Ontario Health
Cancer Care Ontario

Ontario Cervical Screening Program Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario

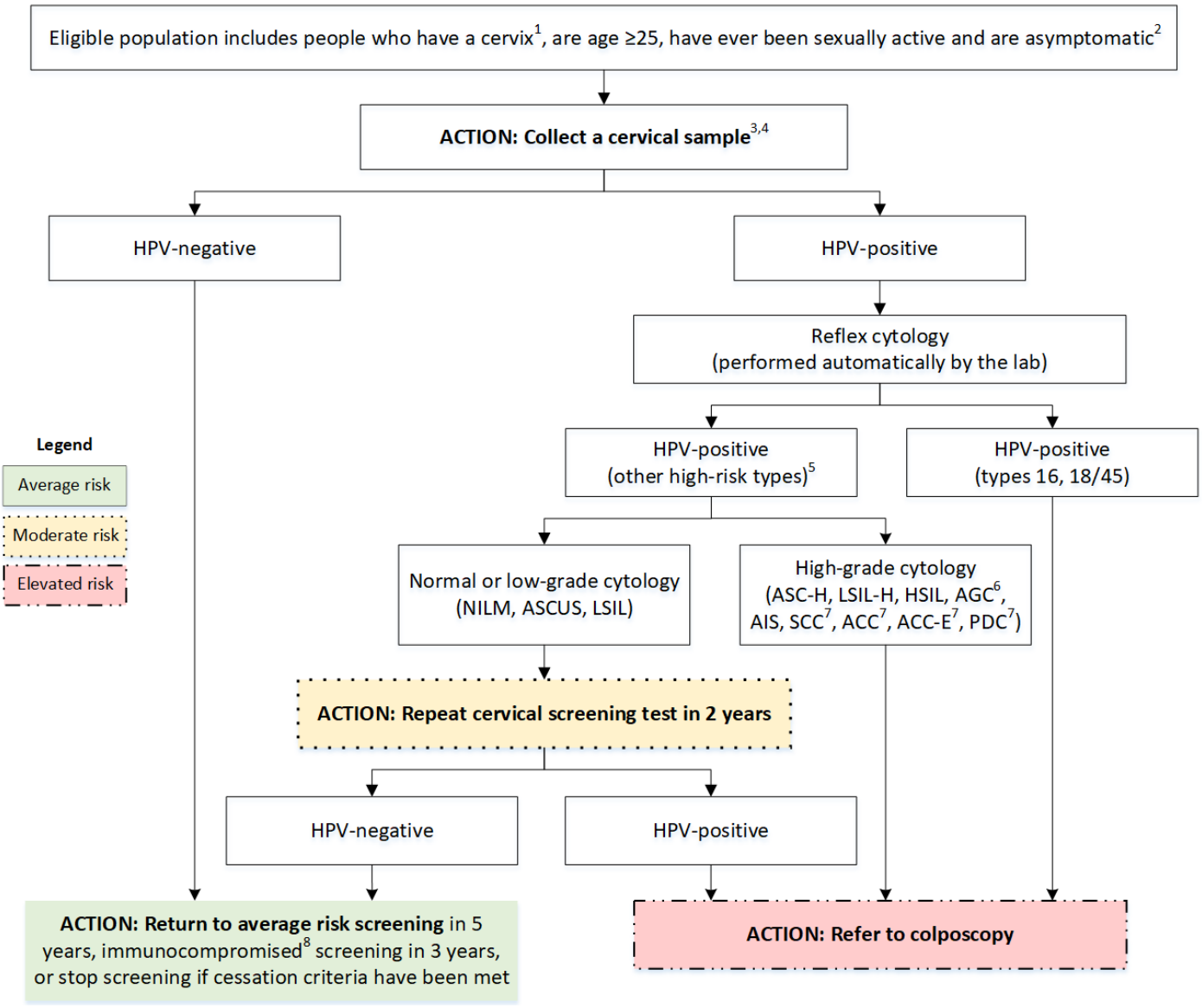
Version 1 - March 2025

Executive summary

This document summarizes the Ontario Cervical Screening Program's recommendations for cervical screening as well as best practice colposcopy pathways for people with abnormal cervical screening results. These recommendations were developed based on the following inputs: primary literature, Ontario data analyses, a jurisdictional scan and expert opinion from a multidisciplinary, international expert panel. Prior to finalizing the draft recommendations, they were shared for input with relevant stakeholder groups and subject matter experts.

The recommendations as well as the supporting evidence and contextual factors (e.g., feasibility and acceptability for the Ontario context) that informed the development of these recommendations are outlined in detail in this document. A summary of the Ontario Cervical Screening Program's risk-based cervical screening pathway and a high-level overview of the colposcopy pathways developed through this process can be found below in Figures I and II, respectively.

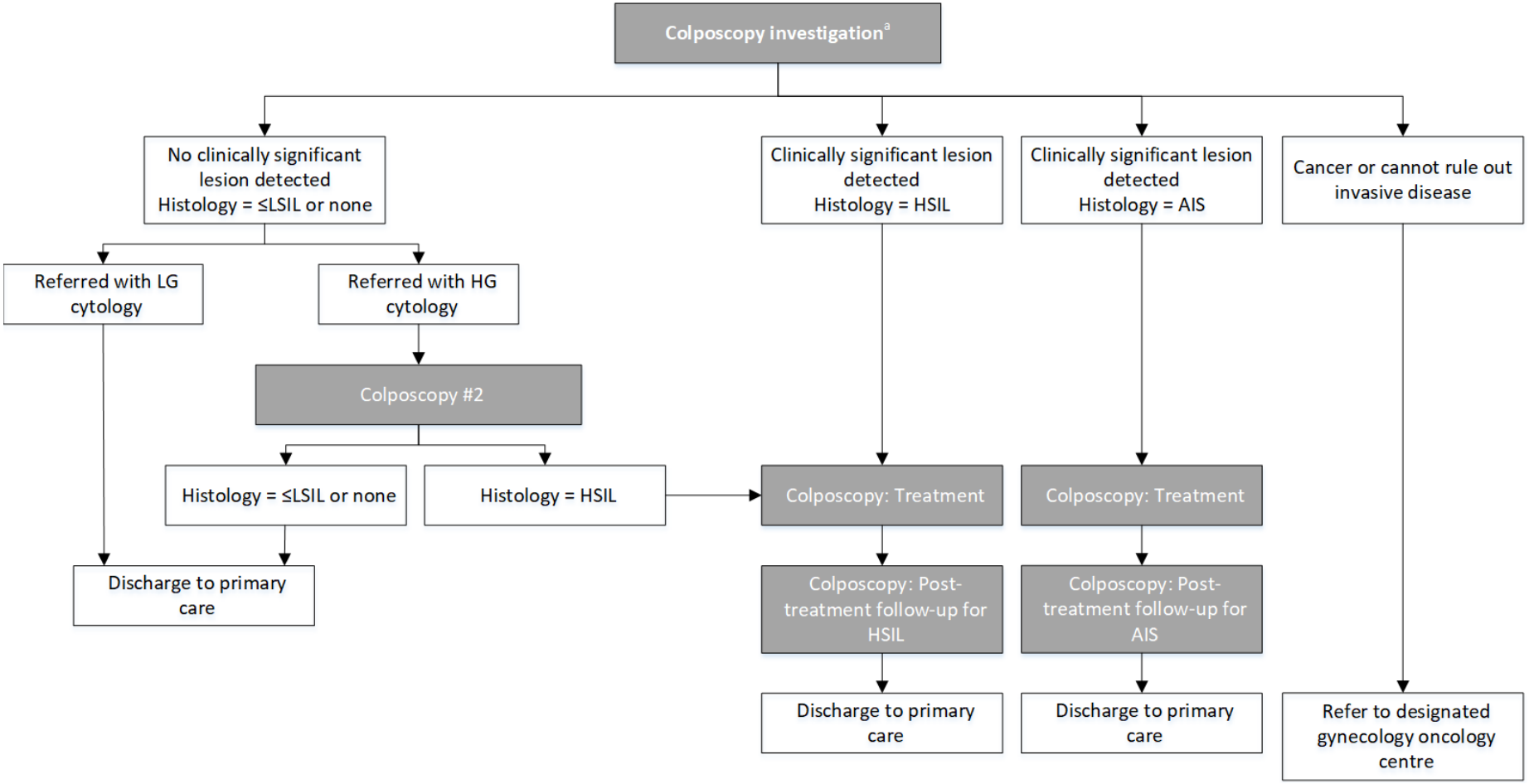
Figure I: Cervical screening pathway



ACC: adenocarcinoma; ACC-E: endocervical adenocarcinoma; AGC: atypical glandular cells; AIS: adenocarcinoma in situ; ASC-H: atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASCUS: atypical squamous cells of undetermined significance; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL; NILM: negative for intraepithelial lesion or malignancy; PDC = poorly differentiated carcinoma; SCC: squamous cell carcinoma

1. Including women, Two-Spirit people, transmasculine people, nonbinary people, pregnant people, post-menopausal people, people who have undergone a subtotal hysterectomy and retained their cervix and people who have had the HPV vaccine. Routine screening is not recommended for people who have had their cervix removed as a result of hysterectomy. For more information, refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance.
2. Any visible cervical abnormalities or abnormal symptoms must be investigated, regardless of age. If a lesion is found during a routine cervical screening test, complete the test and refer the participant to colposcopy or a regional cancer centre. Do not wait for the cervical screening test results to refer someone for next steps.
3. The cervical screening test does not test for non-oncogenic types of HPV, such as those that cause genital warts, or other sexually transmitted infections.
4. If the HPV test component of the cervical screening test is invalid, repeat sample collection at the participant's earliest convenience, within 3 months. If the repeat HPV test is invalid, refer to colposcopy.
5. If the test is HPV-positive (other high-risk types) with unsatisfactory cytology, repeat the cytology test only (i.e., do not repeat the HPV test) at the participant's earliest convenience, within 3 months. If the repeat cytology test is unsatisfactory, refer to colposcopy. After an unsatisfactory cytology result, a course of intravaginal estrogen therapy should be considered for people using transition-related hormone therapy (i.e., androgen therapy) or in post-menopausal people.
6. Includes AGC-N/NOS, AEC-N/NOS (AGC-N = atypical glandular cells, favour neoplastic; AGC-NOS = AGC, not otherwise specified; AEC-N = atypical endocervical cells, favour neoplastic; AEC-NOS = AEC, not otherwise specified).
7. If someone has SCC, ACC, ACC-E or PDC results, refer them urgently to colposcopy or if they have an obvious lesion, consider referral to gynecologic oncology.
8. The following immunocompromised populations may be at higher risk of cervical pre-cancer and cancer, and should screen every three years if their last HPV test was negative: people living with HIV/AIDS, regardless of CD4 cell count; people with congenital (primary) immunodeficiency; transplant recipients (solid organ or allogeneic stem cell transplants); people requiring treatment (either continuously or at frequent intervals) with medications that cause immune suppression for three years or more; people who are living with systemic lupus erythematosus (SLE), regardless of whether they are receiving immunosuppressant treatment; and people who are living with renal failure and require dialysis.

Figure II: High-level overview of OCSP's colposcopy pathways



Legend:

Grey Colposcopy visit

ACC: adenocarcinoma; ACC-E: endocervical adenocarcinoma; AIS: adenocarcinoma in situ; HG: high-grade; HSIL: high-grade squamous intraepithelial lesion; LG: low-grade; LSIL: low-grade squamous intraepithelial lesion; SCC: squamous cell carcinoma

[a]If referred with SCC, ACC, ACC-E or PDC cytology results, the next steps are dependent on if a lesion is grossly visible.

Terminology used in this document for describing cervical screening and colposcopy results

The published literature and Ontario data analyses used to inform the cervical screening and colposcopy recommendations use different terminologies to describe cervical screening and colposcopy result information. In this document, the Ontario Cervical Screening Program (OCSP) will describe cytology and histology results according to the framework summarized in Table 1a and 1b. The OCSP will use the Bethesda System when describing cytology test results (2). Throughout this document and other program materials, human papillomavirus (HPV)-negative is used to refer to people who are negative for oncogenic types of HPV. People who are positive for oncogenic types of HPV will be described as HPV-positive (types 16, 18/45) or HPV-positive (other high-risk types).

The OCSP will use Lower Anogenital Squamous Terminology (LAST), a two-tiered naming system for squamous histology and adenocarcinoma in situ (AIS) for glandular histology (3). Therefore, histology results derived from colposcopy examinations will be described by the OCSP in this document as low-grade squamous intraepithelial lesion (LSIL), high-grade intraepithelial lesion (HSIL) or AIS. Terminology used to describe HSIL histology in the clinical evidence varies among studies (e.g., cervical intraepithelial neoplasia 2/3 [CIN2/3], CIN3, etc.) When referring to a specific study, the terminology used to report results in the specific study will also be described as appropriate.

A summary of the framework used throughout this document can be found in Tables 1a and 1b.

Table 1a: Framework for describing cytology results in the OCSP

Bethesda/OCSP resources[a]	
n/a	NILM
Low grade	ASCUS, LSIL
High grade	ASC-H, LSIL-H[b]
	HSIL
	AGC[c], AEC[c]
	AIS
	SCC, ACC, ACC-E

ACC: adenocarcinoma; ACC-E: endocervical adenocarcinoma; AEC: atypical endocervical cells; AGC: atypical glandular cells; AIS: adenocarcinoma in situ; ASC-H: atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion, ASCUS; atypical squamous cells of undetermined significance; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL; n/a: not applicable; NILM: negative for intraepithelial lesion or malignancy; OCSP: Ontario Cervical Screening Program; SCC: squamous cell carcinoma

[a]This table does not include cervical screening cytology that suggests non-cervical abnormalities.

[b]LSIL-H is not included in the Bethesda System but based on expert opinion, it is an important finding that currently appears on laboratory reports in Ontario, and so the OCSP is including it in addition to the cervical cytology results defined by the Bethesda System.

[c]Given different risks associated with AGC types (i.e., AGC-favour neoplastic and AGC-not otherwise specified), and AEC types (i.e., AEC-favour neoplastic and AEC-not otherwise specified) guidance on management in colposcopy by type is provided.

Table 1b: Framework for describing histology results in colposcopy

CIN	LAST	OCSP resources
Normal	Normal	Normal
CIN1	LSIL	LSIL
CIN2	HSIL[a]	HSIL or pre-cancer
CIN 3		
n/a	n/a	AIS
Cancer	Cancer	Cancer

CIN: cervical intraepithelial neoplasia; HSIL: high-grade squamous intraepithelial lesion; LAST: Lower Anogenital Squamous Terminology; LSIL: low-grade squamous intraepithelial lesion; n/a: not applicable; OCSP: Ontario Cervical Screening Program; SCC: squamous cell carcinoma

[a]A possible histology result may include "high-grade, cannot exclude invasive disease"; this result should be managed as a high-grade squamous intraepithelial lesion (HSIL).

Acronyms and abbreviations

ACC	Adenocarcinoma
ACC-E	Endocervical adenocarcinoma
AIDS	Acquired immunodeficiency syndrome
AIS	Adenocarcinoma in situ
AEC	Atypical endocervical cells
AEC-NOS	Atypical endocervical cells-not otherwise specified
AEC-N	Atypical endocervical cells-favor neoplastic
AGC	Atypical glandular cells
AGC-NOS	Atypical glandular cells-not otherwise specified
AGC-N	Atypical glandular cells-favor neoplastic
ASC-H	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
ASCUS	Atypical squamous cells of undetermined significance
CIN	Cervical intraepithelial neoplasia
DEP	Diagnostic excisional procedure
DES	Diethylbestrol
DNA	Deoxyribonucleic acid
ECC	Endocervical curettage
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
LEEP	Loop electrosurgical excision procedure
LAST	Lower Anogenital Squamous Terminology
LSIL	Low-grade squamous intraepithelial lesion
LSIL-H	Low-grade squamous intraepithelial lesion, cannot exclude high-grade intraepithelial lesion
NILM	Negative for intraepithelial lesion or malignancy
NPV	Negative predictive value
OCSP	Ontario Cervical Screening Program
OR	Odds ratio
PEBC	Program in Evidence-Based Care
SCC	Squamous cell carcinoma
SLE	Systemic lupus erythematosus
VaIN	Vaginal intraepithelial neoplasia

Glossary

Cervical pre-cancer: Abnormal cell growth in the cervix that is considered moderate or severe. Pre-cancer includes the following histology result types:

- HSIL: high-grade squamous intraepithelial lesion; and
- AIS: adenocarcinoma in situ.

Co-test: A co-test is when both a human papillomavirus test and cytology test, are performed on a single cervical specimen. The results of these two tests, are considered together to inform clinical next steps.

Confidence interval: A range of values confidence interval is the range of values above and below a finding in which the true value is likely to fall within.

Colposcopy: An examination of the cervix used to rule out the presence of cervical pre-cancer, or cancer. If a pre-cancer has been detected, treatment can be performed in colposcopy. Multiple visits in colposcopy may be required over an episode of care, depending on the results of the screening test or initial colposcopy visit (including whether treatment was required).

Cytology test: A test that looks for abnormal cell changes in the cervix.

Health care provider: A provider who is able to conduct cervical screening or colposcopy services, including primary care providers (e.g., family physicians, nurse practitioners, and other medical providers under medical directive), midwives and colposcopists (e.g., obstetricians, gynecologists, primary care providers).

High-grade cytology: High-grade cytology includes the following result types:

- LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL;
- ASC-H: atypical squamous cells, cannot exclude HSIL;
- HSIL: high-grade squamous intraepithelial lesion;
- AGC: atypical glandular cells;
- AGC-N: atypical glandular cells – favours neoplastic;
- AGC-NOS: atypical glandular cells – not otherwise specified;
- AEC: atypical endocervical cells;
- AEC-N: atypical endocervical cells – favours neoplastic;
- AEC-NOS: atypical endocervical cells – not otherwise specified;
- AIS: adenocarcinoma in situ;
- SCC: squamous cell carcinoma;
- ACC: adenocarcinoma; and
- ACC-E: endocervical adenocarcinoma; and
- PDC: poorly differentiated carcinoma

Human papillomavirus (HPV): A family of common viruses. There are over 100 types of human papillomavirus. Some types are oncogenic (cancer-causing).

Human papillomavirus test: A test performed on someone to check for the presence of oncogenic types of human papillomavirus.

Low-grade cytology: Low-grade cytology includes the following result types:

- ASCUS: atypical squamous cells of undetermined significance; and
- LSIL: low-grade squamous intraepithelial lesion.

Negative predictive value (for the human papillomavirus test): The likelihood that negative results will correctly identify people who do not have a pre-cancer or cancer and will not develop a pre-cancer or cancer in a set amount of time.

Non-oncogenic human papillomavirus types: Types of human papillomavirus that do not cause cellular changes that lead to cancer. Some non-oncogenic HPV types can contribute to other conditions, such as genital warts. Non-oncogenic HPV types are not detected as part of cervical screening using HPV testing.

Organized cervical screening: The systematic offering of cervical screening to a population or specified segment of a population. Organized cervical screening programs are managed centrally, and use clear, consistent policies and processes. They use current scientific evidence to determine which groups of people are at risk of getting cervical cancer and how often they should get screened. Organized cervical screening programs also track and measure their own quality and performance to monitor how they are doing and help them make recommendations for improvements.

Oncogenic human papillomavirus types: Types of human papillomavirus that can lead to high-grade abnormal cell changes in the cervix and, if left untreated, can lead to cervical cancer over time. Of over 100 types of human papillomavirus, only 13 are known to be oncogenic in the cervix, including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Among these, types 16, 18 and 45 are detected in almost 75% of all squamous cell carcinomas and 94% of adenocarcinomas (4).

Odds ratio: The odds that an outcome (e.g., cervical pre-cancer or cancer) will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.

Partial genotyping: Partial genotyping is used to identify specific oncogenic types of human papillomavirus (HPV) (i.e., HPV 16, HPV 18 and sometimes HPV 45), which are associated with a higher risk or cervical pre-cancer and cancer. When partial genotyping is performed, the remaining oncogenic HPV types are pooled into a single category known as HPV-positive (other high-risk types). Partial genotyping allows for better risk stratification of screening participants and avoids over-investigation and overtreatment.

Participants: Individuals eligible for and who choose to participate in the screening program, according to the Ontario Cervical Screening Program's cervical screening recommendations.

Pathways: Translates the Ontario Cervical Screening Program's cervical screening and colposcopy recommendations into clinical processes.

Positive predictive value (for the human papillomavirus test): The likelihood that positive results will correctly identify people who have a pre-cancer or cancer.

Recommendations: Outline recommendations for cervical screening (e.g., when to start screening, how often to screen, when to stop screening) and follow-up in colposcopy for people with abnormal cervical screening results.

Reflex test: A test performed by a laboratory when the results of a previous test indicate that additional testing is required. The additional test is performed without requiring another order from a health care provider. For the purposes of this document, a reflex test refers to cervical cytology performed on a screening specimen that tests positive for oncogenic human papillomavirus.

Relative risk: The risk of an outcome (e.g., cervical pre-cancer or cancer) in an exposed group, compared to the risk of the outcome occurring in the absence of that exposure.

Specimen: A sample of cells taken from the cervix or vaginal vault for the purposes of screening or colposcopy.

Sensitivity: The effectiveness of a screening test in detecting a cancer or pre-cancer in people who have that cancer or pre-cancer.

Specificity: The effectiveness of a screening test in indicating a normal result in people who do not have that cancer or pre-cancer.

Contents

Introduction

Natural history of HPV

Human papillomavirus (HPV) infections are common and about eighty percent of sexually active people will have at least one HPV infection in their lifetime (5,6). HPV infections are either transient (i.e., the infection clears on its own) or persistent (i.e., the infection does not clear on its own). Evidence shows that most HPV infections are transient, but it can take several years for the infection to clear. One longitudinal study found that 92% of HPV infections clear within seven years (7). This study also found that almost 80% of infections clear within three years, but fewer than 50 percent of HPV infections clear within one year (7).

There are over 100 types of HPV, which can be categorized as oncogenic or non-oncogenic. Non-oncogenic types of HPV do not cause cellular changes that lead to cancer. Whereas oncogenic types of HPV can cause cervical cancer. Currently, about 13 types of HPV are known to be oncogenic. Of these 13 types, types 16 and 18 are the highest risk and responsible for most HPV-related cervical cancer. HPV 45 is also found in a relatively high number of invasive cervical cancers, especially adenocarcinomas (4).

Persistent infections with oncogenic types of HPV may progress to pre-cancer and eventually to cervical cancer if left untreated. Typically, it takes 15 to 20 years for an HPV infection to lead to cervical cancer in people who are immunocompetent (8).

Purpose

The purpose of this document is to summarize the Ontario Cervical Screening Program (OCSP's) recommendations for cervical screening as well as the best practice colposcopy pathways for people with abnormal cervical screening results. The supporting evidence and contextual factors (e.g., feasibility and acceptability for the Ontario context) used to develop these recommendations are also summarized in this document.

Methods: Recommendation development

The recommendations outlined in this document were developed based on the following inputs:

- Rapid reviews of the primary literature
- Ontario data analyses
- Evidence-based screening and colposcopy recommendations from other jurisdictions
- The program's guiding principles
- Expert opinion from a multidisciplinary, international expert panel

In addition, the draft recommendations were shared for input with relevant stakeholder groups and subject matter experts for input prior to finalizing the recommendations.

Rapid reviews of the primary literature

Nine rapid reviews of the primary literature were conducted by Ontario Health (Cancer Care Ontario) to inform the development of the Ontario Cervical Screening Program's (OCSP's) cervical screening recommendations and colposcopy pathways. The research question(s) evaluated in these rapid reviews are summarized in Table 2. An overview of the methods for each rapid review can be found in Appendix A.

Table 2: Rapid reviews of the primary literature research questions

Review title	Research questions
Cervical screening for people who are immunocompromised	Among people who are considered immunocompromised, what are the recommended eligibility requirements, screening modalities and intervals for cervical screening?
Risk of high-grade cervical dysplasia and cervical cancer among people who persistently test HPV-positive with normal or low-grade cytology results in screening	• What is the risk of high-grade cervical dysplasia and cervical cancer for people who are found to be persistently HPV-positive with normal or low-grade cytology in screening? ○ Does risk vary by HPV type, cytology result in screening, age, treatment and management pathway or duration of follow-up?

Risk of high-grade cervical dysplasia among people who persistently test HPV-positive without cytologic or colposcopic evidence of pre-cancer	• What is the risk of high-grade cervical dysplasia among people 25–69 years with persistent HPV infection, normal or low-grade cytology and no colposcopic evidence of pre-cancer?
	  ○ Does risk vary by HPV type, cytology results at referral, treatment status, post-treatment management pathway or duration of follow-up?
	• What is the risk of high-grade cervical dysplasia among people 70 years and older with persistent HPV infection, normal or low-grade cytology and no colposcopic evidence of pre-cancer?
	  ○ Does risk vary by HPV type, cytology results at referral or duration of follow-up?

Risk of high-grade cervical dysplasia and cervical cancer among people who are discharged from colposcopy	Among people who are discharged from colposcopy, what is the risk of high-grade cervical dysplasia and cervical cancer?
Colposcopy management and discharge for individuals referred to colposcopy with AGC cytology results	• What initial work-up and diagnostic strategies are recommended for people referred to colposcopy with a positive HPV test result and AGC cytology results? • What colposcopy management and discharge strategies are recommended for people in colposcopy with a positive HPV test result and AGC cytology results where no high-grade cervical dysplasia and cervical cancer is identified?
Risk of high-grade cervical dysplasia and cervical cancer among people conservatively treated for AIS	• Among people who received conservative treatment[a] for AIS in colposcopy, what is the risk of high-grade cervical dysplasia and cervical cancer following treatment? ○ Does risk vary by age, type of excisional procedure, margin status at excision, HPV status post-treatment, cytology result post-treatment or endocervical curettage result?

Review title	Research questions
Cervical screening following discharge from colposcopy	What cervical screening modalities and intervals do existing guidelines and position or policy statements recommend for people who are discharged from colposcopy?

Cervical screening cessation for people aged 60 and older	For people aged 60 years and older, what do existing HPV-based cervical screening guidelines and position or policy statements recommend as cervical screening cessation criteria?
	• What is the 3-, 5- and 10-year risk of high-grade cervical dysplasia and cervical cancer for people aged 60 and older with a cervix who have had three or more normal cytology results since age 50?
	  ○ Does the risk vary by age?
	• What is the 3-, 5- and 10-year risk of high-grade cervical dysplasia and cervical cancer for people aged 60 and older with a cervix who have had one or more positive HPV tests and normal or low-grade cytology results since age 50?
	  ○ Does the risk vary by age, HPV type or most recent cytology test result?
	• What is the 3-, 5- and 10-year risk of high-grade cervical dysplasia and cervical cancer for people aged 60 and older with a cervix who have had one or more negative HPV tests since age 50?
	  ○ Does the risk vary by age or most recent cytology test result?

Vaginal vault testing following simple or radical hysterectomy for peoples with a history of high-grade cervical dysplasia and early cervical cancer (i.e., FIGO stages 1A, 1B or 2A)	• For people who have had a simple or radical hysterectomy with a history of high-grade cervical dysplasia, what is the risk of VaIN3 and vaginal cancer?
	  ○ Does the risk vary by histology result, type of hysterectomy, hysterectomy margin status, HPV status post-hysterectomy, HPV type post-hysterectomy or cytology result post-hysterectomy?
	• For people who have had a simple or radical hysterectomy with a history of high-grade cervical dysplasia, what is the clinical performance of vaginal vault HPV testing (with or without reflex cytology), HPV/cytology co-testing or cytology testing (with or without reflex HPV testing) for the detection of VaIN3 and vaginal cancer?
	• For people who have had a simple or radical hysterectomy with a history of early cervical cancer (i.e., FIGO stages 1A, 1B or 2A) who have not received radiation or chemotherapy treatment and are no longer under surveillance for recurrence of cervical cancer, what is the risk of VaIN3 and vaginal cancer?
	  ○ Does the risk vary by histology result, type of hysterectomy, hysterectomy margin status, HPV status (including type) post-hysterectomy, or cytology result post-hysterectomy?
	• For people who have had a simple or radical hysterectomy with a history of early cervical cancer (i.e., FIGO stages 1A, 1B or 2A) who have not received radiation or chemotherapy treatment and are no longer under surveillance

Review title	Research questions
	for recurrence of cervical cancer, what is the clinical performance of vaginal vault HPV testing (with or without reflex cytology), HPV/cytology co-testing or cytology testing (with or without reflex HPV testing) for the detection of VaIN3 and vaginal cancer?

AGC: atypical glandular cells; AIS: adenocarcinoma in situ; FIGO: International Federation of Gynecology and Obstetrics; HPV: human papillomavirus; VaIN: vaginal intraepithelial neoplasia

[a]Conservative treatment refers to treatment using an excisional procedure (e.g., cold knife conization, loop electrosurgical excision procedure).

Ontario data

Ontario data analyses were also conducted to inform the development of the OCSP's cervical screening and colposcopy recommendations. Research questions for each data analysis are listed in Table 3. An overview of the methods for each data analysis can be found in Appendix B.

Table 3: Topics and research questions for Ontario data analyses

Topic	Research question
Incidence rates of HSIL, AIS and cervical cancer for people aged 70 and older, 2013–2018	What are the incidence rates per 100,000 cases of HSIL, AIS and cervical cancer stratified by age and screening history for people aged 70 and older?
Divergence of cytology repeated at 1-90 days and 3-6 months after index cytology, 2015–2016	What is the divergence of index cytology and repeat cytology within 6 months?
Baseline risk of HSIL, AIS and cervical cancer following a negative cytology test in screening, 2012–2014	What is the risk of HSIL, AIS and cervical cancer (including both in situ and cervical cancer) over time among people who had a negative cytology test in the past 3 years in screening
Recurrence rates and rates of cervical cancer for people previously treated for HSIL or AIS of the cervix, 2006 – 2010	What is the 5-year recurrence risk of HSIL, AIS or cervical cancer in a large population cohort of people previously treated for HSIL or AIS?
Risks of HSIL, AIS and cervical cancer for people managed without treatment in colposcopy, 2010–2019	What is the risk of HSIL, AIS and cervical cancer over time in people who have undergone colposcopy after a cytology test with low-grade colposcopy biopsies (<LSIL) or no biopsy and without treatment?
Incidence rates of VaIN 2/3 and vaginal cancer for people post-hysterectomy with a history of HSIL, AIS or early cervical cancer, 2005–2015	What are the incidence rates of VaIN 2/3 and vaginal cancer among people post-hysterectomy with a history of HSIL, AIS or early cervical cancer?

AIS: adenocarcinoma in situ; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; VaIN: vaginal intraepithelial neoplasia

Jurisdictional scan

A jurisdictional scan of cervical screening programs and relevant professional organizations and associations was carried out to inform the development of the OCSP's recommendations. A standardized survey was developed by the OCSP and distributed to key contacts at Canadian and international cervical screening programs. The survey was supplemented by a web search of screening program materials as well as guidelines developed by relevant professional organizations/associations. Results gathered from programs that recommend HPV testing for cervical screening were primarily used to inform the OCSP's recommendations.

An overview of the methods used for the jurisdictional scan can be found in Appendix C.

OCSP guiding principles

The OCSP developed the following guiding principles to support expert panel discussions as well as inform the development of the final recommendations:

- Be consistent with OCSP's approach to organized screening
  - The recommendations should be based on the principles of organized screening (9) and consider the balance between the benefits and potential harms of screening and colposcopy for a population
  - The recommendations for a given population (or sub-population) should be proportionate to the immediate and/or long-term risk of high-grade squamous intraepithelial lesion (HSIL), adenocarcinoma in situ (AIS) and cervical cancer.
- Be guided by the evidence
  - The program's goal of reducing cervical cancer-related incidence and mortality should guide the assessment of effectiveness
  - The recommendations should be based on high-quality evidence or the best available evidence if high-quality evidence is not found
- Be feasible to implement (e.g., clear and simple recommendations)
- Be practical for participants and health care providers to adopt
- Be acceptable to the public, health care providers and the screening program
- Integrate well with the planned program design and infrastructure for screening and colposcopy

Expert panel

A multidisciplinary expert panel, co-chaired by the OCSP's Provincial Clinical Lead and Lead Scientist, was convened to contextualize the evidence and, where evidence was insufficient, to provide expert opinion to inform the development of recommendations.

The panel included Ontario, Canadian and international experts in gynecology (n = 8), gynecologic oncology (n = 4), pathology (n = 4), primary care (n = 8) (including primary care providers with experience caring for indigenous populations), research (n = 2), and the general public (n = 2). In addition, people with specific areas of expertise (i.e., vaginal vault testing, testing for transmasculine and nonbinary people, immunocompromised populations and colposcopy) were invited to attend relevant meetings as ad hoc panel members to compliment the expertise of the panel. See Appendix D for a list of panel members and their area of expertise.

Panel members reviewed the evidence and provided input on recommendations through seven webinars as well as five online surveys, which were used to obtain further information on topics following panel meetings (see Table 4).

Table 4: Summary of expert panel activities

Panel meeting #	Topics covered	Follow-up survey conducted post-panel meeting (Survey #)
Meeting 1	• Cervical screening for people who are immunocompromised • Management of invalid HPV and unsatisfactory cytology results	Yes (Survey 1)
Meeting 2	• Colposcopy recommendations for people with abnormal cervical screening results • Cervical screening cessation	No
Meeting 3		Yes (Survey 2)
Meeting 4		No
Meeting 5	• Management of people referred with AIS cytology in colposcopy	No
Meeting 6	• Management of people referred with AGC (including AGC-NOS and AGC-N) cytology in colposcopy • Management of people under 25 in screening and colposcopy	Yes (Survey 3)
Meeting 7	• Guidance for vaginal vault testing • Hysterectomy guidance for people treated for AIS	Yes (Survey 4)

AIS: adenocarcinoma in situ; AGC: atypical glandular cells; AGC-NOS: atypical glandular cells-not otherwise specified; AGC-N-atypical glandular cells-favor neoplastic; HPV: human papillomavirus

Human papillomavirus (HPV) genotyping

The recommendations outlined in this document were developed using risk-based data that stratified HPV types into HPV 16/18 and HPV (other high-risk types) (i.e., all non 16/18 oncogenic HPV types). However, the HPV test platform procured by the OCSP reports results as HPV 16, HPV 18/45 or HPV (other high-risk types). HPV 18 and 45 are grouped together because they are both found in a relatively high number of adenocarcinomas. HPV types 16, 18 and 45 are detected in almost 75% of squamous cell carcinomas and 94% of adenocarcinomas (4).Recommendations outlined in this document for people who have HPV-positive 16/18 results will also apply to people who have HPV-positive 45 results.

The HPV assay was procured after the recommendation development process was complete. As such, the evidence outlined in this document does not reflect risk-based data for HPV 45 individually.

Cervical Screening Recommendations

Screening test

Recommendation

Human papillomavirus (HPV) testing is the recommended cervical screening test in the Ontario Cervical Screening Program (OCSP). Reflex cytology will be performed automatically on specimens that are HPV positive (i.e., the health care provider does not need to order a second test).

Key evidence

A Program in Evidence-Based Care (PEBC) guideline published in 2011 found that there was strong evidence to recommend the HPV test as the primary test for cervical screening (10). The HPV test looks for the presence of oncogenic HPV types in cervical cells. By comparison, cytology detects abnormal cervical cell changes that are primarily caused by an HPV infection. When comparing HPV testing to cytology for the purposes of cervical screening, HPV testing has been found to be more sensitive, and therefore more effective than cytology at identifying people who are at higher risk of developing pre-cancer and cervical cancer (see Table 5).

HPV testing also detects people at higher risk of developing pre-cancer and cervical cancer earlier than cytology. Infection with oncogenic HPV is required for the development of pre-cancer and cervical cancer. However, the HPV infection takes place prior to the development of any cytologic abnormalities. As such, cervical screening with the HPV test provides more opportunities than cytology to identify people at risk of developing pre-cancer and cervical cancer.

Table 5: HPV test vs. cytology

	HPV test	**Cytology**
One-time sensitivity[a] in detecting HSIL and cervical cancer (defined in the study as CIN2+) (range)	96.1% (94.2–97.4%) (11)	53.0% (48.6–57.4%) (11)
One-time specificity[b] in detecting HSIL and cervical cancer (defined in the study as CIN2+) (range)	90.7% (90.4–91.1%) (11)	96.3% (96.1–96.5%) (11)
Detects	Oncogenic types of HPV in the cervix	Abnormal cell changes in the cervix
Interpretation	Objective and reproducible (12)	Subjective (12)

CIN2+: cervical intraepithelial neoplasia 2+; HSIL: high-grade squamous intraepithelial lesion; HPV: human papillomavirus

[a]Sensitivity is the effectiveness of a cervical screening test in detecting pre-cancer and cervical cancer in people who have pre-cancer and cervical cancer (i.e., 96.1% of people with pre-cancer and cervical cancer will be identified with a positive human papillomavirus [HPV] test).

[b]Specificity is the effectiveness of a cervical screening test in indicating a normal result in people who do not have pre-cancer and cervical cancer (i.e., 90.7% of people without pre-cancer and cervical cancer will receive a negative test result).

A negative HPV test result identifies people at a very low risk of developing pre-cancer and cervical cancer over the next several years (10). However, unlike cytology, HPV testing cannot detect the presence or absence of cervical cell changes. As a result, it is a less specific test than cytology (11). This lower specificity means HPV testing is not as good as cytology at correctly identifying someone who does not have a pre-cancer or cancer. This is because many people with a positive HPV result do not have abnormal cell changes.

Partial genotyping and/or reflex cytology can be used with HPV testing to improve the specificity of cervical screening. Currently, about 13 types of HPV are known to be oncogenic. Of these 13 oncogenic types, types 16 and 18 are the highest risk and responsible for most HPV-related cervical cancer. HPV 45 is also found in a relatively high number of invasive cervical cancers, especially adenocarcinomas (4). Partial genotyping is the process of determining if a person has a type of HPV that is more likely to cause cervical cancer (i.e., HPV types 16, 18 and 45) or another oncogenic type of HPV (i.e., HPV [other high-risk types]). A reflex cytology test refers to cytology testing performed automatically (i.e., does not require the health care provider to order a second test) by a laboratory on screening specimens that test positive for HPV. Reflex cytology detects the presence or absence of cervical cell changes and whether those changes are high-grade or low-grade.

The OCSP is implementing both partial genotyping and reflex cytology to improve the specificity of cervical screening. The combined information from the HPV-type and cytology allows for a more precise calculation of a person's risk of pre-cancer and cervical cancer and enables risk-based management of screening participants. Risk-based management ensures that recommended clinical next steps are aligned with a person's risk of pre-cancer and cervical cancer. For instance, some people who test positive for HPV (other high-risk types) can be followed up after a period of time with additional HPV testing to determine if the infection is transient. Whereas people who are at highest risk of developing pre-cancer and cervical cancer (e.g., people who test positive for HPV types 16, 18 and 45) are referred to colposcopy. Colposcopy is a invasive exam with associated potential harms, such as anxiety, discomfort, and pain and in some cases, problems with future pregnancies (13), and should only be recommended for people who are at highest risk of developing pre-cancer and cervical cancer where the benefits of colposcopic examination outweigh the potential harms.

Since the release of the 2011 PEBC guideline, further evidence has been published demonstrating the effectiveness of HPV testing and its benefits in preventing cervical cancer, including clinical trials as well as published studies on the outcomes from jurisdictions that have implemented cervical screening using primary HPV testing (14–16). In addition, the World Health Organization (17) and the Canadian Partnership Against Cancer (18) have endorsed HPV testing as the first-choice screening method for cervical cancer prevention.

Risk-based screening recommendations

The cervical screening recommendations presented in this document are based on a person's immediate or five-year risk of high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS) histology and cervical cancer.

The Ontario Cervical Screening Program (OCSP) created four screening populations. Each screening population is associated with a risk or risk range, which is determined by a person's most recent screening result (i.e., human papillomavirus [HPV] +/- cytology results) and immune status. The clinical next step for each screening population is proportionate to the immediate and/or long-term risk of HSIL or AIS histology and cervical cancer. Immediate risks were used for two screening populations that have shorter timeframes associated with the clinical next step. Whereas a five-year risk was used for one screening population that has a longer timeframe associated with the clinical next step.

The screening populations are listed in Table 6 and the OCSP's cervical screening pathway can be found in Figure 3.

Table 6: Cervical screening population definitions and associated risk of HSIL or AIS histology and cervical cancer

Screening population	Screening history	Clinical next step	Risk for HSIL or AIS histology and cervical cancer
Average risk	• People who have only had HPV negative results • People who have fulfilled criteria to return to screening every five years after discharge from colposcopy • People with an HPV negative after an HPV-positive (other high-risk types) with normal or low-grade cytology[b]	Screen in 5 years	5-year risk of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+)[a]: 0.12%–0.41% (19)
Immunocompromised	• People who are immunocompromised[c] with HPV negative results	Screen in 3 years	Unknown / variable
Moderate risk	• People with a first time HPV-positive (other high-risk types) with normal or low-grade cytology[b]	Follow-up screen in 2 years[d]	Immediate risk of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+): 1.3–3.7%
	• People who have met criteria to return to screening in 2 years after discharge from colposcopy		1.1-6.1% (20,21)
Elevated risk	• People with HPV-positive (types 16, 18/45), regardless of cytology result • People with HPV-positive (other high-risk types) with high-grade cytology[e] • People with an initial HPV-positive (other high-risk types) with normal or low-grade cytology followed by an HPV-positive (regardless of HPV type or cytology result), at their 2-year follow-up screening test	Refer to colposcopy	Immediate risk of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+): ≥6%

AIS: adenocarcinoma in situ; CIN3+: cervical intraepithelial neoplasia 3+; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion

[a]A five-year risk was selected to define the average risk screening population given the five-year screening interval for this population.

[b]Low-grade cytology includes the following result types:

- ASCUS: atypical squamous cells of undetermined significance; or
- LSIL: low-grade squamous intraepithelial lesion.

[c]The following immunocompromised populations are at higher risk of pre-cancer and cervical cancer:

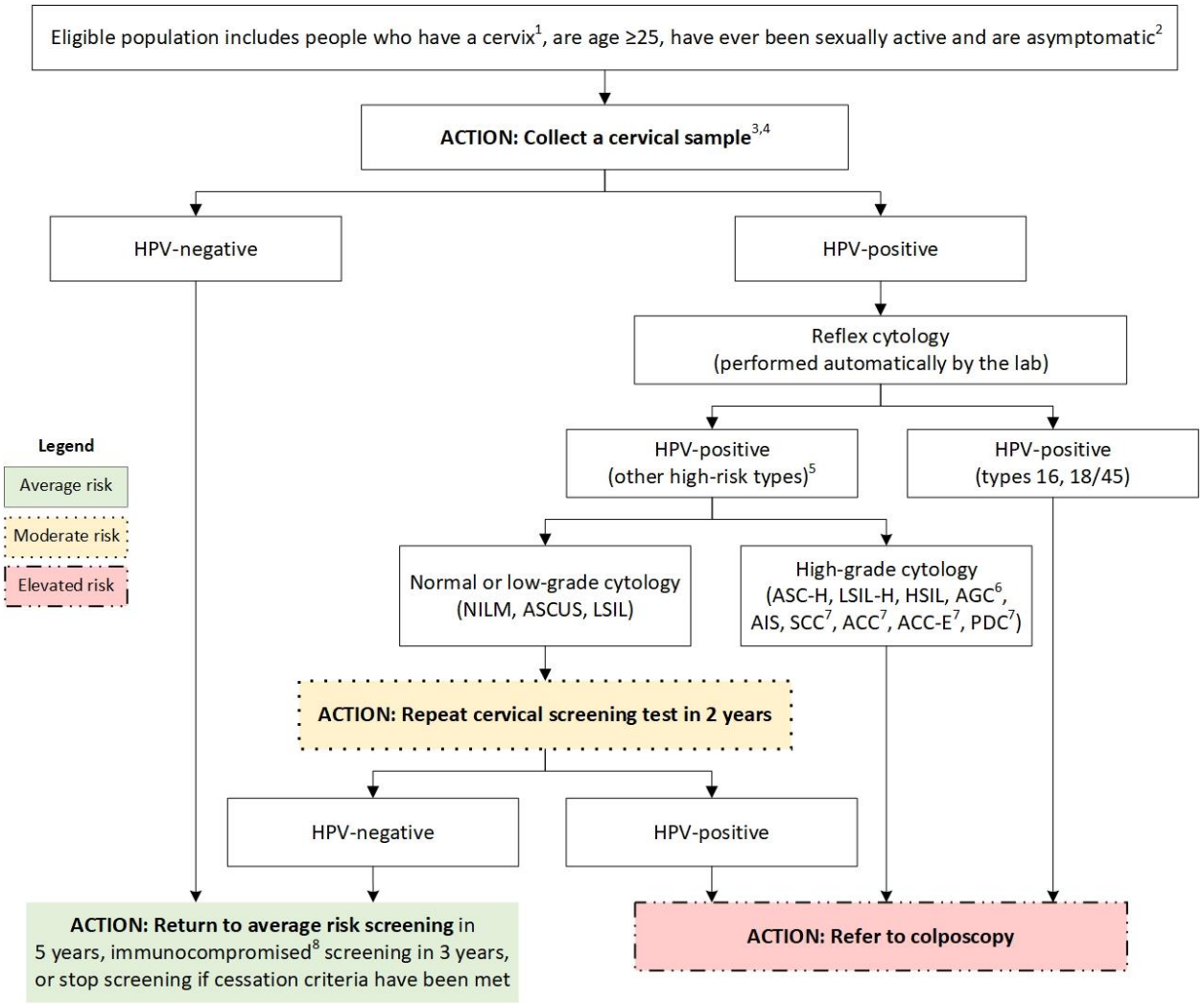
- People who are living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), regardless of CD4 cell count;
- People with congenital (primary) immunodeficiency;
- Transplant recipients (solid organ or allogeneic stem cell transplants);
- People requiring treatment (either continuously or at frequent intervals) with medications that cause immune suppression for three years or more;
- People who are living with systemic lupus erythematosus (SLE), regardless of whether they are receiving immunosuppressant treatment; and
- People who are living with renal failure and require dialysis.

[d]The moderate risk screening populations' immediate risk of high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS) histology and cervical cancer is not sufficient to warrant referral to colposcopy.

[e]High-grade cytology includes the following result types:

- HSIL: high-grade squamous intraepithelial lesion;
- ASC-H: atypical squamous cells, cannot exclude HSIL;
- LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL;
- AGC: atypical glandular cells (includes AGC-N (favor neoplastic) and AGC-NOS (not otherwise specified));
- AEC: atypical endocervical cells (includes AEC-N (favor neoplastic) and AEC-NOS (not otherwise specified));
- AIS: adenocarcinoma in situ;
- ACC: adenocarcinoma;
- ACC-E: endocervical adenocarcinoma;
- SCC: squamous cell carcinoma; or
- PDC: poorly differentiated carcinoma

Figure 3: OCSP's cervical screening pathway



ACC: adenocarcinoma; ACC-E: endocervical adenocarcinoma; AGC: atypical glandular cells; AIS: adenocarcinoma in-situ; ASC-H: atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASCUS: atypical squamous cells of undetermined significance; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL; NILM: negative for intraepithelial lesion or malignancy; PDC = poorly differentiated carcinoma; SCC: squamous cell carcinoma

1. Including women, Two-Spirit people, transmasculine people, nonbinary people, pregnant people, post-menopausal people, people who have undergone a subtotal hysterectomy and retained their cervix and people who have had the HPV vaccine. Routine screening is not recommended for people who have had their cervix removed as a result of a hysterectomy. For more information, refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance.
2. Any visible cervical abnormalities or abnormal symptoms must be investigated, regardless of age. If a lesion is found during a routine cervical screening test, complete the test and refer the participant to colposcopy or a regional cancer centre. Do not wait for the cervical screening test results to refer someone for next steps.
3. The cervical screening test does not test for non-oncogenic types of HPV, such as those that cause genital warts, or other sexually transmitted infections.
4. If the HPV test component of the cervical screening test is invalid, repeat sample collection at the participant's earliest convenience, within 3 months. If the repeat HPV test is invalid, refer to colposcopy.

5. If the test is HPV-positive (other high-risk types) with unsatisfactory cytology, repeat the cytology test only (i.e., do not repeat the HPV test) at the participant's earliest convenience, within 3 months. If the repeat cytology test is unsatisfactory, refer to colposcopy. After an unsatisfactory cytology result, a course of intravaginal estrogen therapy should be considered for people using transition-related hormone therapy (i.e., androgen therapy) or in post-menopausal people.
6. Includes AGC-N/NOS, AEC-N/NOS (AGC-N = atypical glandular cells, favour neoplastic; AGC-NOS = AGC, not otherwise specified; AEC-N = atypical endocervical cells, favour neoplastic; AEC-NOS = AEC, not otherwise specified).
7. If someone has SCC, ACC, ACC-E or PDC results, refer them urgently to colposcopy or if they have an obvious lesion, consider referral to gynecologic oncology.
8. The following immunocompromised populations may be at a higher risk of cervical pre-cancer and cancer, and should screen every three years if their last HPV test was negative: people living with HIV/AIDS, regardless of CD4 cell count; people with congenital (primary) immunodeficiency; transplant recipients (solid organ or allogeneic stem cell transplants); people requiring treatment (either continuously or at frequent intervals) with medications that cause immune system suppression for three years or more; people who are living with systemic lupus erythematosus (SLE), regardless of whether they are receiving immunosuppressant treatment; and people who are living with renal failure and require dialysis.

Recommendations for the average risk screening population

Populations at average risk

The average risk screening population includes people who:

- Have a cervix[a]; and
- Have ever been sexually active[b]; and
- Are asymptomatic; and
- Do not currently fall into an immunocompromised population that is at higher risk of pre-cancer and cervical cancer[c]; and
- Have the following screening history:
    - People who have only had HPV negative test results; or
    - People who have fulfilled criteria to return to screening every five years after discharge from colposcopy
    - People who have an HPV negative result after an HPV-positive (other high-risk types) result with normal or low-grade cytology results

[a]Anyone with a cervix including women, Two-Spirit people, transmasculine people, nonbinary people, pregnant people, post-menopausal people, people who have undergone a subtotal hysterectomy and retained their cervix and people who have had the HPV vaccine. At this time, screening is not recommended for people born without a cervix and transfeminine people with a neovagina because it may not be clinically or scientifically indicated; the OCSP will continue to review this guidance as more evidence becomes available (1). Routine screening is not recommended for people who have had their cervix removed as a result of hysterectomy, for more information refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance document.

[b]Sexual activity is defined as any sexual contact with another person, including any time someone has contact with another person's genitals (private parts). This contact can be with the hands, mouth or genitals. Providers should define what is meant by sexual contact, so their patients understand that it includes people who have had sexual contact with only one person, have had the same sexual partner for a long time, have not had sexual contact in a long time, or have had sexual contact with someone of the same sex.

[c]The following immunocompromised populations are at higher risk of pre-cancer and cervical cancer and should screen every three years:

- People who are living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), regardless of CD4 cell count;
- People with congenital (primary) immunodeficiency;
- Transplant recipients (solid organ or allogeneic stem cell transplants);
- People requiring treatment (either continuously or at frequent intervals) with medications that cause immune suppression for three years or more;
- People who are living with systemic lupus erythematosus (SLE), regardless of whether they are receiving immunosuppressant treatment; and
- People who are living with renal failure and require dialysis.

Key evidence

The average risk screening population is defined based on a five-year risk of HSIL or AIS histology and cervical cancer. A five-year risk is used for the average risk population to provide reassurance that a five-year screening interval is appropriate because the population's risk remains low throughout the time period. Most people eligible for cervical screening fall into this screening population.

The OCSP's risk threshold range for the average risk population is 0.12% to 0.41%. This risk threshold range was selected based on results from Dilner et al. (19) which calculated a five-year risk of HSIL or AIS histology and cervical cancer (defined in the study as cervical intraepithelial neoplasia 3+ [CIN3+]) of 0.25% (95% confidence interval [CI]: 0.12% to 0.41%) for people with negative HPV test results (19).

Age of initiation

Recommendation

Cervical screening for people with a cervix who have ever been sexually active should start at age 25.

Note: Cervical screening under age 25 is not recommended for people who had an early age of first sexual activity. In addition, cervical screening is also not recommended for those over age 25 who have never been sexually active.

Key evidence

Cervical cancer in people under age 25 is extremely uncommon. In Ontario, from 2014 to 2018, only 29 new cases of cervical cancer were diagnosed in people under age 25 (22). Given the low rate of cervical cancer, it is likely that screening in this population has no significant benefit. There are several factors that may be contributing to low rates of cervical cancer among young people including the natural history of oncogenic HPV infections and vaccination coverage.

Infection with oncogenic HPV, which is transmitted through sexual contact, is required for the development of cervical cancer. Younger people may be at higher risk of exposure to HPV because they tend to have a higher number of sexual partners. However, most oncogenic HPV infections in younger people are transient and do not progress to cervical cancer (23). As a result, screening in this population can lead to unnecessary colposcopy, which has associated potential harms.

Multiple studies across different jurisdictions have consistently shown that HPV vaccination leads to a substantial decrease in cervical pre-cancer among young people, even in situations with moderate vaccination coverage (i.e., about 65%) due to herd immunity (24). In Ontario, a publicly funded, school-based HPV vaccination program has been in place since the 2007-08 school year, therefore, people under age 25 in Ontario are likely well protected through vaccination and herd immunity. In the 2021/22 school year, the HPV vaccination coverage rate for school-based immunization programs among 17-year-olds in Ontario was 64.1% (25).

An Ontario case-control study examining the benefits and harms of screening people ages 20 to 24, supports the limited benefit of screening under age 25. The study found that there was no statistically significant difference in cervical screening exposure three to 36 month before an invasive cervical cancer diagnosis in cases (i.e., people diagnosed with cervical cancer) verses controls (i.e., people without a diagnosis of cervical cancer). This finding suggests that, in people ages 20 to 24, cervical screening is not protective against the development of cervical cancer (23).

Given the limited benefit of cervical screening in people under 25 and the potential for risk, the OCSP selected age 25 for the initiation of cervical screening for people who are immunocompetent. This recommendation is aligned with many cervical screening programs that recommend starting screening at age 25 or later, including those in British Columbia, Alberta and Nova Scotia in Canada, and other countries internationally (26–29). Also, Choosing Wisely recommends against any screening under age 25 (30).

Screening interval

Recommendation

People with a cervix who are at average risk of developing pre-cancer and cervical cancer should screen **every five years**.

Key evidence

A five-year screening interval for HPV testing is supported by evidence referenced in the 2011 Program in Evidence-Based Care (PEBC) cervical screening guideline as well as studies published since then that show the risk of HSIL or AIS histology and cervical cancer is low for at least five years after a negative HPV test (10). Table 7 provides an overview of study results referenced in the 2011 PEBC guideline as well as studies published after the literature search that informed the PEBC guideline.

Two of the studies presented in Table 8 compared the five-year risk of HSIL or AIS histology and cervical cancer (defined in the study as cervical intraepithelial neoplasia 3+ [CIN3+]) after a negative HPV test to the three-year risk of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+) after a normal cytology test, which was the recommended screening interval in the OCSP's cytology-based program (see Table 8).These data suggest that a negative HPV test every five years provides at least as much protection as a normal cytology test every three years. There is also published data from long-term studies that demonstrate the protective effect of HPV testing, which further supports a screening interval of five years (see Table 9). Some of the published data presented in Tables 7 and 8 suggests that the protective effect of a negative HPV test extends beyond five years. However, given this is an area of evolving evidence, the OCSP selected a screening interval of five years based on the precautionary principle (i.e., when there are potential harms, scientific uncertainty must be resolved in favor of prevention). A five-year interval also aligns with recommendations from cervical screening programs that have recently implemented HPV testing such as Australia (29).

Table 7: Overview of studies that estimated the long-term cumulative incidence of HSIL or AIS histology and cervical cancer after a negative HPV test

# of years after negative HPV test	Outcome	Cumulative incidence (95% CI)	Author
3	HSIL or AIS histology and cervical cancer (defined in the studies as CIN3+)	0.3% (0.1–0.70%)	Wright et al. (31)
5		0.14% (not reported)	Gage et al. (32)
		0.25% (0.12% to 0.41%)	Dilner et al. (19)
12		3.0% (2.5–3.5%)	Kjaer et al. (33)
14		0.0048%[a] (not reported)	Dijkstra et al. (34)
3	HSIL or AIS histology and cervical cancer (defined in the studies as CIN2+)	0.90% (0.40–2.01%)	Isidean et al. (35)
5		0.04% (0.01–0.17%)[b]	
6		1.41% (1.19–1.65%)	Kitchener et al. (36)

AIS: adenocarcinoma in situ; CIN 3+: cervical intraepithelial neoplasia 3+; CI: confidence interval; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion

[a]Approximate value based on a visual assessment of the figure.

[b]Isidean et al. (35) calculated outcomes for individuals attending routine cervical screening in Montreal and St. John's, Canada. However, five-year incidence was only known for St. John's participants due to the integrated nature of the health care databases in Newfoundland.

Table 8: Published data from long-term studies estimating the negative predictive value of an HPV test

# of years after negative HPV test	Outcome	Negative predictive value[a]	Author
5	HSIL histology and cervical cancer (defined in the study as CIN3+)	0.9968	Elfström et al. (37)
6	HSIL or AIS histology and cervical cancer (defined in the study as CIN3+)	0.997	Dillner et al. (19)

AIS: adenocarcinoma in situ; CIN 3+: cervical intraepithelial neoplasia 3+; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion

[a]The likelihood that negative results will correctly identify people who do not have a high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS) histology and cervical cancer and will not develop these outcomes in the next five years.

Recommendations for the immunocompromised screening population

Populations that are immunocompromised

The immunocompromised screening population includes people who:

- Have a cervix[a]; and
- Have ever been sexually active[b]; and
- Are asymptomatic; and
- Are part of one of the following populations at higher risk of pre-cancer and cervical cancer:
  - People who are living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), regardless of CD4 cell count
  - People with congenital (primary) immunodeficiency
  - Transplant recipients (solid organ or allogeneic stem cell transplants)[c]
  - People requiring treatment (either continuously or at frequent intervals) with medications that cause immune suppression for three years or more
  - People who are living with systemic lupus erythematosus (SLE), regardless of whether they are receiving immunosuppressant treatment
  - People who are living with renal failure and require dialysis

[a]Anyone with a cervix including: women, Two-Spirit people, transmasculine people, nonbinary people, pregnant people, post-menopausal people, people who have undergone a subtotal hysterectomy and retained their cervix and people who have had the HPV vaccine. At this time, screening is not recommended for people born without a cervix and people with a neovagina because it may not be clinically or scientifically indicated; the OCSP will continue to review this guidance as more evidence becomes available (1). Routine screening is not recommended for people who have had their cervix removed as a result of hysterectomy, for more information refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance document.

[b] Sexual activity is defined as any sexual contact with another person, including any time someone has contact with another person's genitals (private parts). This contact can be with the hands, mouth or genitals. Providers should define what is meant by sexual contact, so their patients understand that it includes people who have had sexual contact with only one person, have had the same sexual partner for a long time, have not had sexual contact in a long time, or have had sexual contact with someone of the same sex.

[c] The OCSP encourages health care providers to consider the HPV vaccine prior to transplant in alignment with recommendations from the Trillium Gift of Life Network.

Key evidence

Most cases of cervical cancer are caused by persistent infection with HPV. Immunosuppression may impair a person's ability to clear an HPV infection (38). In addition, it may enhance the speed at which the cervical cellular changes caused by HPV occur, including the progression to cervical cancer. As such, people who are immunocompromised may be at higher risk of pre-cancer and cervical cancer (38).

There is some primary literature showing that people living with HIV/AIDs and organ transplant recipients may be at higher risk of pre-cancer and cervical cancer compared to people who are immunocompetent (39–45). However, there are no high-quality studies examining the risk of pre-cancer and cervical cancer in other immunocompromised populations that control for screening history. As a result, beyond people living with HIV/AIDs and organ transplant recipients, the OCSP identified additional immunocompromised populations at higher risk of developing pre-cancer and cervical cancer based on results from the jurisdictional scan, expert opinion and the precautionary principle (i.e., when there are potential harms, scientific uncertainty must be resolved in favor of prevention). A three-year interval for people requiring treatment with medications that cause immune suppression was selected based on a survey of the expert panel. The interval was included to provide more specific guidance to health care providers trying to determine if a person is receiving long-term treatment. The OCSP recognizes that over-screening may be a consequence of this approach.

Several other populations were considered for inclusion in the OCSP's immunocompromised screening population. However, these populations were **not** included based on expert opinion:

- People with a history of cytotoxic treatment(s) for cancer
- People with Crohn's disease or multiple sclerosis who are not receiving immunosuppressant treatment
- The offspring of people with a cervix exposed in utero to diethylbestrol (DES) (i.e., grandchildren of people who were prescribed DES)

Individuals in the aforementioned groups should be considered to be at average risk of developing pre-cancer and cervical cancer.

The risk of cervical cancer is very heterogenous within and across immunocompromised populations (e.g., people living with HIV/AIDS may be at varying risk levels based on their CD4 cell count (46)). However, in alignment with the guiding principles regarding feasibility of implementation and acceptability for health care providers and the public, the expert panel recommended creating a single risk group for all populations defined to be immunocompromised by the OCSP. Due to limited data and the heterogeneity of pre-cancer and cervical cancer risk in this population, the OCSP was unable to establish a five-year or immediate risk of HSIL or AIS histology and cervical cancer for the immunocompromised screening population. Based on expert panel consensus, jurisdictional scan data and some literature, the OCSP concluded that some people in the immunocompromised screening population have a higher risk of high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma (AIS) histology and cervical cancer than people at average risk, but their risk is lower than people with known HPV-positive results.

Age of initiation

Recommendation

Immunocompromised populations at higher risk of pre-cancer and cervical cancer should start screening at age 25 if they have ever been sexually active.

Note: Cervical screening under age 25 is not recommended for people who had an early age of sexual activity. In addition, cervical screening is also not recommended for those over age 25 who have never been sexually active.

Key evidence

There is no primary literature and no Ontario data on the incidence of pre-cancer and cervical cancer in immunocompromised populations under age 25 or the appropriate age of initiation for cervical screening for these populations. However, cervical cancer among all people under age 25 is extremely uncommon. In Ontario, from 2016 to 2020, 29 new cases of cervical cancer were diagnosed in people under age 25 (22).

Based on input from the expert panel and jurisdictional scan data, the OCSP recommends that people who are immunocompromised as defined by the OCSP should start cervical screening at age 25. This recommendation is in alignment with some other cervical screening programs that have implemented HPV testing including those in Australia, England (47,48).

Screening interval

Recommendation

People with a cervix who have ever been sexually active and are part of an immunocompromised population defined by the OCSP to be at higher risk of pre-cancer and cervical cancer should screen every **three years**.

Key evidence

Based on expert panel feedback and some literature, the OCSP concluded that people who are immunocompromised have a higher risk of HSIL or AIS histology and cervical cancer than people at average risk but have a lower risk than people who are HPV-positive (other high-risk types) with normal or low-grade cytology. Therefore, a screening interval between two- and five-years was considered. The OCSP selected a screening interval of three years based on input from the expert panel, jurisdictional scan data and the precautionary principle. Given the limited evidence, the OCSP recognizes that over-screening may be a consequence of this approach.

Recommendations for the elevated risk screening population

Populations at elevated risk

The elevated risk screening population includes people who:

- Have a cervix[a]; and
- Have ever been sexually active[b]; and
- Are asymptomatic; and
- Have the following screening history:
    - HPV-positive (types 16, 18/45), regardless of cytology result
    - HPV-positive (other high-risk types) with high-grade cytology results
    - HPV-positive result (regardless of type or cytology result) at the two-year repeat screening test (i.e., two consecutive HPV-positive results)

[a]Anyone with a cervix including: women, Two-Spirit people, transmasculine people, nonbinary people, pregnant people, post-menopausal people, people who have undergone a subtotal hysterectomy and retained their cervix and people who have had the HPV vaccine. At this time, screening is not recommended for people born without a cervix and transfeminine people with a neovagina because it may not be clinically or scientifically indicated; the OCSP will continue to review this guidance as more evidence becomes available(1). Routine screening is not recommended for people who have had their cervix removed as a result of hysterectomy, for more information refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance document.

[b]Sexual activity is defined as any sexual contact with another person, including any time someone has contact with another person's genitals (private parts). This contact can be with the hands, mouth or genitals. Providers should define what is meant by sexual contact, so their patients understand that it includes people who have had sexual contact with only one person, have had the same sexual partner for a long time, have not had sexual contact in a long time, or have had sexual contact with someone of the same sex.

Recommendation

People who are at elevated risk of developing cervical cancer require referral to colposcopy.

Key evidence

The elevated risk screening population identifies people with screening results that require referral to colposcopy.

The elevated risk screening population is defined as people with an immediate risk of HSIL or AIS histology and cervical cancer of **greater than or equal to 6%**. For a detailed overview of how this threshold was selected, please see Appendix E.

Published literature was used to determine the immediate risk of HSIL or AIS histology and cervical cancer for various screening result combinations (i.e., different combinations of HPV types and cytology results) to identify which screening results should be included in the elevated risk screening population. A summary of the results from the literature is included in Table 9.

As shown in Table 9, people with **HPV-positive (18) with normal or atypical cells of undetermined significance (ASCUS) cytology results** are included in the elevated risk screening population even though they do not meet the risk threshold for referral to colposcopy. The immediate risk of HSIL or AIS histology and cervical cancer ranges from 2.9% to 3.0% for people with HPV-positive (18) with normal cytology results and 2.9 to 3.5% for people with HPV-positive (18) with ASCUS cytology results (49,50). However, HPV 18 infections are a significant risk factor for glandular disease (AIS and invasive adenocarcinoma), which is harder to detect with cytology (49). As a result, with support from the expert panel, the OCSP has included these screening results in the elevated risk screening population. HPV-positive (other high-risk types) with atypical glandular cells (AGC) cytology are also included in the elevated risk screening population even though they do not meet the risk threshold for referral to colposcopy because there is a high risk of other lower genital tract lesions with AGC cytology results.

Table 9: Immediate risk of HSIL or AIS histology and cervical cancer by cervical screening result for elevated risk population

HPV type	**Cytology**	**Immediate risk of HSIL or AIS histology and cervical cancer** (defined in the studies as CIN3+)	**Author**
HPV 16	Normal	5.3–8.1%[a]	Demarco et al, Stoler et al. (49,51)
	ASCUS	9.0–16.1%	Demarco et al., Wright et al.[b] (49,50)
	LSIL	11–13.0%	Demarco et al., Wright et al.[b] (49,50)

HPV type	Cytology	**Immediate risk of HSIL or AIS histology and cervical cancer** (defined in the studies as CIN3+)	Author
	ASC-H	28	Demarco et al. (49)
	AGC	36	Demarco et al. (49)
	HSIL or AIS histology and cervical cancer (defined in the paper as HSIL+)[c]	60%	Demarco et al. (49)
HPV 18	Normal	2.9–3.0%	Demarco et al., Wright et al.[b] (49,50)
	ASCUS	2.9–3.5%	Demarco et al, Stoler et al. (49,51)
	LSIL	3.1–6.5%	Demarco et al, Stoler et al. (49,51)
	ASC-H	15	Demarco et al. (49)
	AGC	33	Demarco et al. (49)
	HSIL or AIS histology and cervical cancer (defined in the paper as HSIL+)[c]	30%	Demarco et al. (49)
HPV other	AGC	5.4%	Demarco et al. (49)
	HSIL or AIS histology and cervical cancer (defined in the paper as HSIL+)[c]	35%	Demarco et al. (49)

AIS: adenocarcinoma in situ; ASCUS: atypical squamous cells of undetermined significance; CIN 3+: cervical intraepithelial neoplasia 3+; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; NILM: negative for intraepithelial lesion or malignancy

[a]This range is based on two studies. While the lower bound of the risk estimate is below the Ontario Cervical Screening Program's (OCSP) risk threshold for the elevated risk population (immediate risk of high-grade squamous intraepithelial lesion [HSIL], adenocarcinoma in situ [AIS] and cervical cancer: ≥6%), the other study found the immediate risk of HSIL or AIS histology and cervical cancer for this population is at or above the risk threshold. As such, the OCSP has used the precautionary principle and included this group in the elevated risk population.

[b]This study used cervical intraepithelial neoplasia 2+ (CIN2+) as the clinical endpoint.

[c]Adenocarcinoma (ACC), endocervical adenocarcinoma (ACC-E) and squamous cell carcinoma (SCC) are captured under this risk.

Recommendations for the moderate risk screening population

Populations at moderate risk

The moderate risk screening population includes people who:

- Have a cervix[a]; and
- Have ever been sexually active[b]; and
- Are asymptomatic; and
- Have the following screening result:
    - HPV-positive (other high-risk types) result with normal or low-grade cytology result
    - People who have met criteria to return to screening in two years after discharge from colposcopy

[a] Anyone with a cervix including: women, Two-Spirit people, transmasculine people, nonbinary people, pregnant people, post-menopausal people, people who have undergone a subtotal hysterectomy and retained their cervix and people who have had the HPV vaccine. At this time, screening is not recommended for people born without a cervix and transfeminine people with a neovagina because it may not be clinically or scientifically indicated; the OCSP will continue to review this guidance as more evidence becomes available (1). Routine screening is not recommended for people who have had their cervix removed as a result of hysterectomy, for more information refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance document.

[b]Sexual activity is defined as any sexual contact with another person, including any time someone has contact with another person's genitals (private parts). This contact can be with the hands, mouth or genitals. Providers should define what is meant by sexual contact, so their patients understand that it includes people who have had sexual contact with only one person, have had the same sexual partner for a long time, have not had sexual contact in a long time, or have had sexual contact with someone of the same sex.

Key evidence

People in the moderate risk screening population do not meet the OCSP's criteria for referral to colposcopy (i.e., immediate risk of HSIL or AIS histology and cervical cancer is less than 6%). However, because they have a positive HPV result, they do not have a sufficiently low risk to return to average risk screening (i.e., five-year risk of HSIL or AIS histology and cervical cancer is greater than of 0.25% [95% CI: 0.12% to 0.41%).

The moderate risk screening population is defined based on an immediate risk of HSIL or AIS histology and cervical cancer. The OCSP's risk threshold range for the moderate risk screening population is 1.3 to 3.7%. This risk threshold range was selected based on results from Demarco et al. (49) (see Table 10).

Table 10: Immediate and 5-year risks of HSIL or AIS histology and cervical cancer by cervical screening result for moderate risk population

HPV type	Cytology	Immediate risk of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+)	5-year risks of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+)	Author
HPV-positive (other high-risk types)	NILM	1.3%	2.2%	Demarco et al. (49)
	ASCUS	2.8%	4.0%	
	LSIL	3.7%	4.7%	

AIS: adenocarcinoma in situ; ASCUS: atypical squamous cells of undetermined significance; CIN 3+: cervical intraepithelial neoplasia 3+; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; NILM: negative for intraepithelial lesion or malignancy

Recommendation: Screening interval

People at moderate risk of developing HSIL or AIS histology and cervical cancer should have a repeat HPV test (with reflex cytology for people with HPV positive results) in **two years**.

If a person's repeat test is HPV-positive, they should be referred to colposcopy regardless of the HPV type or cytology result. If a person's repeat test is HPV-negative, they can return to screening in five years if immunocompetent or three years if immunocompromised.

Key evidence

A two-year screening interval for the moderate risk population was selected based on the natural history of HPV infections, published literature and results from Australia's cervical screening program.

Most HPV infections are transient, but it can take several years for the infection to clear (7). One longitudinal study found that 92% of HPV infections clear within seven years (7). This study also found that almost 80% of HPV infections clear within three years, but fewer than 50% of HPV infections clear within one year (7). As such, repeat screening at one year will identify a substantial number of transient infections that will resolve on their own with more time. Whereas repeat screening at two years allows more time for clearance of transient HPV infections and avoids unnecessary colposcopy, which has associated potential harms.

In alignment with the HPV infection clearance data, findings from the Australian cervical screening program suggest that re-screening at one year may be too soon to allow people to clear their HPV infection. Australia found that a one-year repeat screening interval for people with HPV-positive (other high-risk types) and normal or low-grade cytology results leads to a significant number of people being referred to colposcopy with two consecutive HPV-positive (other high-risk types) tests with low-grade or normal cytology. When the screening test was repeated at one year, 62.9% were still HPV-positive and of those, 90.0% remained HPV-positive (other high-risk types) with normal or low-grade cytology (52).

As shown below in Table 11, the 2.5-year risk of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+) for people with HPV-positive (other high-risk types) and normal or low-grade cytology results is below the OCSP's referral threshold to colposcopy (≥6%) (53). Furthermore, there is evidence showing that the risk of HSIL or AIS histology and cervical cancer (defined in the studies as CIN3+) remains below 6% at five years, which suggests it may be safe to re-screen this population at an interval longer than two-years (49,53). However, given that data is limited at this time, the OCSP selected a two-year repeat screening interval based on the precautionary principle (i.e., when there are potential harms, scientific uncertainty must be resolved in favor of prevention).

Table 11: 2.5 and 5-year risks of HSIL or AIS histology and cervical cancer by cervical screening result for moderate risk population

HPV type	Cytology	2.5-year risk of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+)	5-year risks of HSIL or AIS histology and cervical cancer (defined in the studies as CIN3+)	Author
HPV-positive (other high-risk types)	Normal	0.9%	2.2%	Gilham et al. (53)
	Low-grade	5.5%	5.7%	
HPV-positive (other high-risk types)	Normal	N/A	2.2%	Demarco et al. (49)
	ASCUS	N/A	4.0%	
	LSIL	N/A	4.7%	

AIS: adenocarcinoma in situ; ASCUS: atypical squamous cells of undetermined significance; CIN 3+: cervical intraepithelial neoplasia 3+; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; NILM: negative for intraepithelial lesion or malignancy

Management of unsatisfactory cytology and/or invalid human papillomavirus (HPV) result

Recommendations

When an HPV test result is invalid or a cytology test result is unsatisfactory, there is no need to delay taking a repeat specimen. A repeat screening specimen should be taken at the participant's earliest convenience, within 3 months. In the case of unsatisfactory cytology results, a standalone cytology test should be conducted (i.e., do not repeat the HPV test).

In the following circumstances, a repeat specimen is **not** required and the person should be referred to colposcopy:

- If the HPV test is positive for types 16/18/45 with unsatisfactory cytology
- If the HPV test is positive for HPV (other high-risk types) with unsatisfactory cytology at a 2-year follow-up test
- After two consecutive unsatisfactory cytology or invalid HPV results

Referral for colposcopy after two consecutive unsatisfactory cytology or invalid HPV results can enable a closer examination of the cervix and surrounding tissue to determine if it is feasible to complete the test or if alternative forms of follow-up are needed. It may also improve a person's experience for someone who has had two unsuccessful tests in primary care to see a different provider for further follow-up.

If an HPV/cytology co-test performed during colposcopy yields an unsatisfactory cytology result, a repeat (standalone) cytology test should be completed in a timely manner.

The use of transition-related hormone therapy (i.e., androgen therapy) in transmasculine and nonbinary people has been associated with a higher rate of unsatisfactory cytology test results. In such circumstances, a course of intravaginal estrogen therapy should be considered after an unsatisfactory cytology result (1). Intravaginal estrogen therapy has also been associated with reduced odds of an atrophic cytology test (which may be reported as unsatisfactory) in post-menopausal people and may be considered in this population as well (54).

Key evidence

Unsatisfactory cytology

In the cytology-based program, the Ontario Cervical Screening Program (OCSP) recommended that unsatisfactory cytology results be repeated three months after the initial sample was taken. This delay reflected a clinical assumption that time is required to allow cells from the surface of the cervix to regenerate to produce an accurate cytology reading. However, this recommendation was not evidence-based and was based on expert opinion that is now felt to be outdated.

There is no published evidence on the optimal timeframe for repeat sampling after an unsatisfactory cytology result. Given the absence of evidence, the expert panel advised that repeating an unsatisfactory cytology result at the participant's earliest convenience is the most person-centred approach. The 3-month timeframe was included to provide guidance for health care providers to help ensure timely screening.

Referral to colposcopy after two consecutive unsatisfactory results is based on jurisdictional scan data and expert opinion. An important consideration identified by the expert panel is that two consecutive unsatisfactory cytology results may be the result of stenosis, which is unlikely to resolve to obtain a satisfactory sample in screening.

Invalid HPV

Invalid HPV test results are unusual and are typically attributable to technical and/or testing-quality related factors. Therefore, delays in repeating an invalid HPV result are also not required.

The recommendation to refer to colposcopy after consecutive invalid HPV tests is based on expert opinion and jurisdictional scan data. It is also consistent with the recommendation for consecutive unsatisfactory cytology results which minimizes complexity for health care providers.

Cessation for average risk and immunocompromised populations

Recommendation: Cervical screening cessation for people ages 65 to 69 with human papillomavirus (HPV) negative test results

People can stop cervical screening if they have had **one** negative HPV test result from age 65 to 69 with the following exceptions:

- People who were not screened from age 65 to 69 should be screened until age 74
- Immunocompromised populations[a] should be screened until age 74
- People who are age 65 to 69, have been discharged from colposcopy and have been advised to screen in 2 years because they have not yet met the criteria to return to average risk screening in five years or immunocompromised screening in 3 years should be screened until age 74

[a]The following immunocompromised populations are at higher risk of pre-cancer and cervical cancer:

- People who are living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), regardless of CD4 cell count;
- People with congenital (primary) immunodeficiency;
- Transplant recipients (solid organ or allogeneic stem cell transplants);
- People requiring treatment (either continuously or at frequent intervals) with medications that cause immune suppression for three years or more;
- People who are living with systemic lupus erythematosus (SLE), regardless of whether they are receiving immunosuppressant treatment; and
- People who are living with renal failure and require dialysis.

Key evidence

Published literature

The Ontario Cervical Screening Program (OCSP) identified five studies that reported the risk of high-grade squamous intraepithelial lesion (HSIL), or adenocarcinoma in situ (AIS) histology and cervical cancer (defined in the studies as cervical intraepithelial neoplasia 3+ [CIN3+]) among those with one or more negative HPV tests after age 50. Risk estimates for this population were generally consistent across studies (see Table 12). These statistics provide reassurance that the long-term risk of HSIL or AIS histology and cervical cancer for people who cease cervical screening after one negative HPV test after age 50 is low.

Table 12: Risk of HSIL or AIS histology and cervical cancer among people aged 50 and older with one or more negative HPV tests by age group and cervical screening result

Screening results after age 50: HPV test result	Screening results after age 50: Most recent cytology result	Age (years)	5-year risk (95% CI) (%)	Author
Outcome: HSIL or AIS histology and cervical cancer				
1 negative HPV test	Normal	50–64	0.06 (0.05–0.07)	Castle et al. (55)
		55–64	0.03 (0.02–0.04)[a]	Landy et al. (56)
		55–59	0.03 (0.02–0.05)[a,b]	
		60–64	0.04 (0.01–0.08) [a,b]	
	ASCUS	55–59	0.28 (not reported)	Katki et al. (57)
		60–64	0.54 (not reported)	
Outcome: Cervical cancer				
1 negative HPV test	Normal	50–64	0.00	Landy et al. (56)
	ASCUS	55–59	0.00	Katki et al. (57)
		60–64	0.26 (not reported)	

AIS: adenocarcinoma in situ; ASCUS: atypical squamous cells of undetermined significance; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion

[a]This study reported its outcome as cervical intraepithelial neoplasia 3 (CIN3) and no cases of invasive cervical cancer were diagnosed during the study period.

[b]These estimates were adjusted for unresolved abnormal screening results.

There are also published data from long-term studies (i.e., 5 and 6 years) that demonstrate the protective effect of HPV testing (see Table 8). Although these data are not specific to an older age cohort, they suggest that a negative HPV test provides a long-term protective effect against HSIL or AIS histology and cervical cancer.

Ontario data

An analysis of incidence rates of HSIL or AIS histology and cervical cancer (defined in the study as CIN3+) for people ages 70 and older in Ontario was conducted. Among people ages 70 and older diagnosed with HSIL or AIS histology and cervical cancer, only 21.9% had a cytology test six months to 10 years before diagnosis (58). These data suggest that a large majority of cervical cancers in people ages 70 and older occur in the under-screened population, therefore, the benefit of continued cervical screening for people with an up-to-date screening history is likely limited.

Jurisdictional scan

The jurisdictional scan found that cervical screening programs have varied cervical screening cessation criteria including the number of HPV tests required to stop screening (range: 1 to 2) and the age of cessation (range: 60 to 74 years of age).

Recommendation: Cervical screening cessation for people ages 65 to 69 with HPV positive test results

People who have a positive HPV test result from age 65 to 69 should follow the appropriate screening and colposcopy pathways until they have a negative HPV test result or until they are age 74, whichever occurs first.

People with a positive HPV test result (regardless of type or cytology result) from age 70 to 74 should be referred to colposcopy[a]. In colposcopy:

- People with HSIL detected at colposcopy should follow the appropriate treatment pathway
- People with a negative colposcopy (i.e., histology = LSIL or no biopsy taken) can be discharged from colposcopy and no further screening is required in primary care

[a]Due to potential discomfort and atrophy (which causes visual inspection issues), use of intravaginal estrogen therapy can be considered if the person has no medical contraindications.

Key evidence

Published literature

Three studies reported the risk of HSIL or AIS histology and cervical cancer (defined in the studies as CIN3+) or cervical cancer among people with one positive HPV test and normal or low-grade cytology after age 50. Risk estimates for this population were generally consistent across studies (see Table 13). These data demonstrate that the risks of HSIL or AIS histology and cervical cancer remains elevated in older people with HPV positive results compared to people with HPV negative results.

Table 13: Risk of HSIL or AIS histology and cervical cancer among people with one positive HPV test after age 50 by age group and cervical screening result

Screening results after age 50: HPV test result	Screening results after age 50: Most recent cytology result	Age	5-year risk of HSIL or AIS histology and cervical cancer (%)	Author
HSIL or AIS histology and cervical cancer				
1 positive HPV test	Normal	55–59	3.30	Gage et al. (59)
		60–64	5.00	
		55–59	3.10	Katki et al. (60)
		60–64	4.10	
	Low-grade[a]	55–59	6.10	Gage et al. (59)
		60–64	6.60	

Screening results after age 50: HPV test result	Screening results after age 50: Most recent cytology result	Age	5-year risk of HSIL or AIS histology and cervical cancer (%)	Author
HSIL or AIS histology and cervical cancer				
		55–59	5.70	Katki et al. (60)
		60–64	5.40	
Cervical cancer				
1 positive HPV test	Normal	55–59	0.38	Katki et al. (60)
		60–64	0.58	
	Low-grade[a]	55–59	0.49	Katki et al. (57)
		60–64	0.93	

AIS: adenocarcinoma in situ; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion

[a]In Gage et al. (2015) (59), low-grade cytology was defined as atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion of (LSIL); whereas in Katki et al. (2013) (57), low-grade was defined as ASCUS only.

Recommendation: Screening for people ages 75 and older

The OCSP does not recommend cervical screening for people ages 75 and older.

Note: People ages 75 and older with any visible cervical abnormalities or abnormal symptoms must be investigated, regardless of age.

Key evidence

The natural history of cervical cancer is very long: typically, it takes 15 to 20 years for an HPV infection to progress to cervical cancer in people who are immunocompetent (8).

When developing eligibility criteria for cervical screening, the OCSP weighed the potential benefits of screening against the potential harms. As people get older, it is generally accepted that the benefits of screening begin to diminish and the potential harms become higher (e.g., from additional testing and intervention) (61). Therefore, cervical screening for people ages 75 and older is not recommended.

Special population: People with a cervix who were exposed to diethylstilbestrol (DES) in-utero

Recommendation

Cervical screening is not recommended for people with a cervix who were exposed to DES in-utero. Instead, these people should be monitored every three years in colposcopy. A decision to cease management in colposcopy should be made by the colposcopist in consultation with their patient based on individual risk.

Key evidence

DES is a medication that was prescribed in Canada from the 1940s until 1971, predominantly to people who were pregnant to prevent miscarriages (62). The medication was discontinued for use in humans when evidence emerged linking prenatal (before birth) DES exposure to a variety of abnormalities of the lower genital tract. One of the effects of DES, which is supported by evidence, is that people exposed in utero to DES have an increased risk of clear cell carcinoma of the vagina and cervix (63). However, clear cell carcinoma is not considered to be mediated by human papillomavirus (HPV) and therefore would not be detected by cervical screening with HPV testing (64).

The Ontario Cervical Screening Program (OCSP) identified two jurisdictions that have implemented HPV-based cervical screening that have recommendations for people who were exposed to DES in utero. Australia recommends annual co-testing with HPV and cytology in colposcopy based on expert consensus (65). England recommends routine cervical screening unless stigmata of DES exposure are present, in which case referral to colposcopy is recommended (48).

Given recommendations between the two jurisdictions vary and the published evidence is limited, the OCSP's recommended management for this population was based on expert opinion. The panel recommended management of people with a cervix exposed to DES in-utero in colposcopy based on the precautionary principle (i.e., when there are potential harms, scientific uncertainty must be resolved in favor of prevention). Furthermore, management in colposcopy will reduce the possibility of clear cell carcinoma of the vagina and cervix going undetected by screening with HPV testing.

Cytology that may suggest non-cervical malignancy

While uncommon, cervical screening cytology can indicate the presence of abnormal cytology suggestive of malignancies that are non-cervical in origin or from an unknown primary cancer. Appropriate next steps for someone who is human papillomavirus (HPV)-positive with cytology results that may or may not be specific to the cervix require clinical judgement and referral to the appropriate specialist. Based on expert consensus, some high-level recommendations are provided below in Table 14.

Table 14. Recommendations for those who are HPV-positive with cervical screening cytology results that are suggestive of non-cervical malignancy

Cytology result	Recommendation
Malignancy Carcinoma Sarcoma	Refer to gynecologic oncology centre for further assessment or regional cancer program, as appropriate.
Extrauterine adenocarcinoma	Refer to gynecologic oncology centre for further assessment or regional cancer program, as appropriate.
Atypical glandular cells of endometrial origin Endometrial adenocarcinoma	Timely workup is important. Refer to colposcopy for assessment of the cervix and endometrial cavity. Endometrial sampling is required and can be done in colposcopy, gynecology or primary care.
Atypical glandular cells of endometrial origin (if SCC/ACC/ACC-E are concurrently seen) Endometrial adenocarcinoma (if SCC/ACC/ACC-E are concurrently seen)	Timely workup is important. Refer to colposcopy for assessment of the cervix and endometrial cavity. Endometrial sampling is required and can be done in colposcopy, gynecology or primary care. If an obvious lesion was present, consider referral to gynecologic oncology.
Endometrial cells detected (in someone ≥45 years)	If person is postmenopausal or has risk factors for endometrial cancer (e.g., diabetes, high BMI, history of polycystic ovarian syndrome, Lynch syndrome) or has abnormal vaginal bleeding, endometrial sampling is required. This can be done in colposcopy, gynecology or primary care.

Colposcopy Recommendations

Colposcopy recommendations

The purpose of colposcopy is to rule out the presence of cervical pre-cancer (i.e., high-grade squamous intraepithelial lesion [HSIL] or adenocarcinoma in situ [AIS]), the immediate pre-cursor to cervical cancer. If a pre-cancer has been detected, treatment can be performed in colposcopy as well as follow-up to ensure that the treatment was successful.

A risk-based approach has been used by estimating the immediate and five-year risks of developing HSIL or AIS in the cervix to determine an "episode of care" in colposcopy. Episodes of care outline various decision points such as the number of colposcopy visits, necessary interventions, tests, when someone may be eligible for discharge and if discharged, the recommended interval(s) for screening post-discharge from colposcopy. Episodes of care are summarized as colposcopy pathways in this document.

When discharging patients from colposcopy, colposcopists should provide clear recommendations on the appropriate screening interval to the referring provider.

Recommendations for colposcopy in pregnancy are out of scope for the Ontario Cervical Screening Program. For information on this topic, please refer to the 2023 Canadian Colposcopy Guideline: A Risk-Based Approach to Management and Surveillance of Cervical Dysplasia.

Repeat cytology at first colposcopy visit

The purpose of the first colposcopy visit is to rule out the presence of cervical pre-cancer through colposcopic investigation. At this visit, the colposcopist will have access to the cytology result obtained during screening (with the exceptions listed below) and therefore cytology does not usually need to be repeated.

Recommendation

Routine repeat cytology at the first colposcopy visit should not be performed if the referral cytology was done within **six months** of the colposcopy visit, except for the following clinical circumstances:

- If people are referred to colposcopy with two consecutive unsatisfactory cytology results
- If people are referred to colposcopy with human papillomavirus (HPV)-positive (types 16, 18/45) and an unsatisfactory cytology result

In these two clinical circumstances, repeat cytology at the initial colposcopy is appropriate to determine risk-based management in colposcopy.

Key evidence

Ontario data

An Ontario data analysis was performed in 2015 to compare the results for people who had a repeat cytology taken within six months of their index cytology test (66). This analysis showed that the practice of repeating cytology is common, with approximately 9,000 repeat cytology tests performed in 2015 at a person's first colposcopy visit. As shown in Table 15, most people (>96%) with a low-grade index cytology result had a low-grade or normal result when cytology was repeated within six months, meaning the result in colposcopy is aligned with the index cytology result.

In contrast, Ontario data showed that the repeat cytology results for people with an index high-grade cytology result had lower agreement (percentage agreement range: 22.8 to 63.3%). However, in cases where the cytology result has changed when repeated, colposcopists should manage the patient based on the highest risk result for patient safety reasons. As such, a lower grade result on a repeat specimen at the first colposcopy visit should not change the patient's management in colposcopy. For example, a person with an index high-grade cytology result and a low-grade cytology result at their first colposcopy visit should be managed as per the high-grade cytology result.

Therefore, based on Ontario data and the importance of managing patients based on the highest risk result to ensure patient safety, repeating cytology at the first colposcopy visit does not add value if the index cytology was performed within six months of the visit.

Table 15: Ontario data (2015): Cytology result for people who had a repeat test 1-180 days from index cytology

Referral cytology result		Repeat cytology result (occurring 1-180 days from index cytology)					
		Normal or low-grade (NILM, ASCUS, LSIL)		High-grade (ASC-H, HSIL, AGC, AIS)		Total	
		N	%	N	%	N	%
Low-grade	ASCUS	4654	97.3%	130	2.7%	4784	100.0%
	LSIL	3166	96.2%	124	3.8%	3290	100.0%
High-grade	ASC-H	195	53.4%	170	46.6%	365	100.0%
	HSIL	155	36.7%	267	63.3%	422	100.0%
	AIS	<5*	50.0%	<5*	50.0%	<5[a]	100.0%
	AGC	132	77.2%	39	22.8%	171	100.0%

AGC: atypical glandular cells; AIS: adenocarcinoma in situ; ASC-H: atypical squamous cells, cannot exclude HSIL; ASCUS: atypical squamous cells of undetermined significance; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; N: sample size, NILM: negative for intraepithelial lesion or malignancy

[a]Sample sizes between 1 and 5 have been suppressed and are shown as "<5".

Jurisdictional scan

The recommendation that colposcopists not perform cytology at the first colposcopy visit (with the exceptions noted above) is supported by the results of a jurisdictional scan, which found that most cervical screening programs using HPV testing do not recommend repeating cytology at the first colposcopy visit, except in very specific clinical circumstances.

Investigation and management of people referred with two consecutive unsatisfactory cytology or invalid HPV results

Recommendation

For people who are referred to colposcopy with two consecutive unsatisfactory cytology results or invalid HPV results, a colposcopic assessment should be performed and a sample taken, if possible. If a sample cannot be obtained, an individualized approach should be taken to determine the appropriate course of action in consultation with the patient. Note that a colposcopy assessment may face the same limitations as screening (e.g., stenosis, atrophy).

In the case of consecutive unsatisfactory cytology results in screening, in particular in the setting of vaginal atrophy (menopause, transition-related hormone therapy use [i.e., androgen therapy]), repeating the cytology test with a course of intravaginal estrogen therapy can be considered in colposcopy because it may improve visualization of the transformation zone (67).

Colposcopy pathway 1: Investigation and management for people referred with HPV-positive and normal (NILM) or low-grade cytology (ASCUS, LSIL)

This pathway applies to people with the following screening results who are referred to colposcopy:

- HPV-positive (types 16, 18/45) with negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL) cytology results at first or repeat test[a] in screening
- HPV-positive (other high-risk types) with NILM, ASCUS, or LSIL cytology results at repeat test[a] in screening

[a]A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology

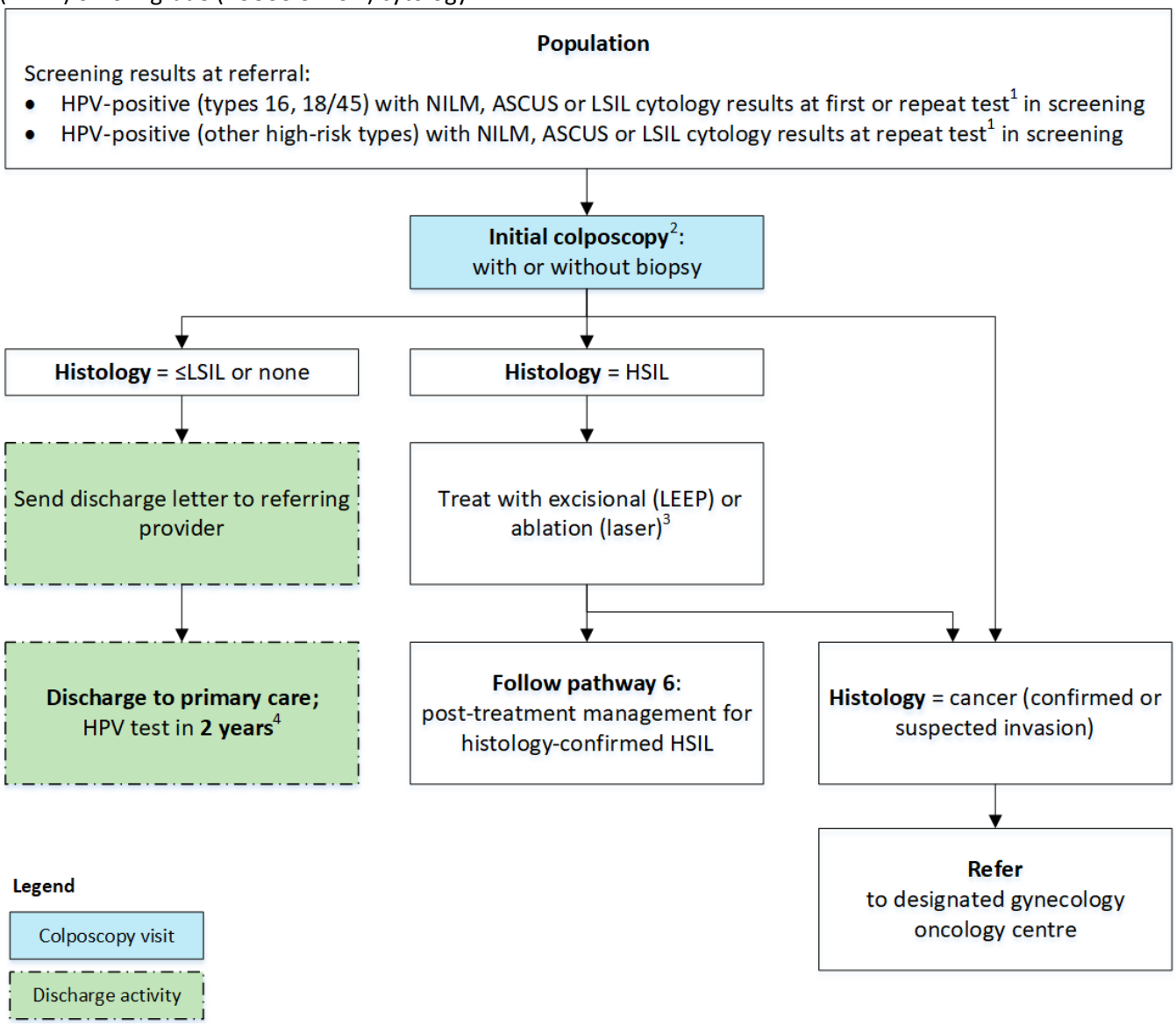
Recommendations

For people referred to colposcopy with HPV-positive (regardless of type) and normal or low-grade cytology results, only one colposcopy visit is required if histology at the initial colposcopy visit is found to be LSIL, or if no biopsy was performed. These patients can be discharged to primary care to resume screening in two years with an HPV test. People with an HPV-positive result (regardless of HPV type or cytology) at their first screening test post-discharge should be referred back to colposcopy.

However, if HSIL histology is detected at the initial colposcopy visit, the patient should be treated and then follow pathway 6 for post-treatment management.

The full recommendations for investigation and management in colposcopy are summarized in Figure 4.

Figure 4: Colposcopy pathway 1: Investigation and management for people referred with HPV-positive and normal (NILM) or low-grade (ASCUS or LSIL) cytology



ASCUS = atypical squamous cells of undetermined significance; HPV = human papillomavirus;
HSIL = high-grade squamous intraepithelial lesion; LEEP = loop electrosurgical excision procedure;
LSIL = low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesion or malignancy

Footnotes:

1. A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years following first-time HPV-positive (other high-risk types) results with normal or low-grade cytology.
2. Routine repeat cytology in colposcopy is not recommended, except for people referred to colposcopy with two consecutive unsatisfactory cytology results, or HPV-positive (types 16, 18/45) results and unsatisfactory cytology.
3. Cryotherapy is not recommended for the treatment of HSIL. Tissue sampling is preferred. However, the mode of treatment is at the discretion of the colposcopist.
4. If someone is age 70 and over, they can be discharged from colposcopy and stop screening. Refer to Cessation for average risk and immunocompromised populations.

Key evidence

Risk of HSIL after a negative colposcopy (i.e., HSIL not detected) for people referred with normal (NILM) or low-grade cytology (ASCUS, LSIL)

Published evidence

Two studies were identified that examined the risks of developing HSIL or cervical cancer after a negative colposcopy for people referred to colposcopy with HPV-positive and normal or low-grade cytology.

One study examined the subsequent risk of developing HSIL (defined in the study as cervical intraepithelial neoplasia 3+ [CIN3+]) following a negative colposcopy (defined in the study as the colposcopy histology results <CIN2). The study found that the risk of developing HSIL was low after one year (absolute risk [AR] range: 1.1 to 1.3%) and the risk only increased slightly at three years (AR range: 1.8 to 2.2%) (68). Similarly, a second study found that, after a single negative colposcopy (defined in the study as <CIN2), the five-year risk of developing HSIL (defined in the study as CIN2+) and cervical cancer was low, ranging from 1.2% to 3.8% and 0.04 to 0.17%, respectively (69).

Therefore, the published evidence suggests that people referred to colposcopy with HPV-positive and normal or low-grade cytology have a low risk of developing HSIL or cervical cancer after a single negative colposcopy up to five years following colposcopy.

Ontario data

Ontario data is consistent with the published evidence (70). Table 16 below summarizes the three- and five-year risks of developing HSIL (defined in the study as CIN3) and cervical cancer in Ontario from 2010 to 2019 stratified by index cytology and biopsy result for people referred to colposcopy with low-grade cytology and had a negative colposcopy (defined in the study as ≤CIN2). Similar to the results described above, these Ontario data show that the risk of developing HSIL and cervical cancer is low after a single, negative colposcopy (68,69).

Table 16: Ontario data for HSIL (defined in the study as CIN3) and cervical cancer risks for people referred with normal (NILM) or low-grade cytology (ASCUS, LSIL) after a negative colposcopy

	Colposcopy finding	**HSIL histology incidence rate (%)**		**Cervical cancer incidence rate (%)**	
		3-year rate	**5-year rate**	**3-year rate**	**5-year rate**
Referral cytology result	NILM	0.69	0.93	0	0.02
	ASCUS	4.31	5.60	0.08	0.11
	LSIL	5.85	7.23	0.04	0.07
Biopsy result	No biopsy	4.11	5.20	0.05	0.08
	Negative	2.85	3.81	0	0.05
	LSIL	7.09	8.32	0	0

ASCUS: abnormal atypical squamous cells of undetermined significance; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; NILM: negative for intraepithelial lesion or malignancy

In addition, Ontario data has been examined to estimate the risk of developing cervical cancer for people who were referred to colposcopy with low-grade cytology and had a negative colposcopy. These data show that people who were referred to colposcopy with low-grade cytology and had a single negative colposcopy had a low risk of developing cervical cancer (odds ratio: 0.3 [95% confidence interval: 0.1 to 1.0]) over five years (71); this study further supports that people in this population are at low risk of developing cervical cancer and therefore do not require further management in colposcopy.

In summary, based on the published evidence and data from Ontario, people referred to colposcopy with HPV-positive results and normal or low-grade cytology and who have had a negative colposcopy are at low risk of developing HSIL and cervical cancer over three to five years.

Resumption of screening in primary care post-discharge from colposcopy

The expert panel weighed various factors to inform when people should resume screening post-discharge from colposcopy. A key factor considered by the expert panel was ease of implementation; the panel felt that it was important for the recommendations to be as simple as possible for health care providers and, where possible, align with existing screening intervals. The expert panel also considered health care provider/public acceptability and felt that aligning to existing intervals used in cervical screening may be more acceptable. Taking these factors into consideration, the expert panel recommended that all patients discharged from colposcopy either resume average risk/immunocompromised screening (i.e., resume screening in five or three-years depending on the individual's immune status) or moderate risk screening (i.e., resume screening in two years if their risk is not low enough to return to average risk (or immunocompromised) screening.

As described above, the findings from the published evidence and Ontario data analyses show that people referred to colposcopy with HPV-positive and normal or low-grade cytology are at low risk of developing HSIL and cervical cancer following colposcopy. However, one of the studies found that the absolute risk of developing HSIL at one and three years after a single negative colposcopy ranged from 1.1% to 2.2% (20), which is higher than the average risk screening population risk level defined by the Ontario Cervical Screening Program (OCSP). Therefore, people discharged from colposcopy pathway 1, should resume screening in two years.

A summary of all post-discharge from colposcopy screening recommendations can be found in the section titled "Post-discharge from colposcopy: Recommendations for screening in primary care".

Colposcopy pathway 2: Investigation and management for people referred with HPV-positive and high-grade cytology (ASC-H, LSIL-H, HSIL), excluding AIS

This pathway applies to people with the following screening results who are referred to colposcopy:

- HPV-positive (types 16, 18/45) with atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion, cannot exclude high-grade intraepithelial lesion (LSIL-H), or high-grade squamous intraepithelial lesion (HSIL) cytology results at first or repeat test[a] in screening
- HPV-positive (other high-risk types) with ASC-H, LSIL-H, or HSIL cytology results at first or repeat test[a] in screening

[a]A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology.

Recommendations

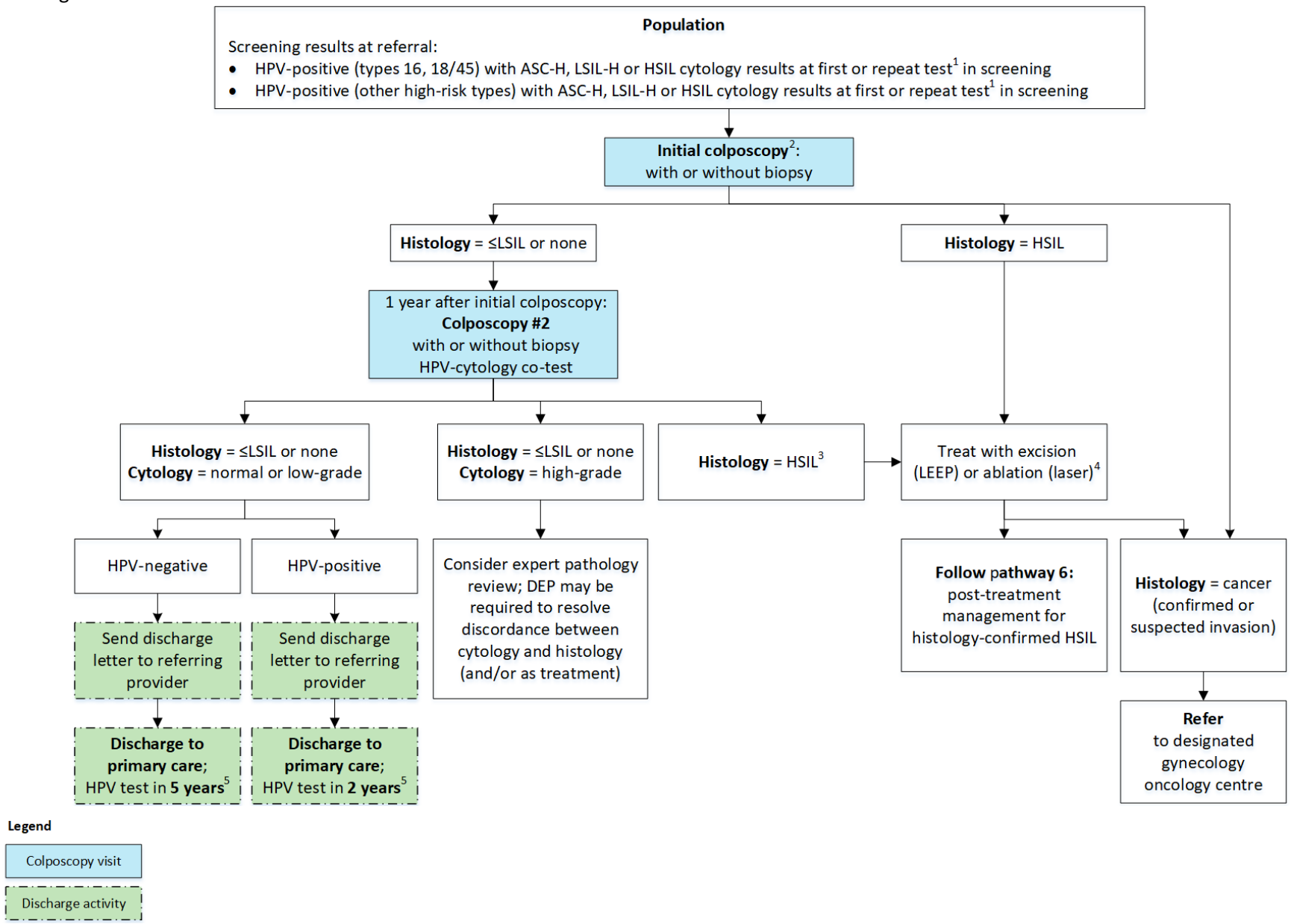
For people referred to colposcopy with HPV-positive (regardless of type) and high-grade cytology results (ASC-H, LSIL-H, HSIL) excluding AIS, a minimum of two colposcopy visits are required.

if no biopsy was taken at either visit, the patient can be discharged back to screening in primary care. An HPV/cytology co-test should be performed at the second colposcopy visit, the results of which will inform when to resume screening in primary care. For people discharged to cervical screening in primary care in two years, any HPV-positive result (regardless of HPV type or cytology) at their first screening test post-discharge should be referred back to colposcopy.

If HSIL histology is detected at either visit, the patient should be treated and then follow pathway 6 for post-treatment management.

The full recommendations for investigation and management in colposcopy are summarized in Figure 5.

Figure 5: Colposcopy pathway 2: Investigation and management for people referred with HPV-positive and high-grade cytology (ASC-H, LSIL-H or HSIL), excluding AIS



AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion;
DEP = diagnostic excisional procedure; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion;
LEEP = loop electrosurgical excision procedure; LSIL = low-grade squamous intraepithelial lesion;
LSIL-H = low-grade squamous intraepithelial lesion, cannot exclude HSIL

Footnotes:

1. A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology.
2. Routine repeat cytology in colposcopy is not recommended, except for people referred to colposcopy with: two consecutive unsatisfactory cytology results, or, HPV-positive (types 16, 18/45) results and unsatisfactory cytology.
3. Regardless of HPV test result.
4. Cryotherapy is not recommended for the treatment of HSIL. Tissue sampling is preferred. However, the mode of treatment is at the discretion of the colposcopist.
5. If someone age 70 to 74 is HPV-negative, they can be discharged from colposcopy and stop screening. If someone age 70 and older is discharged from colposcopy to primary care and has a negative result at the 2-year screening test, they can also stop screening. Anyone discharged after age 74 can stop screening, regardless of the pathway interval. Refer to Cessation for average risk and immunocompromised populations.

Key evidence

Risk of HSIL after a negative colposcopy (i.e., HSIL not detected) for people referred to colposcopy with high-grade cytology (ASC-H, LSIL-H, HSIL) excluding AIS

Published evidence

Two studies were identified that examined the risks of developing HSIL and cervical cancer after a negative colposcopy for people referred to colposcopy with HPV-positive and high-grade cytology results. One study examined the risk of developing HSIL and cervical cancer (defined in the study as cervical intraepithelial neoplasia 3+ [CIN3+]) following a negative colposcopy (defined in the study as the colposcopy histology results < CIN2) for people referred with HPV-positive and high-grade cytology results. The results showed that, for this population group, the risk of developing HSIL and cervical cancer was moderate at one year (absolute risk [AR]: 7.69%; confidence interval [CI] not reported) and this risk increased at three years (AR: 9.3%; CI not reported) (68). Similarly, another study found that, after a single negative colposcopy (defined in the study as the colposcopy histology results <CIN2), the five-year risk of developing HSIL (defined in the study as CIN2+) ranged from 3.8% to 15% (69). This study also reported a low five-year risk of developing cervical cancer, ranging from 0.72 to 2.1% (69). The results of these studies showed that the risk of developing HSIL and cervical cancer is too high to discharge people after a single negative colposcopy.

The published literature also provides data about the risks of developing HSIL stratified by the results of tests performed during colposcopy. The second study described above provided data on the risk of developing HSIL over five years by follow-up strategy in colposcopy (i.e., cytology alone, HPV testing alone, or HPV/cytology co-testing) for people referred to colposcopy with high-grade cytology results and where the initial colposcopy was negative (69). The risk of developing HSIL over five years was low (2.2% [95% CI: 0.7 to 6.9%]) for people with a negative HPV/cytology co-test (defined by the study as a negative HPV test and normal cytology) in colposcopy. This risk was substantially lower than the risk of HSIL over five years for people with a negative cytology test alone (7.0% [p=0.06]; 95% CI not reported). In addition, while the risk of HSIL over five years for people with a negative HPV/cytology co-test was also lower than the risk observed for people with a negative HPV test alone (4.4 [p=0.4]; 95% CI not reported), the magnitude of the difference was smaller (69). Overall, the results showed that a negative HPV/cytology co-test in colposcopy provides more reassurance against developing HSIL compared to cytology or HPV testing alone.

Ontario data

Ontario data is consistent with the published evidence (70). Table 17 below summarizes the three- and five-year risks of developing HSIL (defined in the study as CIN3) and cervical cancer in Ontario from 2010 to 2019 stratified by biopsy result for people referred to colposcopy with high-grade cytology who had a negative colposcopy (defined in the study as ≤CIN2). Similar to the results described above, the Ontario data shows that the risk of developing HSIL and cervical cancer for people referred to colposcopy with high-grade cytology remains moderate after a single negative colposcopy (68,69).

Table 17: Ontario data for HSIL (defined in the study as CIN3) and cervical cancer risks for people referred with high-grade cytology after a negative colposcopy

	Colposcopy finding	HSIL histology incidence rate (%)		Cervical cancer incidence rate (%)	
		3-year rate	5-year rate	3-year rate	5-year rate
Biopsy result	No biopsy	17.7	20.0	1.25	1.68
	Negative[a]	13.0	15.1	0.78	1.04
	LSIL	18.9	20.0	0	0

HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion

[a]Cervical cancer incidence rate includes 13 squamous cell carcinoma and 6 adenocarcinoma index cytology.

In addition, Ontario data has been examined to estimate the risk of developing cervical cancer for people referred to colposcopy with high-grade cytology and who had a negative colposcopy (defined by the study as no treatment performed). These data show that, after a single negative colposcopy visit for people referred with high-grade cytology, the risk of developing cervical cancer remained moderate (odds ratio [OR]: 6.6 [95% CI: 3.9 to 11.0]). However, this risk is significantly reduced after two or more negative colposcopies (OR: 1.1 [95% CI: 0.5 to 2.4]) (71). Taken together with the published literature, the Ontario data shows that the risk of HSIL and cervical cancer is too high to discharge people after one negative colposcopy but that a second negative colposcopy reduces a person's risk of HSIL and cervical cancer enough to discharge them from colposcopy to resume cervical screening in primary care.

Resumption of screening in primary care post-discharge from colposcopy

Published evidence

The expert panel weighed various factors to inform when people should resume screening post-discharge from colposcopy which are described in detail in colposcopy pathway 1.

One study was identified that was used to help determine which screening intervals people should resume screening at post-discharge from colposcopy pathway 2 (70). This study examined the immediate- and five-year risks of developing HSIL and cervical cancer (defined in the study as CIN3+) for people referred to colposcopy with HPV-positive and high-grade cytology results who subsequently had an HPV-negative result in colposcopy (72). The study found that people with a negative colposcopy and an HPV-negative result in colposcopy had low immediate- and five-year risks of developing HSIL and cervical cancer (0.14%; CI not reported and 0.80%; CI not reported, respectively), which means that this population meets the criteria to return to average (or immunocompromised) risk screening. However, for people with HPV-positive results and normal or low-grade cytology in colposcopy, while the immediate- and five-year risks of developing HSIL and cervical cancer if cytology is normal or low-grade (5.0% to 6.0%; CI not reported and 12% to 17%; CI not reported, respectively) are too high to return to average risk (or immunocompromised) screening, these risks are not high enough to support a person remaining in colposcopy given the potential harms associated with over-management in colposcopy such as anxiety, discomfort, pain and in some cases, problems with future pregnancies. Therefore, people referred to colposcopy with HPV-positive and high-grade cytology results can be discharged after two negative colposcopies; people with HPV-negative and normal or low-grade cytology results in colposcopy can return to average (or immunocompromised) screening (in five or three years) and people with HPV-positive and normal or low-grade cytology results in screening can resume screening in two years.

A summary of all post-discharge from colposcopy screening recommendations can be found in the section titled "Post-discharge from colposcopy: Screening intervals in primary care".

Colposcopy pathway 3: Investigation and management for people referred with HPV-positive and AGC or AEC cytology (including AGC-NOS, AEC-NOS, AGC-N and AEC-N)

This pathway applies to people with the following screening results upon referral to colposcopy:

- HPV-positive (types 16, 18/45) with atypical glandular cells-not otherwise specified (AGC-NOS), atypical endocervical cells-not otherwise specified (AEC-NOS), atypical glandular cells-favor neoplastic (AGC-N) or atypical endocervical cells-favor neoplastic (AEC-N) cytology results at first or repeat test[a] in screening
- HPV-positive (other high-risk types) with AGC-NOS, AEC-NOS, AGC-N or AEC-N cytology results at first or repeat test[a] in screening

[a]A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology.

Recommendations

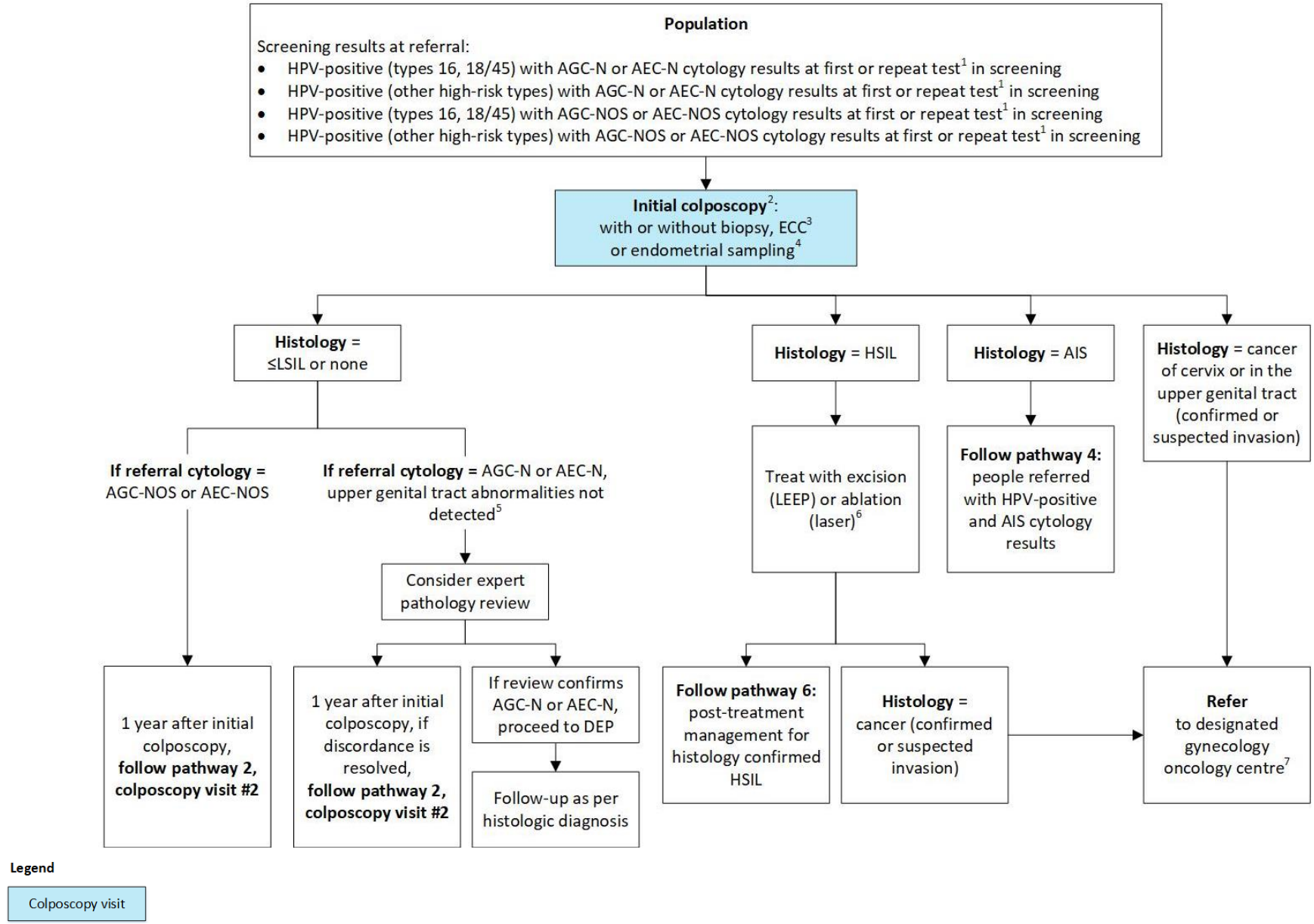
For people referred to colposcopy with HPV-positive (regardless of type) and AGC-NOS, AEC-NOS, AGC-N or AEC-N cytology results, a minimum of one colposcopy is required. The patient's histology then determines which pathway the patient should follow.

For patients referred with AGC-NOS or AEC-NOS cytology with low-grade squamous intraepithelial lesion (LSIL) histology (or if no biopsy was taken) at the first colposcopy visit, the patient should return to colposcopy in one year and follow pathway 2 (investigation and management for people referred to colposcopy with HPV-positive and high-grade cytology results).

For patients referred with AGC-N or AEC-N cytology with LSIL histology (or if no biopsy was taken) and no upper genital tract abnormalities detected at the first colposcopy visit, an expert pathology review should be considered. If discordance is resolved by the pathology review, then the patient should return to colposcopy in one year and follow pathway 2 (investigation and management for people referred to colposcopy with HPV-positive and high-grade cytology results). If the pathology review confirms AGC-N or AEC-N, then a diagnostic excisional procedure (DEP) is required, and subsequent follow-up is based on the histologic diagnosis.

The full recommendations for investigation and management in colposcopy are summarized in Figure 6.

Figure 6: Colposcopy pathway 3: Investigation and management for people referred with HPV-positive and AGC or AEC cytology (including AGC-NOS, AEC-NOS, AGC-N and AEC-N)



AEC-N = atypical endocervical cells-favor neoplastic; AEC-NOS = atypical endocervical cells-not otherwise specified; AGC-N = atypical glandular cells-favor neoplastic; AGC-NOS = atypical glandular cells-not otherwise specified; AIS = adenocarcinoma in situ; DEP = diagnostic excisional procedure; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion

Footnotes:

1. A repeat test is defined as an HPV test (with reflex cytology for people with HPV-positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology.
2. Routine repeat cytology in colposcopy is not recommended, except for people referred to colposcopy with two consecutive unsatisfactory cytology results, or, HPV-positive (types 16, 18/45) and unsatisfactory cytology. In the absence of cervical pathology, consider pelvic ultrasound to address potential upper genital tract abnormalities.
3. If separate endocervical sampling is desired and ECC is not possible, consider vigorous sampling with endocervical brush.
4. Endometrial sampling may be required in appropriate clinical circumstances (e.g., endometrial cells in someone who is post-menopausal). In the Ontario Cervical Screening Program, people with AGC-N cytology will have HPV-positive results, so the risk of cervical malignancy is high. However, in circumstances where HPV status is negative or unknown, refer to Ontario Health's Endometrial Cancer Diagnosis Pathway for guidance on endometrial sampling.
5. Refer to designated gynecology centre as appropriate if upper genital tract lesion is suspected.
6. Cryotherapy is not recommended for the treatment of HSIL. Tissue sampling is preferred. However, the mode of treatment is at the discretion of the colposcopist.
7. Grade 1, stage 1 endometrial cancers can be managed by a general gynecologist. Stage 2 disease should be excluded before hysterectomy.

Key evidence

Investigation at first colposcopy visit

Published evidence

AGC cytology

The immediate risk of developing HSIL or AIS histology and cervical cancer is high for people referred with AGC cytology. A study reported the immediate risk of HSIL (defined in the study as CIN2/3), AIS and cervical cancer for people with AGC-NOS cytology ranges from 9 to 41% (95% confidence interval [CI]: not reported) (73). In addition, the study found the immediate risk of developing HSIL or AIS histology and cervical cancer for people with AGC-N cytology ranges from 27 to 96% (95% CI: not reported) (73). These results demonstrate that both AGC-N and AGC-NOS are high-grade cytology results. However, given the higher risk observed for people with AGC-N cytology, the OCSP recommends considering additional follow up for people referred to colposcopy with AGC-N cytology if LSIL is detected or no biopsy was taken at the first colposcopy.

Not only are people with AGC cytology at significant risk of developing cervical cancer, they are also at risk of developing other gynecological malignancies. A large population-based study in Ontario found that, of people with index AGC cytology, 1.05% were diagnosed with cervical cancer, 1.8% were diagnosed with endometrial cancer and 0.14% were diagnosed with ovarian cancer (74). This study was performed before HPV testing was implemented in the OCSP so the results include all people with AGC cytology, regardless of HPV status. When HPV testing is implemented in Ontario, the pathway will be specific for people referred to colposcopy with HPV-positive results. For people with AGC cytology and a known HPV-positive result, the final histologic diagnosis is more likely to be associated with the cervix than other gynecological malignancies, therefore, the first step is to rule out cervical pre-cancer/cancer. However, if cervical malignancies have been ruled-out, people with AGC cytology may require additional investigations (e.g., endometrial sampling) for other gynecological pathology, during their investigation in colposcopy (75).

AEC cytology

AEC-N cytology (atypical endocervical cells-favor neoplastic) and AEC-NOS cytology (atypical endocervical cells-not specified) are types of AGC cytology. The positive predictive value (PPV) of AEC is 81.1%, therefore, there is a significant for risk of CIN2 or greater (76). Given this PPV, it is recommended that people with AEC-NOS cytology (regardless of type) should be managed the same as AGC-NOS, and people with AEC-N cytology should be managed the same as AGC-N.

Management in colposcopy

Published evidence

Two studies were found that provide data on the risk of HSIL and cervical cancer over time for people referred to colposcopy with AGC cytology who have LSIL detected at first colposcopy (68,69). Results showed that, for people referred to colposcopy with AGC cytology and LSIL histology is detected at colposcopy, the cumulative risk of HSIL and cervical cancer (defined in the study as CIN3+) at five years is 1.2 to 3.8% (95% confidence interval [CI]: not reported) (69). Similarly, another study found that the one- and three-year risks of HSIL and cervical cancer (defined in the study as CIN3+) for people referred to colposcopy with HPV-positive and AGC cytology results and LSIL histology is detected at colposcopy (or no biopsy was taken) was 5.6% (95% CI: 1.3 to 9.9%) and 8.0% (95% CI: 1.5 to 14.5%), respectively (68). These studies suggest that the risk of HSIL and cervical cancer is too high to discharge people after one negative colposcopy (defined as histology = LSIL or no biopsy taken); thus, these people require additional follow up in colposcopy.

Refer to colposcopy pathways 2, 4 and 6 for a summary of the evidence related to the recommendations for people with ≥LSIL or none, HSIL, or AIS histology respectively.

Colposcopy pathway 4: Investigation and management for people referred with HPV-positive and AIS cytology

This pathway applies to people with the following screening results upon referral to colposcopy:

- HPV-positive (types 16, 18/45) with adenocarcinoma in situ (AIS) cytology results at first or repeat test[a] in screening
- HPV-positive (other high-risk types) with AIS cytology results at first or repeat test[a] in screening

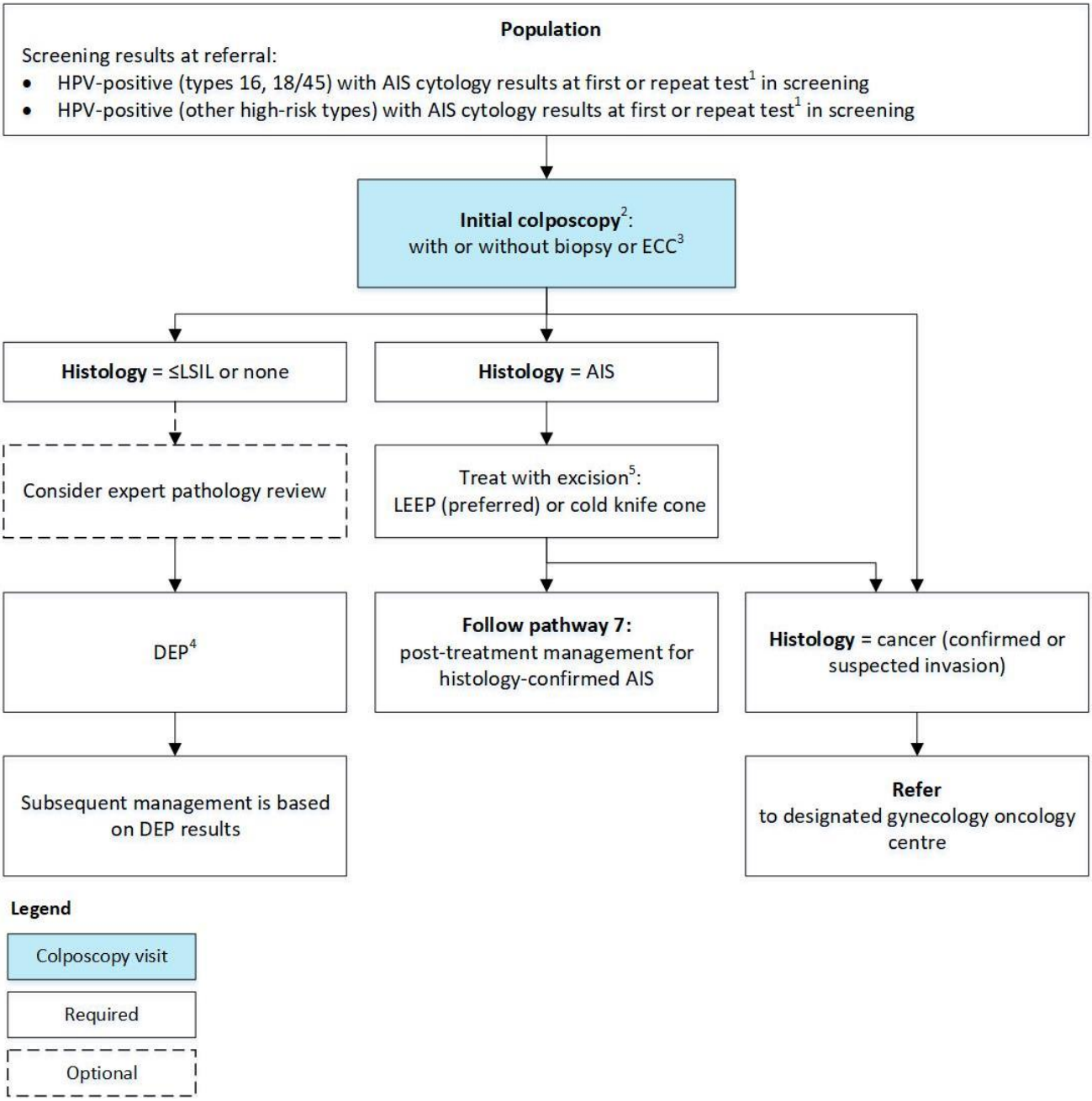
[a]A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology.

Recommendations

For people referred to colposcopy with HPV-positive (regardless of type) and AIS cytology results, a minimum of one colposcopy is required. The patient's histology results from the first colposcopy visit then determines which pathway the patient should follow. Patients with AIS histology should be treated and then follow pathway 7 for management post-treatment. For patients with low-grade squamous intraepithelial lesion (LSIL) histology (or if no biopsy was taken), an expert pathology review should be considered followed by a diagnostic excisional procedure (DEP) to determine next steps.

The full recommendations for investigation and management in colposcopy are summarized in Figure 7.

Figure 7: Colposcopy pathway 4: Investigation and management for people referred with HPV-positive and AIS cytology results



AIS = adenocarcinoma in situ; DEP = diagnostic excisional procedure; ECC = endocervical curettage; HPV = human papillomavirus; LEEP = loop electrosurgical procedure; LSIL = low-grade squamous intraepithelial lesion

Footnotes:

1. A repeat test is defined as an HPV test (with reflex cytology for people with HPV-positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology.
2. Routine repeat cytology in colposcopy is not recommended, except for people referred to colposcopy with two consecutive unsatisfactory cytology results, or, HPV-positive (types 16, 18/45) and unsatisfactory cytology.
3. If separate endocervical sampling is desired and ECC is not possible, consider vigorous sampling with endocervical brush.
4. Due to the high positive predictive value of AIS cytology, DEP is almost always required.

5. To treat people with histology-confirmed AIS, LEEP is acceptable in most cases. The decision to perform a cone biopsy for AIS should be based on the topography of the cervix, the diagnosis and the purpose of intervention (i.e., to confirm histologic diagnosis and ideally achieve negative margins).

Key evidence

Published evidence

Published evidence was not identified that evaluated the risks of developing HSIL and AIS histology and cervical cancer for people referred to colposcopy with AIS cytology. However, a study identified the high positive predictive value of AIS cytology for HSIL and AIS histology and cervical cancer (defined by the study as high-grade cervical disease) as 91% (77); as such, a diagnostic excisional procedure (DEP) is recommended in most cases. Other jurisdictions, such as Australia, British Columbia, Italy, and England, also recommend a DEP for people referred to colposcopy with AIS cytology, with subsequent management dependent on the histology results.

Colposcopy pathway 5: Investigation and management for people referred with HPV-positive and SCC, ACC, ACC-E or PDC cytology

This pathway applies to people with the following screening results upon referral to colposcopy:

- HPV-positive (types 16, 18/45) with squamous cell carcinoma (SCC), adenocarcinoma (ACC), endocervical adenocarcinoma (ACC-E), or poorly differentiated carcinoma (PDC) cytology results at first or repeat test[a] in screening
- HPV-positive (other high-risk types) with SCC, ACC, ACC-E or PDC cytology results at first or repeat test[a] in screening

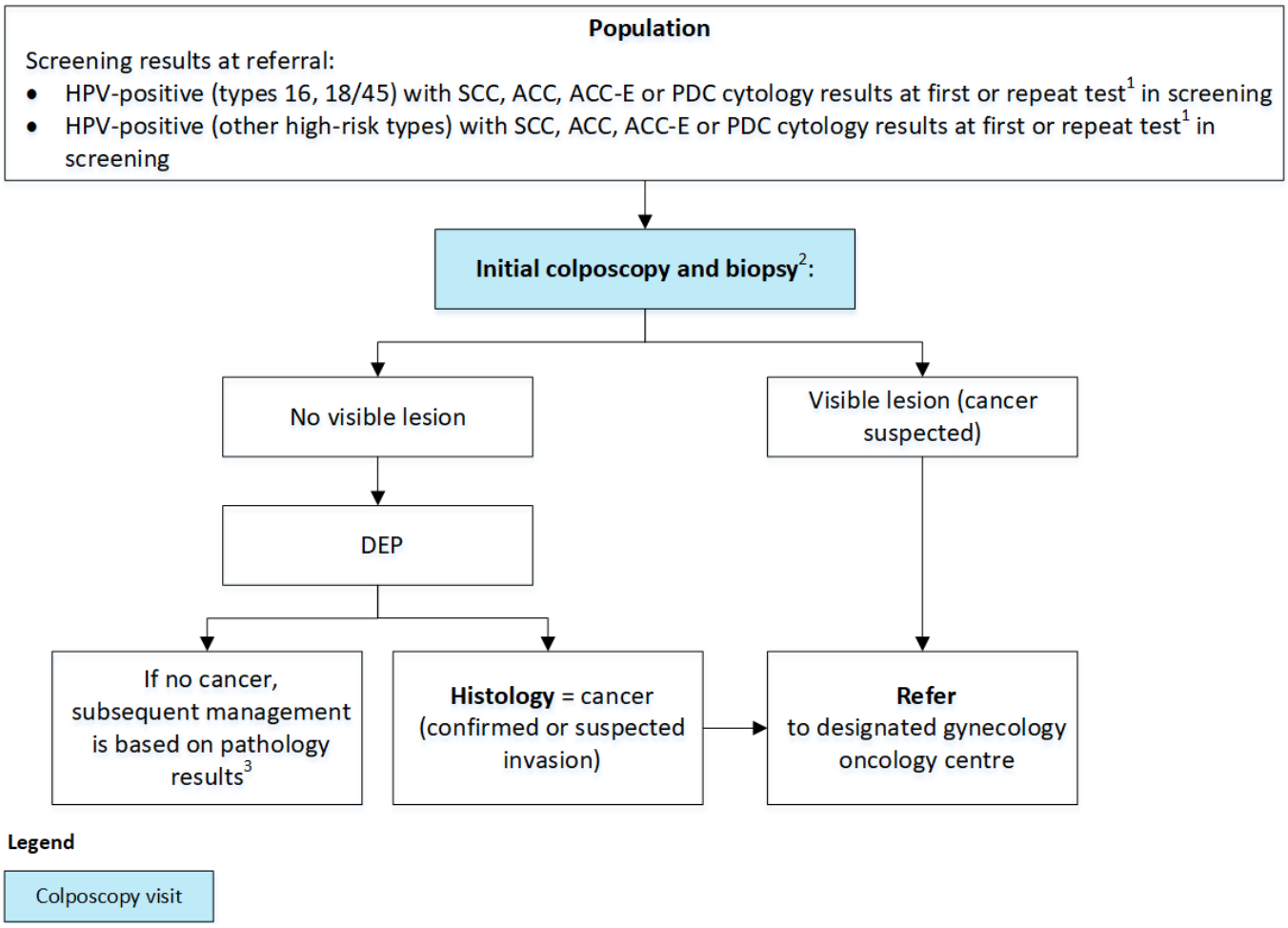
[a]A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) results with normal or low-grade cytology.

Recommendations

Management in colposcopy is dependent upon whether a visual lesion is seen during the initial colposcopy.

The full recommendations for investigation and management in colposcopy are summarized in Figure 8.

Figure 8: Colposcopy pathway 5: Investigation and management for people referred with HPV-positive and SCC, ACC, ACC-E or PDC cytology results



ACC: adenocarcinoma; ACC-E: endocervical adenocarcinoma; DEP: diagnostic excisional procedure; HPV: human papillomavirus; PDC = poorly differentiated carcinoma; SCC: squamous cell carcinoma

Footnotes:

1. A repeat test is defined as an HPV test (with reflex cytology for people with HPV positive results) in screening performed two years after a first-time HPV-positive (other high-risk types) with normal or low-grade cytology.
2. Routine repeat cytology in colposcopy is not recommended, except for people referred to colposcopy with two consecutive unsatisfactory cytology results, or HPV-positive (types 16, 18/45) results and unsatisfactory cytology.
3. When someone's cytology is suggestive of cancer and they have a negative DEP, the risk of a non-cervical malignancy remains. Consider further investigation in colposcopy or expert consultation (e.g., Regional Cancer Centre).

Key evidence

A review of the literature and Ontario data was not conducted for this pathway. Recommendations for the investigation and management of this population are based on expert opinion, including consultation with internal experts at Ontario Health.

Colposcopy pathway 6: Post-treatment management for histology-confirmed HSIL

This pathway is for people treated for high-grade squamous lesion (HSIL) in colposcopy (see pathway 7 for patients treated for adenocarcinoma in situ [AIS]).

Recommendations

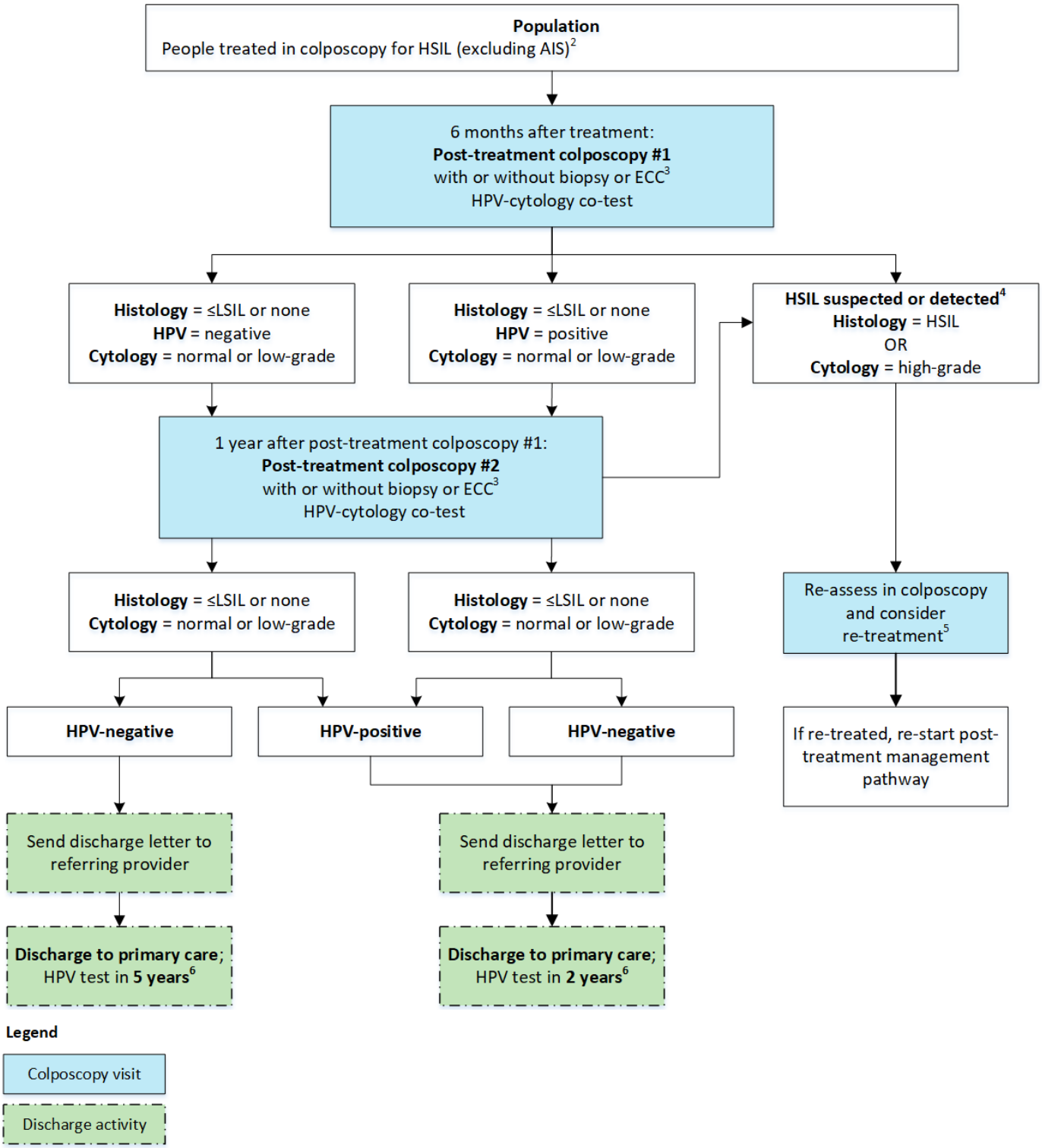
Following treatment for histology-confirmed HSIL, people should remain in colposcopy for two post-treatment visits. Human papillomavirus (HPV)/cytology co-testing is recommended at both post-treatment visits with or without biopsies and/or endocervical curettage (ECC).

If **both** post-treatment colposcopies are negative (i.e., histology is LSIL, or, biopsies were not taken), patients can be discharged to primary care to resume cervical screening. The results of the HPV/cytology co-tests will inform when to resume screening in primary care. For people being discharged to resume screening in two years, any HPV-positive result (regardless of HPV type or cytology) post-discharge should be referred back to colposcopy.

However, if HSIL cytology or histology is detected during either post-treatment colposcopy visit, re-assessment and potential re-treatment of the lesion is required.

The full recommendations for post-treatment management in colposcopy are summarized in Figure 9.

Figure 9: Colposcopy pathway 6: Post-treatment management for histology-confirmed HSIL[1]



AIS = adenocarcinoma in situ; ECC = endocervical curettage; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion

Footnotes:

1. This pathway refers to squamous lesions only. For AIS, please refer to Pathway 7.

2. Follow post-treatment pathway regardless of margin status at treatment. If treatment results in hysterectomy, refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance.
3. If separate endocervical sampling is desired and ECC is not possible, consider vigorous sampling with endocervical brush.
4. Regardless of HPV result.
5. Repeat excision required if persistent disease is identified during post-treatment visits in colposcopy.
6. If someone age 70 to 74 is HPV-negative, they can be discharged from colposcopy and stop screening. If someone age 70 and older is discharged from colposcopy to primary care and has a negative result at the 2-year screening test, they can also stop screening. Anyone discharged after age 74 can stop screening, regardless of the pathway interval. Refer to Cessation for average risk and immunocompromised populations.

Key evidence

Published evidence/Ontario data

A published study from Ontario assessed the risk of reoccurrence of HSIL and cervical cancer (defined in the study as cervical intraepithelial neoplasia 3+ [CIN3+]) after treatment of HSIL. The study showed that the risk of recurrence at five years post-treatment was approximately 6.1% (78). This risk is not sufficiently low to discharge people from colposcopy immediately after treatment of HSIL (78).

Strategy for risk assessment

Two studies were identified that examined various testing strategies to support risk-assessment post-treatment of HSIL.

One study assessed the risk of developing HSIL (defined in the study as CIN2+) over five years post-treatment stratified by testing strategy (i.e., cytology alone, HPV testing alone, or HPV/cytology co-testing) (79). The results showed that two HPV/cytology co-tests (defined by the study as a negative HPV test and normal cytology) post-treatment is more sensitive for the detection of HSIL compared to cytology or HPV testing alone. The cumulative five-year risk of developing HSIL post-treatment was lowest for people with two negative HPV/cytology co-tests (1.5% [95% CI: 0.3 to 7.2]) followed by a single negative HPV/cytology co-test (2.4% [95% CI not reported]). For HPV testing or cytology alone, the five-year risk of developing HSIL was lower after two negative tests compared with a single negative test (HPV tests: 2.7% vs. 3.7%, p=0.7; cytology: 2.7% vs. 4.2%, p=0.2). Overall, this study demonstrates that, post-treatment for HSIL, HPV/cytology co-testing is preferred compared with HPV testing or cytology alone, and, that two negative HPV/cytology co-tests identify people with the lowest five-year risk of HSIL recurrence.

Another study was identified which supports the use of two HPV/cytology co-tests post-treatment for HSIL (80). The study assessed the risk of HSIL (defined in the study as CIN2/3 and high-grade CIN not otherwise specified) recurrence after two negative HPV/cytology co-tests 12 months apart in a retrospective analysis. The study demonstrated that, post-treatment for HSIL, people with two negative HPV/cytology co-tests had a lower risk of HSIL recurrence at five years (0.08%) compared to people with two negative HPV tests (0.26%) although the difference was not statistically significant (p=0.2). This study supports the recommendation to perform the HPV/cytology co-tests 12 months apart.

The five-year risk for developing HSIL differed between the two studies described above. However, the five-year risk of HSIL recurrence for people with two negative HPV/cytology co-tests after treatment described in the second study above showed a risk low enough to return to average risk screening, as per the OCSP's screening population definitions. Of note, the two studies described above are derived from the United States where HPV/cytology co-testing is performed outside of the colposcopy setting. However, in Ontario, this population will remain in colposcopy for two-post treatment visits and will not be discharged unless both colposcopy visits are negative and if cytology results from the HPV/cytology co-tests are normal or low-grade. As such, the risk of HSIL recurrence at five years in the Ontario context is assumed to be sufficiently low to return to average risk (or immunocompromised) screening after discharge from colposcopy.

Based on the published evidence and expert opinion, two post-treatment visits with HPV/cytology co-testing 12 months apart was selected for the pathway because it was felt to be acceptable and feasible to implement for colposcopy providers.

Resumption of screening in primary care post-discharge from colposcopy

The published evidence described above found that people treated for HSIL with two negative HPV/cytology co-tests post-treatment have a low risk of HSIL recurrence and can return to average risk (or immunocompromised) screening in primary care.

However, people treated for HSIL who have HPV-positive results (with normal or low-grade cytology) at one or both of their post-treatment colposcopy visits have a risk of HSIL recurrence that is too high to return to average risk (or immunocompromised) screening. Given that the risk of recurrence is not high enough to support a person remaining in colposcopy given the potential harms associated with over-management in colposcopy such as anxiety, discomfort, pain and in some cases, problems with future pregnancies, this population should return to cervical screening in two years post-discharge from colposcopy. This population should continue screening at the two-year interval until they have achieved two negative consecutive HPV tests (can include HPV-negative result at the second post-treatment colposcopy visit). However, if a person has an HPV-positive result (regardless of HPV type or cytology result) during screening post-discharge from colposcopy at the two-year interval, they should be referred back to colposcopy.

A summary of all post-discharge from colposcopy screening recommendations can be found in the section titled "Post-discharge from colposcopy: Recommendations for screening in primary care".

Colposcopy pathway 7: Post-treatment management for histology-confirmed AIS

This pathway is for people treated in colposcopy for histology-confirmed adenocarcinoma in situ (AIS).

Recommendation

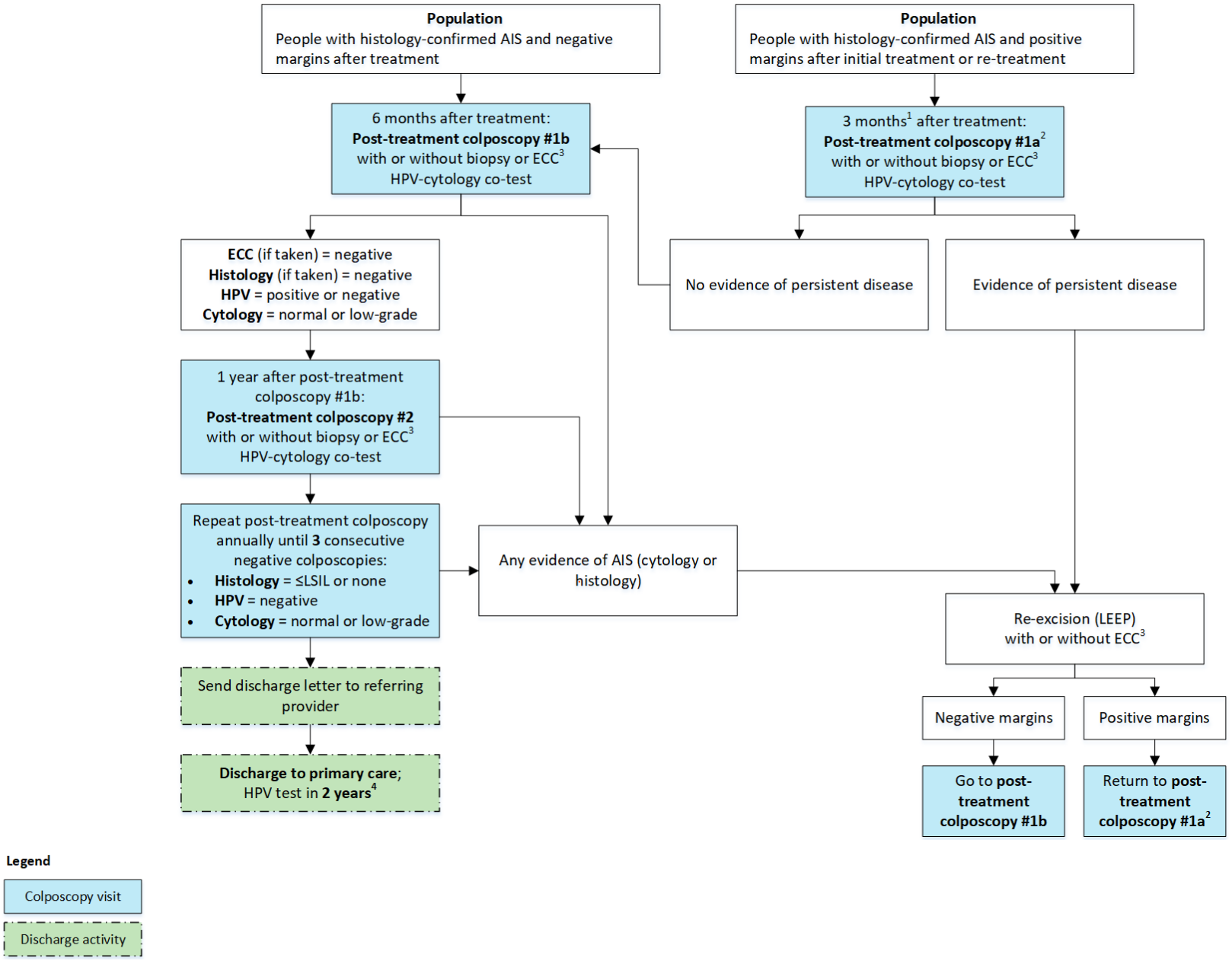
Margin status at treatment and post-treatment colposcopy visits are a key predictor of disease recurrence and/or progression. As a result, the post-treatment colposcopy recommendations differ by margin status. However, regardless of margin status, if evidence of AIS (i.e., high-grade cytology result or AIS histology) is detected at any post-treatment visit, re-treatment is required.

People with histology-confirmed AIS and **positive margins** after treatment in colposcopy should remain in colposcopy until negative margins are achieved. Following that, the negative margin pathway should be followed to determine eligibility for discharge from colposcopy.

People with histology-confirmed AIS and **negative margins** after treatment should remain in colposcopy for five post-treatment visits. Human papillomavirus (HPV)/cytology co-testing is recommended at all post-treatment visits. After five consecutive annual negative colposcopies (defined as histology=LSIL or none), patients can be discharged to primary care.

All people treated for histology-confirmed AIS discharged to primary care should resume cervical screening in two years with the HPV test (with reflex cytology for people with HPV positive results). Any HPV-positive result (regardless of HPV type or cytology result) during screening post-discharge from colposcopy at the two-year interval should be referred back to colposcopy. The full recommendations for post-treatment management of histology-confirmed AIS are summarized in Figure 10. The pathway starts after the initial colposcopy visit and management of AIS (see "Colposcopy pathway 4: Investigation and management for referral of HPV-positive, AIS cytology").

Figure 10: Pathway 7: Post-treatment management for histology-confirmed AIS



AIS = adenocarcinoma in situ; ECC = endocervical curettage; HPV = human papillomavirus; LEEP = loop electrosurgical excision procedure

Footnotes:

1. Wait approximately three months to reevaluate the cervix for adequate healing and improve the accuracy of colposcopic evaluation.
2. For hysterectomy recommendations, refer to Recommendation: Hysterectomy for patients treated for adenocarcinoma in situ (AIS). If treatment results in hysterectomy, refer to the Ontario Cervical Screening Program's Vaginal Vault Testing Guidance document.
3. If separate endocervical sampling is desired and ECC is not possible, consider vigorous sampling with endocervical brush.
4. If someone age 70 and older is discharged from colposcopy to primary care and has a negative result at the 2-year screening test, they can stop screening. Anyone discharged after age 74 can stop screening, regardless of the pathway interval. Refer to Cessation for average risk and immunocompromised populations.

Key evidence

The OCSP recommendations for management of people in colposcopy following treatment for histologically confirmed AIS are based on results from a rapid review of the literature on the risk of HSIL and cervical cancer among people conservatively treated for AIS (see Appendix A for more information) and expert opinion.

Margin status

Positive margins are a risk factor for AIS recurrence and progression to cervical cancer. A rapid review on the risk of high-grade cervical dysplasia and cervical cancer among people conservatively treated for AIS was conducted in 2021. One systematic review and 15 cohort studies were identified. All studies found that, in people treated for AIS, the cumulative risk of recurrence and progression to cervical cancer was higher in those with positive margins at treatment and post-treatment compared to those with negative margins (78,81–96). In the studies reported in the systematic review, the one- to 10-year risk for progression to cervical cancer for people with positive margins ranged from 0.0% to 33.3% (97). The one- to 10-year risk for progression to cervical cancer for people with negative margins ranged from 0.0% to 14.3% (97). Positive margins are a risk factor for AIS recurrence and progression to cervical cancer.

Two studies with large sample sizes identified in the rapid review found the cumulative risk of recurrence and progression to cancer was higher in people with positive margins compared to people with negative margins. A retrospective study evaluated the long-term outcomes of patients who underwent excisional management of AIS (84). This study found that the proportion of people with residual or recurrent disease was higher for people with positive margins (28.7%) compared to people with negative margins (4.3%). The study also showed a higher rate of progression to cervical cancer in those with positive excisional margins at treatment (2.3%; 3/129) compared to patients with negative excisional margins at treatment (1.3%; 6/460). Similarly, the second study, retrospectively analyzed 207 patients treated for AIS and found that persistent/recurrent AIS was substantially higher in the patients with positive margins compared to those with negative margins (47.2% vs. 9.3%) (87). Thus, people with histology-confirmed AIS and positive margins after treatment should remain in colposcopy until negative margins are achieved.

Determining eligibility for discharge

HPV status

HPV status is also associated with AIS recurrence and progression to cervical cancer. A key study on this topic examined 166 consecutive patients who were treated for AIS (98). Using a univariate and multivariate population averaged generalized estimating equation model in a longitudinal setting, the study showed that a positive HPV test was the only independent predictor of AIS recurrence, and it was the most powerful predictor of progression to cervical cancer. While the univariate model showed that patients with positive margins at treatment were 80 times more likely to have a recurrence of AIS than those with negative margins, this increased risk was not observed when controlling for HPV status (98). Given the importance of HPV status in determining a person's risk of AIS persistence, recurrence and progression to cervical cancer as shown by this study, HPV tests can provide important data to inform risk-based management of people treated for AIS in colposcopy.

Cytology testing in colposcopy after treatment for AIS

Abnormal cytology results after treatment are a risk factor for AIS recurrence (78). A population-based study from Ontario evaluated the risk of AIS recurrence after treatment stratified by post-treatment cytology results. The study found the risk of recurrence of HSIL (defined in the study as CIN3) and AIS was significantly different (p=0.0001) when considering the results of serial cytology test results. Following treatment for AIS, people with three or more normal cytology results were at the lowest risk of recurrence (3.4%), and the risk of recurrence increased as the number of normal cytology results decreased (4.6% for those with two normal cytology results, 7.1% for those with one normal cytology result and 37.5% for those with no normal cytology results) (78). Therefore, cytology testing post-treatment for AIS can provide useful data to inform risk-based management of people treated for AIS in colposcopy.

HPV/cytology co-testing in colposcopy after treatment for AIS

While HPV testing and cytology testing independently provide useful data for the risk-based management of people treated for AIS, HPV/cytology co-testing is more sensitive for the detection of AIS recurrence compared to HPV testing or cytology testing alone. A study that provided data on the relative performance of HPV and cytology tests in AIS detection found, of 118 patients diagnosed with AIS or cervical cancer, 92 patients (78%) were HPV-positive and had high-grade cytology results, while 15 patients (12.75%) were HPV-positive and had normal cytology results (study did not define normal) and 11 patients (9.3%) were HPV-negative and had high-grade cytology results (99). Another study examined the sensitivity of HPV/cytology co-testing for the detection of AIS persistence at two post-treatment colposcopy visits. The study found that the sensitivity of HPV/cytology co-testing for the detection of AIS persistence was 90% at the first post-treatment colposcopy follow-up visit and 100% at the second post-treatment colposcopy follow-up visit (100). These studies suggest that HPV/cytology co-testing improves the detection of AIS and cervical cancer compared to HPV testing or cytology testing alone. Therefore, HPV/cytology co-testing can provide useful data to inform risk-based management of people treated for AIS in colposcopy.

Duration of follow-up

An Ontario study examined the incidence of cervical cancer within five-years of treatment for AIS or HSIL (defined in the study as CIN3) (78). The study found that people treated for AIS were more likely to develop cervical cancer during follow up (2 cases or 0.39%; n=509) than people treated for HSIL (29 cases or 0.20%; n = 14,668) (78). Based on these data, people treated for AIS are at higher risk of developing cervical cancer than people treated for HSIL so should remain in colposcopy longer than those treated for HSIL.

Another study examined 69 patients undergoing follow-up (mean= 40.9 months) in colposcopy after treatment for AIS (92). Eight cervical cancers were detected during follow up; 100% of these cancers were detected during the first 36 months of follow-up. These findings are similar to a population-based study from Ontario (78) which found the median time from treatment for AIS to cervical cancer was 35 months. Therefore, these studies suggest that follow-up of at least 35 to 36 months after treatment for AIS is needed before discharge from colposcopy.

Resumption of screening in primary care post-discharge from colposcopy

Based on the published evidence described above, people treated for AIS have an increased risk of AIS recurrence and progression to cervical cancer so require careful follow-up. In addition to recommending longer follow-up in colposcopy, the expert panel recommended more intensive cervical screening in primary care post-discharge from colposcopy for people treated for AIS. As such, the expert panel recommended that people return to moderate risk screening with the HPV test (with reflex cytology for people with HPV positive results) two years after discharge from colposcopy. People with HPV-negative results should continue to screen at a two-year interval until they have had three consecutive negative HPV tests over eight years. If a person has an HPV-positive result (regardless of HPV type or cytology result) at one of the screening tests during this eight-year period post-discharge from colposcopy, they should be referred back to colposcopy.

A summary of all post-discharge from colposcopy screening recommendations can be found in the section titled "Post-discharge from colposcopy: Recommendations for screening in primary care".

Recommendation: Hysterectomy for patients treated for AIS

In Ontario, hysterectomy has been historically recommended for patients treated for AIS who have completed childbearing. However, in some circumstances, the risk of surgery may outweigh the very small risk of residual AIS and/or cervical cancer. Therefore, the Ontario Cervical Screening Program recommends considering hysterectomy for patients treated for AIS in the circumstances summarized below.

- Hysterectomy can be considered when childbearing is complete in the following circumstances:
  - Negative margins cannot be achieved despite adequate diagnostic excisional procedure (DEP) excision,
  - Cervix cannot be assessed adequately (e.g., post-treatment stenosis),
  - People who are persistently positive for HPV (people who have consecutive negative HPV results after treatment for AIS are unlikely to benefit from hysterectomy), or
  - People who are not able to follow post-treatment recommendations, in particular those with residual risk of AIS.
- When childbearing is not complete, or there is a desire to preserve fertility, decisions about whether hysterectomy is an appropriate treatment option must be individualized, and a discussion should take place between patients and their health care providers about the risks and benefits of hysterectomy and management in colposcopy.

Key evidence

Guidance on hysterectomy for patients treated for AIS was developed based on recommendations from other jurisdictions as well as from expert panel input. Hysterectomy was the preferred treatment if fertility is not desired in the United States (as per the ASCCP), British Columbia, France, Germany, Italy, Japan, and the United Kingdom. In circumstances where fertility is desired, the aforementioned jurisdictions note fertility sparing management is acceptable for patients. Australia does not recommend hysterectomy for people treated for AIS with negative margins. New Zealand does not recommend hysterectomy without a prior adequate excision that includes excision of the endocervical canal to exclude cervical cancer.

Post-discharge from colposcopy: Recommendations for screening in primary care

This section outlines the recommendations for cervical screening with human papillomavirus (HPV) testing (with reflex cytology for people with HPV positive results) after people are discharged from colposcopy. This section provides a summary of the post-discharge screening recommendations; more information about the key evidence used to determine the risk-based recommendations for when to resume screening post-discharge from colposcopy can be found in the respective colposcopy pathway sections earlier in this document.

Recommendations

People discharged from colposcopy will either return to average risk screening in five years (or immunocompromised screening in three years) or moderate risk screening in two years.

When to resume screening and the recommended interval for screening thereafter depends on several factors including whether the person was treated during colposcopy and HPV/cytology co-test(s) results prior to discharge from colposcopy.

People discharged from colposcopy to moderate risk screening (i.e., screening in two years) follow the same approach for management of HPV-positive results as people in the moderate risk screening population prior to referral to colposcopy. Therefore, people discharged from colposcopy to moderate risk screening in primary care with an HPV-positive result, regardless of HPV type or cytology result, should be referred back to colposcopy.

The recommendations for screening in primary care post-discharge from colposcopy are summarized in Tables 18 and 19.

Table 18: Post-discharge cervical screening recommendations for people **not treated** in colposcopy (i.e., HSIL or AIS not detected in colposcopy)

First post-discharge screening interval			Second post-discharge screening interval	
Referral cytology from primary care	**HPV status at discharge from colposcopy**	**Action**	**Screening result at first recall**	**Action**
Normal (NILM) or low-grade (ASCUS or LSIL)	N/A (HPV test not repeated in colposcopy)	Screen in two years	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years
			HPV-positive[b]	Re-refer to colposcopy
High-grade (ASC-H, LSIL-H, AGC, HSIL, AEC)	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years	N/A	
	HPV-positive [b]	Screen in two years	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years
			HPV-positive[b]	Re-refer to colposcopy

AIS: adenocarcinoma in situ; AGC: atypical glandular cells; ASC-H: atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASCUS: abnormal atypical squamous cells of undetermined significance; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL; NILM: negative for intraepithelial lesion or malignancy; N/A: not applicable

[b]Regardless of human papillomavirus (HPV) type or cytology result.

Table 19: Post-discharge cervical screening recommendations for people **treated** in colposcopy (i.e., high-grade squamous intraepithelial lesion [HSIL] or adenocarcinoma in situ [AIS] treated)

First post-discharge screening interval			Second post-discharge screening interval		Third post-discharge screening interval		Fourth post-discharge screening interval	
HPV result at first post-treatment colposcopy visit	**HPV result at discharge**	**Action**	**Screening result**	**Action**	**Screening result**	**Action**	**Screening result**	**Action**
People treated for HSIL								
HPV-negative	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years	N/A					
HPV-negative	HPV-positive[a]	Screen in two years	HPV-negative	Re-screen in two years	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years	N/A	
					HPV-positive[a]	Re-refer to colposcopy		
			HPV-positive[a]	Re-refer to colposcopy	N/A			
HPV-positive	HPV-negative	Screen in two years	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years	N/A			

First post-discharge screening interval			Second post-discharge screening interval		Third post-discharge screening interval		Fourth post-discharge screening interval	
HPV result at first post-treatment colposcopy visit	**HPV result at discharge**	**Action**	**Screening result**	**Action**	**Screening result**	**Action**	**Screening result**	**Action**
			HPV-positive[a]	Re-refer to colposcopy				
HPV-positive	HPV-positive[a]	Screen in two years	HPV-negative	Re-screen in two years	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years	N/A	
					HPV-positive[a]	Re-refer to colposcopy		
			HPV-positive[a]	Re-refer to colposcopy	N/A			
People treated for AIS								
Regardless of first post-treatment HPV test result	HPV-negative	Screen in two years	HPV-negative	Re-screen in two years	HPV-negative	Re-screen in two years	HPV-negative	Return to average risk screening in five years or immunocompromised screening in three years
							HPV-positive[a]	Re-refer to colposcopy
					HPV-positive[a]	Re-refer to colposcopy	N/A	

First post-discharge screening interval			Second post-discharge screening interval		Third post-discharge screening interval		Fourth post-discharge screening interval	
HPV result at first post-treatment colposcopy visit	**HPV result at discharge**	**Action**	**Screening result**	**Action**	**Screening result**	**Action**	**Screening result**	**Action**
			HPV-positive[a]	Re-refer to colposcopy	N/A			

AIS: adenocarcinoma in situ; HSIL: high-grade squamous intraepithelial lesion; HPV: human papillomavirus; N/A: not applicable

[a]Regardless of human papillomavirus (HPV) type or cytology result.

Conclusion

This document summarizes the Ontario Cervical Screening Program's (OCSP) recommendations for cervical screening as well as colposcopy guidance for people with abnormal cervical screening results. These recommendations were developed based on multiple sources of evidence and contextual factors (e.g., feasibility and acceptability for the Ontario context). This document reflects the OCSP's full detailed program guidance. Several user-friendly resources and products for provider and public will be available upon the launch of human papillomavirus testing through the program.

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Appendix A: Rapid literature reviews

Nine rapid reviews of the primary literature and three evidence inventories were conducted by Ontario Health (Cancer Care Ontario) to inform the development of the Ontario Cervical Screening Program's (OCSP's) cervical screening and colposcopy recommendations. An overview of the methods for each rapid review can be found in the table below.

Review title	**Research question(s)**	**Review type**	**Search date**	**Filter applied**	**Result number** (# of unique results)	**Quality assessment**
Cervical screening for people who are immunocompromised	Among people who are considered immunocompromised, what are the recommended eligibility requirements, screening modalities and intervals for cervical screening?	Evidence inventory	Electronic database search: February 21, 2020 Guidelines database and targeted website search: February 21 to March 5, 2020	English language Publication year: 2010–2020	398	n/a
Risk of high-grade cervical dysplasia and cervical cancer among people who persistently test HPV-positive with normal or low-grade cytology results in screening	• What is the risk of high-grade cervical dysplasia and invasive cervical cancer for people who are found to be persistently HPV-positive with normal or low-grade cytology in screening? ○ Does risk vary by HPV type, cytology result in screening, age, treatment and management pathway or duration of follow-up?	Rapid review and meta-analysis	Electronic database search: December 13, 2019	English language Publication year: 2009–2019	Electronic database search: 1,658 unique results	n/a
Risk of high-grade cervical dysplasia among people who persistently test HPV-positive without cytologic or colposcopic evidence of pre-cancer	• What is the risk of high-grade cervical dysplasia among people 25–69 years with persistent HPV infection, normal or low-grade cytology and no colposcopic evidence of pre-cancer? ○ Does risk vary by HPV type, cytology results at referral to colposcopy, treatment status, screening algorithm	Rapid review	Electronic database search: August 9, 2019	English language Publication year: 2009–2019	Electronic database search: 1,033 unique results	n/a

Review title	Research question(s)	Review type	Search date	Filter applied	Result number (# of unique results)	Quality assessment
	post colposcopy evaluation or duration of follow-up? • What is the risk of high-grade cervical dysplasia among people 70 years and older with persistent HPV infection, normal or low-grade cytology and no colposcopic evidence of pre-cancer? ○ Does risk vary by HPV type, cytology results at referral to colposcopy or duration of follow-up?					
Risk of high-grade cervical dysplasia and invasive cervical cancer among people who are discharged from colposcopy	Among people who are discharged from colposcopy, what is the risk of high-grade cervical dysplasia and cervical cancer?	Evidence review	Electronic database search: January 15, 2018 (phase 1: systematic review), February 21, 2020 (Phase 2: rapid review)	English language Publication year: 2000 – 2018 (phase 1); 2018-2020 (phase 2)	Electronic database search: 14 unique results (phase 1); 3 unique results (phase 2)	Newcastle-Ottawa Scale for cohort studies: Overall study quality was assessed as good in 3 studies, fair in 5 and poor in 9 studies
Colposcopy management and discharge for people with AGC cytology results	• What initial work-up and diagnostic strategies are recommended for people referred to colposcopy with a positive HPV test result and AGC cytology results? • What colposcopy management and discharge strategies are recommended for people in colposcopy with a positive HPV	Evidence inventory	Electronic database search: September 4, 2020 Guidelines database and targeted website search: September 4 to 8, 2020	English language Publication year: 2010–2020	Electronic database search: 222 Guidelines database and	n/a

Review title	Research question(s)	Review type	Search date	Filter applied	Result number (# of unique results)	Quality assessment
	test result and cytologic result of AGC where no high-grade dysplasia and cervical cancer is identified?				targeted website search: 31	
Risk of high-grade cervical dysplasia and invasive cervical cancer among people conservatively treated for AIS	• Among people who received conservative treatment for AIS in colposcopy, what is the risk of high-grade cervical dysplasia and cervical cancer following treatment? • Among people who received conservative treatment for AIS, what is the risk of high-grade cervical dysplasia and cervical cancer following treatment? ○ Does risk vary by age, type of excisional procedure, margin status at excision, HPV status post-treatment, cytology result post-treatment or endocervical curettage result?	Rapid review	Electronic database search: January 6, 2021	English language Publication year: 2010–2020	Electronic database search: 382	AMSTAR: 2 low quality studies included EPHPP: 16 studies included; 10-strong, 2-moderate and 4-weak studies
Cervical screening following discharge from colposcopy	What cervical screening modalities and intervals do existing guidelines and position or policy statements recommend for people eligible for discharge from colposcopy?	Evidence inventory	Electronic database, website, professional association and government bodies search: February 20, 2020	English language Publication year: 2010–2020	112	n/a
Cervical screening cessation for people aged 60 and older	For people aged 60 years and older, what do existing HPV-based cervical screening guidelines and position or policy statements recommend as cervical screening cessation criteria? • What is the 3-, 5- and 10-year risk of high-grade cervical dysplasia and cervical cancer for people aged 60 and older with a cervix	Rapid review	Electronic database search: July 13, 2020	English language Publication year: 2010–2020	Electronic database search: 587	EPHPP: 7 studies included; all studies were weak

Review title	Research question(s)	Review type	Search date	Filter applied	Result number (# of unique results)	Quality assessment
	who have had 3 or more normal cytology results since age 50? ○ Does the risk vary by age? • What is the 3-, 5- and 10-year risk of high-grade cervical dysplasia and cervical cancer for people aged 60 and older with a cervix who have had 1 or more positive HPV tests and normal or low-grade cytology results since age 50? ○ Does the risk vary by age, HPV type or most recent cytology test result? • What is the 3-, 5- and 10-year risk of high-grade cervical dysplasia and cervical cancer for people aged 60 and older with a cervix who have had 1 or more negative HPV tests since age 50? ○ Does the risk vary by age or most recent cytology test result?					
Vaginal vault testing following simple or radical hysterectomy for people with a history of high-grade cervical dysplasia or early cervical cancer	• For people who have had a simple or radical hysterectomy with a history of high-grade cervical dysplasia, what is the risk of VaIN3 and vaginal cancer? ○ Does the risk vary by histology result, type of hysterectomy, hysterectomy margin status, HPV status post-hysterectomy, HPV type post-hysterectomy or cytology result post-hysterectomy? • For people who have had a simple or radical hysterectomy with a history of high-grade cervical dysplasia, what is the clinical performance of vaginal vault HPV testing	Rapid review	Electronic database search: April 9, 2021	English language	916	AMSTAR 2: critically low quality, EPHPP: 7 studies included: 1-moderate, 6-weak

Review title	Research question(s)	Review type	Search date	Filter applied	Result number (# of unique results)	Quality assessment
	(with or without reflex cytology), HPV/cytology co-testing or cytology testing (with or without reflex HPV testing) for the detection of VaIN3 and vaginal cancer? • For people who have had a simple or radical hysterectomy with a history of early cervical cancer who have not received radiation or chemotherapy and are no longer under surveillance for recurrence of cervical cancer, what is the risk of VaIN3 and vaginal cancer? ○ Does the risk vary by histology result, type of hysterectomy, hysterectomy margin status, HPV status post-hysterectomy, HPV type post-hysterectomy or cytology result post-hysterectomy? • For people who have had a simple or radical hysterectomy with a history of early cervical cancer who have not received radiation or chemotherapy and are no longer under surveillance for recurrence of cervical cancer, what is the clinical performance of vaginal vault HPV testing (with or without reflex cytology), HPV/cytology co-testing or cytology testing (with or without reflex HPV testing) for the detection of VaIN3 and vaginal cancer?					

AMSTAR: MeaSurement Tool to Assess systematic Reviews; AGC: atypical glandular cells; AIS: adenocarcinoma in situ; EPHPP: Effective Public Health Practice Project; GRADE: Grading Of Recommendations, Assessment, Development And Evaluations; HPV: human papillomavirus; VaIN: vaginal intraepithelial neoplasia

Appendix B: Ontario data

Ontario data analyses were conducted to measure current performance of cervical screening and inform the development the Ontario Cervical Screening Program's (OCSP's) cervical screening and colposcopy recommendations. An overview of the methods for each data analysis can be found in the table below.

Year the analysis was performed	Topic	Research question	Data period	Data sources	Technical notes
2020	Incidence rates of HSIL and cervical cancer for people ages 70 and older	What are the incidence rates per 100,000 cases of HSIL and cervical cancer in Ontario stratified by age and screening history for people ages 70 and older?	2013–2018	• OCR • CytoBase • OHIP • RPDP	• Index date is based on January 1st of each year • HSIL and cervical cancer identified in OCR • Exclusions: People under the age of 70, people with prior hysterectomy, people who previously had cervical cancer, people who have had treatment in colposcopy in the past three years, people with missing or invalid HIN, non-Ontario residents and people who died before the index date
2021	Divergence of cytology repeated at 1-90 days and 3-6 months after index cytology	What is the divergence of index cytology and repeat cytology within 6 months?	2015–2016	• OCR • CytoBase • OHIP	• Cytology test results identified in CytoBase • Colposcopies, hysterectomies, and treatment data identified from OHIP • Cervical cancers identified in OCR • If a patient had multiple repeat cytology tests within 180 days after the index cytology date, the first result was defined as the repeat cytology result
2020	Baseline risk of HSIL and cervical cancer following a negative cytology test in screening, 2012–2014	What is the risk of HSIL and cervical cancer (including both in situ and cervical cancer) over time among people who had a negative cytology test in the past 3 years in screening	2012–2014 (normal cytology in this period) followed for 5 years up to 2019	• OCR • CytoBase • OHIP	• Index date is based on the first normal cytology test from 2012 to 2014 for each individual • Normal cytology tests identified in CytoBase • HSIL and cancer identified in OCR • Exclusions: people under 25 and over 69; people who had treatment in colposcopy or abnormal cytology results within the 3 years prior to the normal cytology result; people with hysterectomy or cancer prior to normal cytology results index cytology

Year the analysis was performed	Topic	Research question	Data period	Data sources	Technical notes
2020	Recurrence rates and rates of cervical cancer for patients previously treated for HSIL or AIS of the cervix	What is the 5-year recurrence risk of HSIL, AIS or cervical cancer in a large population cohort of people previously treated for HSIL or AIS?	2006–2010	• OCR • CytoBase • OHIP • RPDP • CIHI	• Index date is based on the first date of treatment after the HSIL or AIS diagnosis • Exclusions: people younger than 21 years at index date, people with no follow-up cytology tests in the 5 years after treatment in colposcopy, people who did not have treatment within 6 months of their HSIL/AIS diagnosis, people who had previous treatment for cervical abnormalities within 5 years prior, people who had a prior hysterectomy, people who have a history of invasive cervical cancer, in situ cervical cancer or histologies other than HSIL or AIS, and people who had a missing or invalid HIN or a missing date of birth
2021	Risks of HSIL, AIS and cervical cancer for people managed without treatment in colposcopy, 2010–2019	What is the risk of HSIL, AIS and cervical cancer over time in people who have undergone colposcopy after a cytology test with low-grade colposcopy biopsies (<CIN1/LSIL) or no biopsy and without treatment?	2012–2013	• OCR • CytoBase • OHIP • RPDP • ePath	• Identify those who had a cytology test between 6 months and 14 days prior to the index colposcopy • All colposcopy records identified from OHIP • Exclusions: people under age 21, people who received treatment in colposcopy or a biopsy within the 2 years prior to the index colposcopy, people with a hysterectomy or cervical cancer prior to index colposcopy, people who received treatment in colposcopy or had a hysterectomy, carcinoma in-situ, or cancer in the 3 months after the index colposcopy and people with an HSIL, AIS and cervical cancer result within 3 days (before or after) of index colposcopy
2021	Rates of VaIN 2/3 and vaginal cancer for people with a history of HSIL and cervical cancer	What are the incidence rates of VaIN 2/3 and vaginal cancer in Ontario from 2010–2021 among people with a history of high-grade cervical dysplasia or cervical cancer?	Rates of vaginal cancer and pre-cancer: 2010–2021 History of HSIL, AIS and cervical	• OCR • CytoBase • CIHI • DAD/NACRS	• The index date is date of HSIL, AIS and cervical cancer diagnosis • Cytology test results identified in CytoBase • Hysterectomies identified from DAD/NACRS • HSIL, AIS and cervical cancer, vaginal pre-cancers and cancers identified in OCR • Exclusions: people under age 21, people with HSIL, AIS and cervical cancer diagnosis prior to 2005

Year the analysis was performed	Topic	Research question	Data period	Data sources	Technical notes
			cancer: 2005–2015		

AIS: adenocarcinoma in situ; CIHI: Canadian institute for health information; DAD/NACRS: discharge abstract database/the national ambulatory care reporting system; HIN; health insurance number; HSIL: high-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; OHIP: Ontario health insurance plan; OCR: Ontario Cancer Registry; RPDP: registered persons database; VaIN: vaginal intraepithelial neoplasia

Appendix C: Jurisdictional scan questions

Countries: Australia, Canada (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Prince Edward Island and Saskatchewan), Denmark, Finland, Ireland, Italy, Netherlands, New Zealand, Norway, Spain, Sweden, England, Scotland

Associations: ASCCP, American Cancer Society

Approach:

- Survey (see list of questions below) completed via phone call or filled out offline and shared via email
- Web searches

Date: Summer 2020 (note: As topic specific question came up, the Ontario Cervical Screening Program continued to reach out to relevant stakeholders)

Questions:

- Is screening in your jurisdiction opportunistic or organized?
- How is human papillomavirus (HPV) testing being used in screening and/or colposcopy?
- Does your program use HPV genotyping information to inform screening and/or colposcopy recommendations?
- Has HPV testing been fully implemented in your program?
- How many labs do HPV testing in your program?
    - What type of labs (e.g., public health, run by screening program, hospital labs or private labs, other) do HPV testing in your program?
- Which HPV test(s) does your program use?
- What is the age of initiation for screening with HPV testing?
- Does the screening strategy differ between age groups?
- What are your program's screening algorithms?
- Does your program have any processes in place to support referral to colposcopy?
- What are your program's screening cessation criteria?
- If you switched from cytology to HPV testing in primary screening, did the age of initiation change?
- Do your program's screening recommendations differ for people who are immunocompromised and/or immunosuppressed?
- Does the program have a recommendation for how soon cytology should be repeated after an unsatisfactory result?
- How are results reported to providers (e.g., are HPV test and cytology results reported together)? If possible, can you please provide any examples of standard reports?
- What is your program's target wait time from abnormal result to colposcopy?
- If this target is not met, what is considered an acceptable wait time?
- Is the accepted wait time different depending on a person's HPV type (e.g., HPV 16/18+) or cytology result (e.g., HSIL)?

- Do you have any practices in place to help ensure participants who require referral to colposcopy are referred in a timely manner and not lost to follow-up?
- Does your program provide clinical management recommendations in colposcopy?
- At a person's first colposcopy visit after referral due to an abnormal screening test, is the cytology test repeated?
- Is HPV testing used in colposcopy?

- How do you assess eligibility for discharge from colposcopy?
- What are the program's recommendations for screening (test and interval) in primary care after someone is discharged from colposcopy?
    - Do the recommendations differ for individuals who are persistently HPV positive?
    - Are the recommendations stratified by whether or not the person was treated in colposcopy?
    - Are the recommendations stratified by age?
    - Are the recommendations different for people who are immunocompromised / immunosuppressed?
- Does your program make recommendations for screening people post-total hysterectomy (e.g., vaginal vault testing)?
- Did your program experience any challenges with switching to HPV testing as the primary screening test (e.g., provider change management, colposcopy capacity)?
- Do you have any key learnings you would like to share?
- Has your program experienced any ongoing barriers since switching to HPV testing?
- Is self-sampling available in your program?
- Who is self-sampling offered to (e.g., under or never screened individuals)?
- How is self-sampling provided (e.g., direct mail of self-sampling device, offered in clinician's office) and how are completed self-collected samples returned for testing?
- Is a different HPV test platform and HPV assay used to test specimens collected through self-sampling?
- Are results from specimens collected through self-sampling reported differently from clinician-collected samples?
- Who receives follow-up cytology and how is it managed (e.g., are participants called or sent correspondence letters indicating they need to complete follow-up cytology)?
- Were any new or revised laboratory requirements, processes or test performance criteria incorporated in your program to support the inclusion of specimen collection through self-sampling?
- Were there any lessons learned from piloting or conducting self-sampling within your cervical screening program?

Appendix D: Expert panel members and acknowledgements

Panel members

We would like to acknowledge the members of the expert panel for their contributions to the development of the Ontario Cervical Screening Program's (OCSP's) Human papillomavirus (HPV)-based cervical screening and colposcopy recommendations and their review of this guidance document. Please see the table below for a list of panel members and their area of expertise.

All panel members completed a conflict of interest form before participating. Several non-pertinent conflicts of interest were disclosed by panel members at the onset of the expert panel process (see Table below). These conflicts of interest were deemed non-pertinent by OCSP because either panel members disclosed relationships with organizations where OCSP wanted panel representation or disclosed affiliations with commercial organizations that were deemed to be of minimal risk to bias panel outcomes.

Name	Role/Affiliation	Non-pertinent conflicts of interest disclosed
Praveen Bansal, MD, FCFP	Regional Primary Care Lead, Mississauga Halton/Central West Regional Cancer Program	None disclosed
Deborah Bateson, MA (Oxon), MSc (LSHTM), MB BS[b,c]	Medical Director, Family Planning New South Wales, Australia Clinical Associate Professor, Discipline of Obstetrics, Gynecology and Neonatology, University of Sydney, Australia	None disclosed
James Bentley, MBChB, FRCSC	Professor, Department Head, Obstetrics & Gynecology, Izaak Walton Killam Health Centre, Nova Scotia, Canada	Received a research grant from Merck (2013–2020)
Rita Boutette	Public advisor	None disclosed
Ann Burchell, PhD[a]	Research Director, Department of Family and Community Medicine, St Michael's Hospital, Ontario, Canada Scientist, MAP Centre for Urban Heath Solutions, Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, Ontario, Canada Associate Professor, Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Ontario, Canada	Part of a research consulting agreement with Inovio Pharmaceuticals Incorporated (2018–2021)
Dustin Costescu, MD, FRCSC	Cervical Screening and Colposcopy Lead, Hamilton Niagara Haldimand Brant Regional Cancer Program	Offered honorariums from Bayer (2018–present), Merck (2018–present) and Searchlight (2020)

Name	Role/Affiliation	Non-pertinent conflicts of interest disclosed
	Assistant Professor, McMaster University, Ontario, Canada Obstetrician-gynecologist, Ontario, Canada	Received research grants from Bayer (2017–2020) and Mithra (2019) Accepted a speaking engagement for Bayer (ongoing) and Merck (ongoing)
Allan Covens, MD, FRCSC[b]	Affiliate Scientist, Sunnybrook Health Sciences Centre, Ontario, Canada Head, Gynecologic Oncology, Sunnybrook Health Sciences Centre, Ontario, Canada	None disclosed
Sarah Ferguson, MD, FRCSC	Ontario Gynecologic Cancer Lead, Ontario Health (Cancer Care Ontario) Director of Research, Gynecologic Oncology, University Health Network, Ontario, Canada Gynecologic oncologist, Ontario, Canada	None disclosed
Helena Frecker, MD, FRCSC	Obstetrician and gynecologist, Michael Garron Hospital, Ontario Canada Assistant Professor, University of Toronto, Faculty of Medicine, Ontario Canada	
Zeina Ghorab, MD, MSc, DABP (AP/CP, HP, Cytopathology)	Director of Cytopathology Sunnybrook Health Sciences Centre. Associate Professor, Laboratory Medicine &Pathobiology, University of Toronto, Ontario, Canada	None disclosed
Sue Hranilovic, NP-PHC[c]	Primary Health Care Nurse Practitioner, Department of Family and Community Medicine, St. Michael's Hospital Academic Family Health Team, Wellesley St. Jamestown Health Centre, Ontario, Canada Adjunct Lecturer, University of Toronto, Lawrence S. Bloomberg Faculty of Nursing, Ontario, Canada	None disclosed
Warner Huh, MD	Gynecologic Oncologist, University of Alabama, USA Former President of American Society for Colposcopy and Cervical Pathology	Provided consultancy work for Dysis (2020–2021) and Actum (2020–2021)

Name	Role/Affiliation	Non-pertinent conflicts of interest disclosed
Naana Jumah, MD, FRCSC	Cervical Screening and Colposcopy Lead, North East Regional Cancer Program Obstetrician, Thunder Bay Health Sciences Centre, Ontario, Canada	None disclosed
Hormuzd A. Katki, MS, PhD	Senior Investigator, National Cancer Institute, USA	None disclosed
Michelle Khan, MD, MPH, FACOG[c]	Obstetrician, Lucille Packard Children's Hospital, USA Gynecologist, Stanford Health Care, USA Clinical Associate Professor, Obstetrics & Gynecology, Stanford University School of Medicine, USA	None disclosed
Rachel Kupets (Co-Chair), MD, MSc, FRCSC	Lead Scientist, Ontario Cervical Screening Program, Ontario Health (Cancer Care Ontario) Gynecologic Oncologist, Sunnybrook Health Sciences Centre, Ontario, Canada Associate Professor, Obstetrics & Gynaecology, University of Toronto, Ontario, Canada	None disclosed
Hugh Langley, MD, CCFP	Regional Indigenous Cancer Lead and Regional Primary Care Lead, Southeast Regional Cancer Program Assistant Professor, Queen's University, Ontario, Canada Senior Medical Advisor, Ministry of Health Family physician, Ontario, Canada	None disclosed
Aisha Lofters, MD, FCFP	Provincial Primary Care Lead, Ontario Health (Cancer Care Ontario) Family physician, Ontario, Canada Associate Professor, Family & Community Medicine, University of Toronto, Ontario, Canada	None disclosed

Name	Role/Affiliation	Non-pertinent conflicts of interest disclosed
Marie-Hélène Mayrand, MD, PhD, FRCSC	Principal Scientist, CHUM Research Centre, Quebec, Canada Chair, Research and Graduate Studies Committee – Department of Obstetrics-Gynecology, University of Montreal, Quebec, Canada Gynecologist, Quebec, Canada	None disclosed
Meg McLachlin, MD, FRCPC	Gynecology Pathologist, London Health Sciences Centre, Ontario, Canada Professor, Western University, Ontario, Canada	None disclosed
Anna Barbara Moscicki, MD[a]	Pediatrician, UCLA Medical Centre, USA Division Chief, Adolescent and Young Adult Medicine, UCLA Medical Centre, USA	Offered an honorarium from Merck (2018–2020)
Joan Murphy (Co-Chair), MD, FRCSC	Clinical Lead, Ontario Cervical Screening Program Trillium Health Partners, Ontario, Canada	None disclosed
Gina Ogilvie, MD DrPH FCFP	Senior Public Health Scientist, British Columbia Centre for Disease Control, British Columbia, Canada Senior Research Advisor, British Columbia Women's Hospital and Health Centre, British Columbia, Canada Physician, British Columbia Women's Hospital and Health Centre, British Columbia, Canada	
Erin Peltier, MD, FCFP	Regional Indigenous Care Lead, North East Regional Cancer Program Family physician, Ontario, Canada	None disclosed
Rebecca Perkins, MD, MSc[c]	Associate Professor of Obstetrics and Gynecology, Boston University School of Medicine/Boston Medical Center, USA Gynecologist, USA	None disclosed

Name	Role/Affiliation	Non-pertinent conflicts of interest disclosed
Aaron Pollett, MD, MSc, FRCPC	Provincial Head, Pathology & Laboratory Medicine Program, Ontario Health (Cancer Care Ontario) Anatomic pathologist and co-Director, Division of Diagnostic Medical Genetics, Mount Sinai Hospital, Ontario, Canada	None disclosed
Coleman Rotstein, MD, FRCPC, FASC, FIDSA[a]	Professor, University of Toronto, Ontario, Canada Director of Oncologic Infectious Diseases, Princess Margaret Hospital, Ontario, Canada Co-director of Transplant Infectious Diseases, University Health Network, Ontario, Canada	Accepted a speaking engagement for Roche Canada (2019–2020)
Marion Saville, MB ChB, Am Bd, FIAC, Grad Dip Med, GAICD	HPV Testing Implementation Project Subject Matter Expert, Ontario Health (Cancer Care Ontario) Executive Director, Australian Centre for the Prevention of Cervical Cancer, Melbourne, Australia Cytopathologist, Australia	Acted as an investigator on the Compass Trial for which her employer organization, VCS Foundation, has received test kits and partial funding from Roche (2016–2020)
Tamara Siddall, MD, FCFP	Regional Primary Care Lead, Erie St. Clair Regional Cancer Program Family physician, Ontario, Canada	None disclosed
Rena Spevack Orr	Public advisor	None disclosed
John Tidy, BSc, MBBS, MD, FRCOG[b]	Professor of Gynaecological Oncology Director Sheffield Trophoblastic Disease Centre, Weston Park Hospital	Provided consultancy work for Zilico Ltd (2010–2022) Holds worldwide patents in Electrochemical Impedance Spectroscopy from Zilico Ltd (2010–2022)
Nicolas Wentzensen, MD, PhD[b]	Head, Clinical Epidemiology Unit, National Cancer Institute, USA	None disclosed
Mark Yudin, MD, MSc[a]	Obstetrician/Gynecologist, St. Michael's Hospital, Ontario, Canada Associate Scientist, Li Ka Shing Knowledge Institute, Ontario, Canada	None disclosed

Name	Role/Affiliation	Non-pertinent conflicts of interest disclosed
Nicole Zavagnin, MD, FCFP	Regional Primary Care Lead, North West Regional Cancer Program Family physician, Ontario Canada	None disclosed

[a]Subject matter experts in cervical screening for immunocompromised populations.
[b]Subject matter experts in persistence and screening post-discharge from colposcopy.
[c]Subject matter experts in vaginal vault testing/testing for transmasculine and nonbinary people.

Appendix E: Referral threshold

Selecting a risk threshold for the elevated risk screening population

The elevated risk screening population consists of people with screening results that require referral to colposcopy.

The elevated risk screening population is defined based on an immediate risk of high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS) histology and cervical cancer after a positive screening test result. The Ontario Cervical Screening Program's (OCSP's) risk threshold for the elevated risk population is greater than or equal to 6%. This risk threshold was selected based on the OCSP's cytology-based screening recommendations, jurisdictional scan data, input from expert panel members.

Ontario data: OCSP's cytology-based screening recommendations

In the cytology-based program, the OCSP recommended referral to colposcopy for people with high-grade cytology or two consecutive low-grade cytology results a year apart (101). Therefore, people with an immediate risk of HSIL or AIS histology and cervical cancer (defined in the analysis as CIN3+) from 4.8% to 7.3% were referred to colposcopy. This range was used as a reference point to define the risk threshold for the elevated risk screening population for the human papillomavirus (HPV)-based recommendations.

Jurisdictional scan

Each jurisdiction must select a specific risk threshold for referral to colposcopy that is appropriate for their specific setting based on factors such as available colposcopy resources, the screening recommendations (e.g., screening intervals, screen test modality) and the acceptable trade-off of potential benefits versus the potential harms of colposcopy. For instance, the US-based ASCCP colposcopy referral threshold is a 4% immediate risk of HSIL or AIS histology and cervical cancer (defined by the ASCCP as CIN3+) (102), whereas England's cervical screening program's referral threshold is a five-year cumulative HSIL risk from 9.5% to 13.6% (53). Given the need to customize recommendations to Ontario's setting and program, jurisdictional scans were presented to the expert panel as examples but did not directly inform risk threshold selection.

Expert panel

An expert panel comprised of multidisciplinary experts in the field of cervical screening and colposcopy was consulted in 2019 to inform the development of a referral threshold for colposcopy for the OCSP. This panel was convened prior to the expert panel described in the OCSP's Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document. Based on the risk of HSIL or AIS histology and cervical cancer used as the referral threshold in the OCSP's cytology-based screening program, published literature, and expert opinion, the OCSP selected a referral threshold of an immediate risk of HSIL or AIS histology and cervical cancer that is greater than or equal to 6%.

The referral threshold for the elevated risk population was reconfirmed with the expert panel that was convened to inform the development of the OCSP's HPV-based cervical screening and colposcopy pathways.

Referral threshold expert panel members

Name	Role/Affiliation
Trina Buick, BsCN, MSc, PhD	Member, Ontario Cancer Research Ethics Board, Toronto, Ontario Nurse Clinician Scientist, Sunnybrook Health Sciences Centre, Toronto, Ontario
Lisa Del Giudice, MD, MSc	Regional Regional Primary Care Lead, Toronto Central Regional Cancer Program Family physician, Sunnybrook Health Sciences Centre, Toronto, Ontario
Rachel Kupets (Co-Chair), MD, MSc, FRCSC	Lead Scientist, Ontario Cervical Screening Program, Ontario Health (Cancer Care Ontario) Gynecologic Oncologist, Sunnybrook Health Sciences Centre, Ontario, Canada Associate Professor, Obstetrics & Gynaecology, University of Toronto, Ontario, Canada
Aisha Lofters, MD, PhD, CCFP	Provincial Primary Care Lead, Ontario Health (Cancer Care Ontario) Family physician, Ontario, Canada Associate Professor, Family & Community Medicine, University of Toronto, Ontario, Canada
Meg McLachlin, MD, FRCPC	Gynecology Pathologist, London Health Sciences Centre, Ontario, Canada Professor, Western University, Ontario, Canada
Joan Murphy (Co-Chair), MD, FRCSC	Clinical Lead, Ontario Cervical Screening Program Trillium Health Partners, Ontario, Canada
Gina Ogilvie, MD, DrPH, FCFP	Senior Public Health Scientist, British Columbia Centre for Disease Control, British Columbia, Canada Senior Research Advisor, British Columbia Women's Hospital and Health Centre, British Columbia, Canada Physician, British Columbia Women's Hospital and Health Centre, British Columbia, Canada
Danielle Vicus, MD, FRCSC	Gynecologic Oncologist, Sunnybrook Health Sciences Centre, Ontario, Canada
Karla Willows, MD, FRCSC	Gynecologic Oncologist, QEII Health Sciences Centre, Halifax, Nova Scotia

Name	Role/Affiliation
Ingeborg Zehbe, PhD, DSc	Associate Professor, Lakehead University, Thunder Bay, Ontario