginal intercourse and vaginal/oral and/or vaginal/digital sexual activity.

Figure 1: Primary cervical screening with HPV testing (women 30-65)<sup>5</sup> (adapted from Cuzick et al. 2008 (10)).



**KEY EVIDENCE**

**HPV with Cytology Triage**

Due to the higher sensitivity of HPV testing compared to conventional cytology, the rate of colposcopy referral with HPV testing alone is higher than the rate with conventional cytology. For example, in the Canadian Cervical Cancer Screening Trial (CCCaST) RCT, the rate of referral to colposcopy after a positive HPV test alone was 6.1%, compared to a referral rate of 2.6% for conventional cytology results of atypical squamous cells of undetermined significance (ASCUS).

A triage test can reduce the number of colposcopy referrals and increase the specificity of the screening algorithm. In CCCaST, HPV with Pap triage resulted in a 1.1% rate of referral based on ASCUS. Results from the intervention arm of the Swedescreen RCT showed that

<sup>5</sup> This screening algorithm should be reviewed for currency prior to its implementation as results from subsequent screening rounds of the HPV RCTs are expected in the next one to two years.

primary HPV screening followed by cytology triage and repeat HPV testing of HPV-positive women with normal cytology maintained a high positive predictive value (PPV) (22.0%; 95% CI, 16.7 to 28.1) compared to cytology testing alone (25.3%; 95% CI, 18.5 to 33.2). The Finnish Public Health Trial found the frequency of colposcopy referrals was 1.2% in both the conventional cytology arm at a threshold of low-grade squamous intraepithelial lesion (LSIL), and the HPV with cytology triage arm of their trial. PPVs for the detection of CIN were not significantly different: 34.4% (95% CI, 29.9 to 39.2) with HPV testing with cytology triage and 25.7% (95% CI, 21.6 to 30.2) with cytology testing alone. For CIN3+, the PPV was 9.9% (95% CI, 7.2 to 13.2) with HPV testing with cytology triage and 8.1% (95% CI, 5.7 to 11.1) with cytology testing alone.

#### **Repeat HPV Testing after One Year with HPV Positive/Cytology Negative or ASCUS Results and Referral to Colposcopy if Persistently HPV Positive**

Persistent lesions have a higher likelihood of progressing to cervical cancer (11), although persistence in itself may not be unequivocally related to carcinogenicity (12). Castle et al. found that the short-term persistence of HPV infection for at least one year was an important predictor of CIN2+ (13). In women who tested HPV positive at enrolment and negative after about one year (nine-21 months), the cumulative incidence of CIN2+ after three years was 1.2% (95% CI, -0.2 to 2.5); however, the three-year cumulative incidence of CIN2+ in women who tested positive for carcinogenic HPV at study enrolment and again after approximately one year was 17.0% (95% CI, 12.1 to 22.0). Consequently, the authors recommend referral to colposcopy after two consecutive positive HPV tests occurring a year apart, even in the event of initially negative or ASCUS cytology results.

#### **Repeat HPV Testing at Five-Year Intervals after HPV Negative Results**

- A significantly higher detection rate of CIN2+ in the baseline screening round of several RCTs (3,5-6,8), compared to cytology, indicates that HPV testing is highly sensitive to prevalent cases. The high level of sensitivity means that HPV testing has a negative predictive value (NPV) that lasts for years (14).
- Six years after a positive HPV test, pooled cohort data found a cumulative incidence rate for CIN3+ of 0.27% (95% CI, 0.12 to 0.45), which was lower than the rate after three years with a positive cytology test (0.51%; 95% CI, 0.23 to 0.77) (15). This indicates that retesting at five-year intervals would entail a low level of risk.
- The risk of CIN3+ after a negative HPV test is low: in a Danish cohort study the 12-year absolute risk of CIN3+ after a negative HPV DNA test in women with normal cytology was 3.0% (95% CI, 2.5 to 3.5%) (12).

#### **QUALIFYING STATEMENTS**

The authors of this guideline anticipate that HPV testing will not be implemented immediately in Ontario for funding and infrastructure reasons. The screening algorithm (Figure 1) should be reviewed for currency prior to implementation because results from subsequent screening rounds of the HPV RCTs are expected in the next one to two years. In particular, the recommendation for repeat HPV testing of women with HPV-positive results and ASCUS should be reviewed.

A variation on this algorithm includes genotyping for HPV 16 and/or HPV 18 immediately after a positive HPV test and cytology results of normal, ASCUS or LSIL, based on the rationale that HPV 16 has been shown to be more persistent and more often associated with high-grade lesions, and HPV 18 is more often associated with difficult to detect lesions in the endocervical canal (10). Positivity for either of these types may require immediate colposcopy.

## **RECOMMENDATION**

### **Age of Screening Cessation**

Screening may be discontinued after the age of 65 provided there is an adequate negative screening history in the previous 10 years (i.e., two or more negative tests) and a final negative HPV test at age 65. Women who do not meet these requirements should continue with screening at recommended intervals. This is a change from the previous recommendation of cessation at age 70. This recommendation is largely consensus-based, taking into account the low rate of cervical cancer in this age group among women who have previously been adequately screened, the potential discomfort of the procedure, and difficulties with visualization of the squamocolumnar junction in older women.

### **KEY EVIDENCE**

This recommendation is the consensus of the authors.

## **PART 2: INTERIM RECOMMENDATIONS (TO BE FOLLOWED UNTIL HPV TESTING IS IN PLACE)**

### **INTERIM RECOMMENDATION**

#### **Primary Screening Test for Women under 30 Years of Age**

There is insufficient evidence to make a recommendation for primary screening testing for women less than 30 years of age. Therefore, on an interim basis until more information is available, the authors endorse the recommendation contained in the 2005 version of this guideline: primary screening with cytology testing, preferably liquid-based.

### **KEY EVIDENCE**

Most of the RCTs included women 29 years of age and over, because they were conducted within organized screening programs in countries where younger women are not part of the population invited for screening. Another reason for this restriction was to maximize the performance of both Pap and HPV testing (15,16). Of the trials that did include younger women, one found that the specificity of HPV testing for CIN2+ and CIN3+ for the age group 25 to 34 years was significantly lower than the specificity for the entire study population of women aged 25 to 64 years (17). The other RCT that included women aged 25 to 29 years found a significant increase in the detection of CIN2 in this age group in the first screening round with HPV testing, that was accompanied by only a slight decrease in the second round, suggesting that a large number of CIN2 lesions that were destined to regress had been detected and treated (8). Optimal cervical cancer screening for women younger than 30 years of age is still an area in need of research (16). Therefore, the authors endorse the previous recommendations from the 2005 version of this guideline until more information becomes available.

### **QUALIFYING STATEMENTS**

- Women with Pap tests that lack transformation zone components (i.e., endocervical and/or metaplastic cells) may continue screening at the regular intervals recommended by the guideline.
- The above statement does not include women with test results of “unsatisfactory”, who should undergo repeat screening in three months.

### **INTERIM RECOMMENDATION**

#### **Age of Screening Initiation**

Cytology testing should commence at 21 years of age for sexually active women.



## KEY EVIDENCE

Three case-control studies were the highest level of research evidence found in the systematic review. One case-control study found no protective effect for screening at ages 22 to 24 years; the odds ratio (OR) of developing cancer (all stages) at 25 to 29 years was 1.11 (95% CI, 0.83 to 1.50) for those screened at 22 to 24 years compared to those not screened at 20 to 24 (18). Another case-control study found a protective effect for screening from age 24 and up (19). A third smaller study found screening to be less effective in younger women (20).

## RATIONALE

After weighing the available evidence, the authors of this guideline have concluded that the harms of screening women under 21 years of age significantly outweigh the benefits. In the opinion of the authors, the potential for adverse reproductive outcomes with treatment, anxiety related to the testing procedure, and the anxiety and potential stigma associated with positive test results considerably outweigh the benefits of screening in women younger than 21 years of age (21-24), given the relatively high rate of HPV infection (25), rarity of cervical cancer in women under 25 years, and the up to decades-long time period of progression from HPV infection to cervical cancer (26).

In the opinion of the working group, evidence regarding the necessity, utility, and/or effectiveness of screening in women 21 to 24 years is not as clear; the authors of this guideline are not convinced that the harms outweigh the benefits of screening for these women. Therefore, the consensus is that lesions in these women should be detected and treated where appropriate in order to minimize the potential for their progression to cervical cancer. The reasons for this are:

- The authors of this guideline consider that rates of high-grade lesions may be used as a surrogate for cancer risk. The rate of high-grade squamous intraepithelial lesion (HSIL) (CIN2 or CIN3) in women aged 20 to 29 who underwent screening in Ontario in 2003 was 0.5%, which is equivalent to diagnosis in approximately 1,500 women (14). The treatment of these women, where appropriate, reduces the risk of microinvasive or invasive cancer for the estimated 3% of 21- to 24-year olds with CIN3 who could be expected to develop cervical cancer by age 25 (27).
- Although the gap has more recently narrowed, the rate of attendance for cervical screening has traditionally been highest among women under 30 years of age (28). Screening women in their early 20s provides an opportunity to establish a patient-physician relationship, and the hope is that this would facilitate ongoing screening at appropriate intervals throughout the recommended age range for such screening. Furthermore, the interaction provides an opportunity to give accurate information about LSIL and other health promotion topics (29).
- Screening young women is an established practice and is accepted by patients and clinicians as a beneficial activity that reduces the risk of cervical cancer and provides peace of mind regarding reproductive health (30).
- The screening participation rate, however, fell by 1.1% in women 20 to 29 years of age in Ontario between 2000-2002 and 2006-2008 (28). Greater decreases have been recorded in other developed countries (31). This trend indicates that participation by physicians and women is decreasingly less likely to occur in the absence of good mechanisms to invite and recall women for screening. Such mechanisms, however, are now under development in Ontario.
- The incidence of cervical cancer has declined by about 2.0%-2.5% per year since 1981 in all age groups from 20 to 34 years and over, suggesting that cervical screening has had a positive impact on all age groups. That is, the age standardized rate declined for women aged 20-34 in Ontario from approximately 11 in 100,000 in 1981 to 9 in 100,000 in 2002

(32).

The guideline authors do recognize that there is also a potential for harm with screening in this age group. The potential harms related to treatment of CIN are adverse reproductive outcomes, including premature rupture of membranes, low birth weight, and preterm delivery (23). The early detection and treatment of CIN3 in young women, however, might prevent some cancers developing to a stage where treatment could result in compromised fertility. Based on the information available at this time, the authors of this guideline consider that the benefit of eliminating potential cases of invasive cervical cancer in this age group outweighs the reproduction-related harms, as well as the potential anxiety, fear, and uncertainty related to abnormal screening tests, intensified screening, colposcopy, biopsy, and treatment for CIN.

#### **QUALIFYING STATEMENTS**

- Women who are not sexually active<sup>6</sup> by age 21 may delay cervical screening.
- Women who have never been sexually active do not require cervical screening.
- Further information on HPV testing is anticipated that will inform the optimal age of initiation of cervical screening. The interim recommendation to begin screening at 21 years of age should be reviewed within 24 months of the publication of this guideline.

#### **INTERIM RECOMMENDATION**

##### **Screening Interval**

Women should be screened every three years.

#### **KEY EVIDENCE**

The previous guideline recommended three annual negative screens before lengthening the screening interval to two to three years. A cohort study published since that guideline did not find a benefit with annual screening (33), and this corroborates evidence presented in the previous version of this guideline, which showed that the excess risk with screening every three years compared to annually was approximately 3 in 100,000 (34).

#### **INTERIM RECOMMENDATION**

##### **Age of Screening Cessation**

The authors endorse the age of cessation presented in the 2005 version of this guideline:

- Screening may be discontinued after the age of 70 if there is an adequate negative cytology screening history in the previous 10 years (i.e., three to four negative cytology tests).

#### **KEY EVIDENCE**

Key evidence for this recommendation is presented in the 2005 PEBC guideline *Cervical Screening: A Systematic Review*.

#### **RECOMMENDATION**

##### **Screening of Special Populations**

The authors endorse the recommendations for screening of special populations contained in the 2005 version of this guideline:

- Immunocompromised women such as those currently taking long-term immunosuppressants or those who are HIV positive should receive annual screening.
- Screening can be discontinued in women who have undergone total hysterectomy for

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<sup>6</sup> Sexually active is defined as vaginal intercourse and vaginal/oral and/or vaginal/digital sexual activity.

benign causes with no history of cervical dysplasia or HPV. Women who have undergone subtotal hysterectomy (with an intact cervix) should continue screening according to the guidelines.

- Indications for screening frequency for pregnant women should be the same as for women who are not pregnant. Manufacturers' recommendations for the use of individual screening tools in pregnancy should be considered.
- Women who have sex with women should follow the same cervical screening regimen as women who have sex with men.

#### **KEY EVIDENCE**

Key evidence for this recommendation is presented in Section 2 (systematic review section) of the 2005 PEBC guideline *Cervical Screening* (1).

#### **Methods**

*Targeted Peer Review:* During the guideline development process, seven targeted peer reviewers from outside Ontario considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks prior to completion of the draft report, three nominees were contacted by email and asked to serve as reviewers. All three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on July 7, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Working Group reviewed the results of the survey.

*Professional Consultation:* Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Practitioners from the areas of family medicine or primary care, gynecology and those in our database with an interest in hpv testing and/or screening were surveyed. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on July 7, 2011 and the consultation period ended on August 23, 2011. The Working Group reviewed the results of the survey.

## Results

*Targeted Peer Review:* Key results of the feedback survey completed by the three reviewers are summarized in Table 1.

**Table 1. Responses to nine items on the targeted peer reviewer questionnaire.**

Question	Reviewer Ratings (N=3)					Missing
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)	
<b>1. Rate the guideline development methods.</b>				2	1	
<b>Comments</b> <ul style="list-style-type: none"> <li>Occasionally the authors interpreted the evidence based on a consensus of their opinions. But this was clearly stated</li> <li>Not all parts of this guideline are able to draw upon supporting level 3 evidence, e.g. effect of extending the screening interval. I think more of the HPV biology story would have helped support the guideline.</li> <li></li> </ul>						
<b>2. Rate the guideline presentation.</b>			1		2	
<b>Comments</b> <ul style="list-style-type: none"> <li>I had no problem following this guideline and locating references when needed</li> <li>Well done</li> <li>The interim guidelines seem somewhat less complete/thorough. Also the presentation of the 2 guidelines is confusing. It may help to use similar bullet points for both.</li> </ul>						
<b>3. Rate the guideline recommendations.</b>				2	1	
<b>Comments</b> <ul style="list-style-type: none"> <li>I was very impressed with the concept of setting the direction of travel very firmly and then putting in place interim guidelines. I wondered if another reason for interim guidelines for the younger women would be because of the unknown nature of the effect of vaccination? Is there high coverage in Ontario or is this unlikely to be a factor?</li> <li>The guidelines are appropriate and easy to use in practice, except for the point raised at item 5.</li> </ul>						
<b>4. Rate the completeness of reporting.</b>					3	
<b>Comments</b> <ul style="list-style-type: none"> <li>The decision about the length of the screening interval with HPV+ is primarily based upon cohort analyses. These do not seem to have been critically reviewed but summarized. For example are there methodologic concerns, are the populations used similar to Ontario etc.</li> <li>The methods were well described and sound.</li> </ul>						
<b>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</b>			1		1	1
<b>Comments</b> <ul style="list-style-type: none"> <li>There was little analysis of the approach taken to patients who have been vaccinated against HPV 16/18. While the recommendation may be unchanged a clinical guideline requires explicit consideration of this group of women.</li> <li>A second issue which, I felt, received insufficient attention was the consideration of harms. I think these are of two major types: potential anxiety/concern associated with a positive HPV (STI) test result versus an abnormal pap smear and the rate of referral to colposcopy, which can be used as a surrogate for other potential harms. HPV with cytology triage is unlikely to identify more CIN2/3 but the follow-up of the persistent HPV+ will. Will the new algorithm result in more or fewer women going to colposcopy?</li> <li>Excellent summary of current knowledge</li> <li>Since Pap testing will be used for a few years, I would need to know who to refer for colposcopy as long as the Pap test is the main test.</li> </ul>						

6. What are the barriers or enablers to the implementation of this guideline report?						
<b>Barriers</b>						
<ul style="list-style-type: none"> <li>Barriers are the acceptance of the pap smear and that, to date, it has been the most effective of any cancer screening test.</li> <li>The main barrier to the principal recommendation will be the widespread availability of HPV testing. Also, a major effort of information (both for health care providers and women) will be needed to ensure that the changes are not perceived as service/budget cuts.</li> </ul>						
<b>Enablers</b>						
<ul style="list-style-type: none"> <li>The approval of an HPV test for use in screening seems to be the highest priority for moving towards implementation of the guideline.</li> <li>A great enabler will be a program, however the details of that program are very important. The hazard of potential overtesting with HPV is considerably greater than with the pap smear.</li> </ul>						
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)	Not applicable
7. Rate the overall quality of the guideline report.					1	
8. I would make use of this guideline in my professional decisions.		1		1		1
9. I would recommend this guideline for use in practice.				1	2	

**Additional Comments**

**Reviewer 1:**  
I would not use it in my practice a great deal because we are in a different jurisdiction with different rules. However, a couple of points were useful.

- I did not see the point of a variation on the algorithm for genotyping HPV positive women. The Evidence section shows that 77% will be 16/18 positive, so why not go for immediate colposcopy without further testing. Is this cost-effective and worth the wait for the results?
- The recommendation for screening cessation should include the phrase “and no abnormal results” as per the ACOG guidelines quoted in the evidence section p6
- The statement on p8 of the recommendations concerning the success of screening in women 20-34 does not match with the evidence for these women quoted on p2 about little decline in women of this age group
- The recommendation “Immunocompromised women such as those currently taking long-term immunosuppressants” needs further definition. Would they include women on DMARDs? Or just those who have had a solid organ transplant? This is from the 2005 guidelines and does not appear to have been further considered
- A number of references are made to the ARTISTIC trial and that follow up is continuing. In fact the results of that follow up into a third round have been published and this sentence could be updated. See Kitchener HC, Gilham C, Sargent A, Bailey A, Albrow R, Roberts C, Desai M, Mather J, Turner A, Moss S, Peto J. *A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial.* Eur J Cancer. 2011 Apr;47(6):864-71.

**Reviewer 2:**  
I enjoyed reading this guideline. I think the authors are to be complimented.  
An issue is the recommendation to not send women HPV+ with ASCUS to colposcopy. The rationale of using HPV testing is that significant CIN2+ is missed by cytology and that this can lead to cancer if not treated. However the HPV+.ASCUS group is known to have a significant risk of CIN2+ being present. Thus, I assume, that the major rationale for not scoping is that by retesting at 12 months the benefit:harm ratio is improved. It would be good to present this.

**Reviewer 3:**

- The interval to be screened may differ from the interval for recall (for example 3 year intervals may be the target and women who have not gone to screening after 4 years may receive a letter). You may want to clarify this
- The trials you mentioned showed this remarkable performance by sending ALL HPV positive women to colposcopy. There was no cytology triage. Most experts agree that such a strategy will generate too many referrals.
- Unfortunately, the only trial that used cytology triage of HPV + women, did not find a statistically significant advantage in their first analysis. They did in a subsequent analysis when restricting age groups. Screening with a primary human papillomavirus test does not increase detection of cervical cancer and intraepithelial neoplasia 3. Kotaniemi-Talonen L, Anttila A, Malila N, Tarkkanen J, Laurila P, Hakama M, Nieminen P. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. So I personally would like more data before concluding that cytology triage works
- again no triage of HPV+women
- Your group can decide to make this recommendation [algorithm, Figure 1], but I don't think it should be labeled evidence-based (Table 1, page 2). This algorithm is a suggestion of experts and we may have data before 2013 (FOCAL) but in my opinion we do not enough data now to consider it evidence-based
- ASCUS HPV pos and LSIL HPV+ are the same. I am not aware of any evidence that suggests it is safe to defer colposcopy for one year in women over 30 who are ASCUS HPV positive
- I think that key argument [for HPV testing with cytology triage] has to focus on NPV and not PPV. By nature, a triage test will limit the number of referrals and increase PPV. NO surprise there: you will find more disease in women with 2 abnormal tests. What health care providers and women will want to know is HOW SAFE is it to simply follow HPV positive women without investigating them NPV relates to safety
- Do you want to indicate that Bethesda terminology should be used and who should go to colposcopy (until HPV testing is available)
- I do not think that reviews and meta analysis warrant the statement that LBC should be "preferably" used
- This is not the reason. Most RCTs WERE conducted in settings where screening starts before 30. Women younger than 30 were left out because previous cross sectional studies had shown that too many were positive with too few significant lesions to consider HPV testing in the younger age group
- The flow is not entirely clear jumping from young women to satisfactory/unsatisfactory smears. Is that only for young women?
- why 3 months?
- I think this is a dangerous argument. We have had physicians arguing that we should continue Pap testing in adolescent because otherwise they may not get tested for STIs! To me, it's a little bit like saying we should do mammograms on 25 year olds so we can discuss contraception...I don't think we should be doing tests in order to see women for OTHER tests they need. If your review of the literature convinces you that 21-24 year olds need cervical cancer screening, fine (I'm convinced!). However, if not, then you should recommend 25 as the starting age.
- If you are planning to review the guidelines in a few years, you may want to comment that as vaccinated girls will approach the age of screening initiation, this may also impact recommendations
- and the PPV of the tests [will become increasingly important as young women are vaccinated].
- This [rate of progression] is not really lower. Rule of thumb: app. 1% of CIS progress to cancer per year
- Why then do you recommend LBC in the previous document?
- The biggest problem of using serology is that we would know of past/present exposure
- I have never heard of the HC2 technology referred to as a "modified ELISA" but this is far from my area of expertise, I will let you discuss it with other experts!
- What about the Quebec guidelines?
- Wouldn't it be necessary for the interim?

***Modifications/Actions/Response to Targeted Peer Reviewer Comments***

1. A reference was added to Section 1 to point the reader to more of the HPV biology story that is presented in Section 2. This information was not included in Section 1 in the interest of keeping it succinct.

2. The suggestion to have the same or similar bullet points for both sets of recommendations was accomplished by adding an age of initiation heading to the HPV-based set of recommendations and some wording changes were made in order to align the headings more closely.
3. The recommendations for screening age range and interval were based on best available evidence, which included cohort analyses. By nature, these forms of evidence are not as high quality as randomized controlled trials; however, they met the inclusion criteria for this systematic review and thus were considered appropriate for inclusion. A note was added to the recommendations' "Key evidence" explaining that the interval recommendations are based on a combination of cohort and natural history studies and consensus.
4. Mention was made of the impact of vaccination against HPV 16/18 in the Introduction in Section 2. This version of the guideline did not take this subgroup into account specifically because it was felt that the recommendations should not be modified for them at this time, as the vaccination program has not been in place long enough in Ontario (i.e., since 2007).
5. Harms of testing and costs with an HPV-based testing algorithm are mentioned in the Discussion in Section 2 of the report. In short, the estimates from the study by Kulasingam et al. show that HPV-based testing beginning at age 25 would be more cost-effective than cervical screening.
6. Recommendations for whom to refer to colposcopy are beyond the scope of this guideline.
7. One reviewer questioned the rationale of genotyping HPV positive women because 77% will be HPV 16/18 positive. We have presented this as an option to be considered when HPV testing has been implemented, although a full analysis would have to be conducted to conclude that this is the best option. Note that the statistic "77%..." actually refers to the percentage of cervical cancers caused by HPV 16 and 18.
8. In order to harmonize the evidence for the interim age of initiation recommendation with the information presented in Section 2, the bullet with information about the decline in cervical cancer (from 11/100,000 to 9/100,000 between 1981 and 2002) was removed.
9. The recommendation that immunocompromised women should receive annual screening was revised to emphasize that the two groups specified are not an exhaustive list. A more thorough list of women who would fit into the category of immunocompromised was beyond the scope of this guideline.
10. One reviewer pointed out that further results from the ARTISTIC trial have been published. The Working Group plans to systematically update the literature search prior to publication, and the third round ARTISTIC results will be added (along with any other new results) at that time.
11. Two reviewers expressed concerns about repeat testing of women with HPV-positive results and ASCUS. A note is included in the qualifying statements that this recommendation should be revisited prior to implementation.
12. The research question was amended to clarify that we are interested in the interval at which women should be screened, not the interval at which they should be recalled for screening.
13. Modified the description of the HPV-based recommendations in Table 1 from "evidence-based" to indicate that they are based on a combination of evidence and expert consensus.
14. The emphasis on PPV in the key evidence section for the HPV-testing algorithm was reduced.

15. “Preferably liquid-based” was retained in the interim recommendation for cytology screening because this recommendation was adopted from the previous version of the guideline. Revisiting whether or not LBC is preferred over conventional cytology was beyond the scope of this guideline.
16. The lack of flow in the interim recommendation for primary screening test was addressed by removing the age group 21 to 29 from the heading to make it clear that this recommendation refers to all women.
17. Further clarification was added for the qualifying statement that women with test results of “unsatisfactory” should undergo repeat screening in three months.
18. In light of reviewer comments, the following statement was removed from the rationale for screening women under 30 years of age:
  - Although the gap has more recently narrowed, the rate of attendance for cervical screening has traditionally been highest among women under 30 years of age (28). Screening women in their early 20s provides an opportunity to establish a patient-physician relationship, and the hope is that this would facilitate ongoing screening at appropriate intervals throughout the recommended age range for such screening. Furthermore, the interaction provides an opportunity to give accurate information about LSIL and other health promotion topics (29).
19. A qualifying statement was added that as vaccinated girls approach the age of screening initiation, this may also impact recommendations.
20. The importance of PPV was added to the last paragraph of the background information on cervical screening in Section 2.
21. Removed “by contrast” from the statement about the progression rate of CIN3 to invasive cancer in England.
22. Removed the statement “LBC has been found to have a lower rate of unsatisfactory smears than conventional cytology but has not been found to be more sensitive or specific with respect to the detection of histologically confirmed high-grade CIN” because it was considered to be inconsistent with the recommendations for LBC contained in the previous version of this guideline.
23. Removed mention of the immunologic response to HPV from the background information on cervical screening tests.
24. The Quebec guidelines were added to Appendix 4.
25. Clarified in the Discussion in Section 2 that HPV triage of ASCUS/LSIL cytology results will still be necessary in the interim until HPV testing is adopted.

*Professional Consultation:* One hundred and six responses were received, for an overall response rate of 23%. The majority of respondents were family medicine specialists (52%). Key results of the feedback survey are summarized in Table 2.

**Table 2. Responses to four items on the professional consultation survey.**

General Questions: Overall Guideline Assessment	Number (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0 (0)	4 (4)	6 (6)	46 (44)	48(46)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0 (0)	7 (7)	8 (8)	27 (26)	60 (59)



3. I would recommend this guideline for use in practice.	1 (1)	7 (7)	7 (7)	33 (32)	55 (53)
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#### 4. What are the barriers or enablers to the implementation of this guideline report?

##### Barriers:

- HPV testing is not currently funded for primary screening in Ontario.
- Current OHIP billings and preventive health bonuses. These would need to be aligned quickly prior to disseminating the guideline.
- Education is needed for patients and practitioners because this is a big change from current practice
- “Practicing in an interim state may lead to low adoption of the interim recommendations”
- Many value the regular visit for cervical screening to screen for other issues. Examples of issues mentioned by practitioners ranged from sexually transmitted infections to spousal abuse.
- Low attendance at cervical screening with some cultural groups. Focus on these groups would be good (South Asian women were mentioned specifically).
- Some patients currently still insist on yearly Paps.

##### Enablers:

- Implementation of a population-based screening program in Ontario.
- A strong knowledge translation effort will be needed for these guidelines to be adopted in Ontario.

#### Summary of Written Comments from Professional Consultation

The main points contained in the written comments were:

<i>Comment number</i>	<i>Comment</i>	<i>Modifications/Actions/Response</i>
1.	Patients and physicians are still making appointments based on annual or biannual guidelines. Information from CCO will be extremely important to convince patients about safety of new guidelines.	The Working Group agrees that an information campaign is extremely important. This point was emphasized in the Discussion in Section 2. An education campaign is being developed by Cancer Care Ontario.
2.	The Pap also provides an opportunity to do STI tests.	The Working Group recognizes that Pap tests are valued for many reasons by patients and practitioners. For this reason, a conservative interim initiation age was chosen by the Working Group.
3.	Vaginal intraepithelial neoplasia can be picked up in women who have had a hysterectomy. Vaginal vault cytology every 5 years would pick this up.	The Working Group acknowledges the importance of vaginal vault cytology, but this topic specifically was beyond the scope of the research questions for this project.
4.	More information on how practitioners should respond to questions from patients about HPV vaccination’s impact on the need for screening.	At this time, HPV vaccination has not been in place for long enough to impact the recommendations for screening. The next iteration of this guideline will likely address specific recommendations for the vaccinated

		cohort.
5.	Review of the technique for performing HPV DNA testing - clarify whether this is a blood test, same procedure as cytology testing, and whether HPV and cytology samples would be gathered concurrently.	Changes were made to Section 1 under the recommendation for HPV testing to clarify that it is not a blood test; a sample of cells is needed from the cervix.
6.	Some of the items in the rationale for an interim screening initiation age of 21 seem too opinion-based.	The Working Group agreed that the rationale for cervical screening could be made more succinct. The more opinion-based bullets were removed and the arguments summarized to improve clarity and readability.
7.	There may be a lower level of uptake of the interim recommendations.	The Working Group acknowledges that there may be a lower level of uptake of the interim recommendations, but felt strongly that guidance was needed until HPV testing is approved in the province, particularly with respect to the age of screening initiation.
8.	The guideline is too long and wordy - it needs to be more concise. A flowchart is needed for the interim recommendations.	The guideline was edited to make it more concise, incorporating some of the suggestions outlined above, and removing information about special populations from the interim recommendations.
9.	As mentioned under “barriers”, education of patients and practitioners will be needed to implement this guideline.	The Working Group strongly agrees that an education campaign will be important to ensure uptake of these guidelines.
10.	The potential for misuse or overuse of the HPV test is greater than for Pap testing because the recommended interval for HPV screening is longer.	The potential for misuse or overuse of the HPV test was noted in the Discussion in Section 2. A mention of this was added to the qualifying statements in Section 1.
11.	Looking for more clarification for what to do with special populations, such as immunocompromised women.	Guidance for special populations was beyond the scope of the systematic review for this guideline. In order to make it clear that this topic was not included in the literature search, the recommendations for special populations were removed from Section 1 and the recommendations from the previous guideline were added as a separate Section 4 to the document.
12.	Asked for a clarification of whether the 5-year interval refers to all women or only to women with presumed stable risk for exposure.	The 5-year interval for screening applies to all women who are at normal risk, as defined in the research questions.

13.	The guideline hardly touches on AGUS or glandular lesions. The guideline should make some reference to these.	As the research questions did not specifically address glandular lesions, these were not specifically addressed in the guidelines; however, the NTCC results showing a reduction in adenocarcinomas with HPV testing is mentioned in the key evidence for HPV testing. This section was revised to emphasize this key information.
14.	Include other primary care practitioners as intended users.	Other primary care practitioners were added to the target users and specialists was clarified to be clear that we are referring to gynecology specialists.
15.	There may have been some confusion that we were recommending starting screening at age 30 with HPV testing.	An age of initiation recommendation stating specifically that there was insufficient evidence to make a recommendation for age of screening initiation was added to the HPV-based set of recommendations for clarity.
16.	Ignoring ASCUS for a year is a concern.	Moved ASCUS from the cytology negative box of the algorithm to the cytology positive box (referral for colposcopy)

### Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Cervical Screening Guideline Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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In Review