Ontario Cervical Screening Program Interim Guidance to Support the Transition Years Following the Launch of Human Papillomavirus Testing in Ontario: Cervical Screening and Colposcopy Recommendations for People ages 21 to 24

Version 1 - March 2025

Ontario Health
Cancer Care Ontario

Contents

Acronyms and Abbreviations

ACC	Adenocarcinoma
ACC-E	Endocervical adenocarcinoma
AIS	Adenocarcinoma in situ
AGC	Atypical glandular cells
AGC-N	Atypical glandular cells-favor neoplastic
AGC-NOS	Atypical glandular cells-not otherwise specified
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 high-grade squamous intraepithelial lesion
OCSP	Ontario Cervical Screening Program
SCC	Squamous cell carcinoma

Introduction

Purpose

The purpose of this document is to provide interim guidance for cervical screening and colposcopy for people ages 21 to 24 who started screening before the formal change in the age of initiation for the Ontario Cervical Screening Program (OCSP). When human papillomavirus (HPV) testing is launched in the OCSP, the age of initiation for cervical screening will change from age 21 to age 25. As a result, there will be a transitional period after this change during which cervical screening and colposcopy decisions will need to be made for people under the age of 25 who started screening before the implementation of HPV testing.

Methods

The OCSP's interim guidance for cervical screening and colposcopy for people ages 21 to 24 during the transitional period after HPV testing is launched in Ontario was developed based on the following inputs:

- Rapid review of the primary literature on management of people under 25 in colposcopy
- 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 provincial, national and international stakeholder groups and subject matter experts for review prior to finalization.

For more details on the methods, please refer to the Methods: Recommendation development section of the OCSP's Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document.

Interim guidance: Cervical screening for people ages 21 to 24

Table 1 summarizes the Ontario Cervical Screening Program's (OCSP's) interim guidance for screening people ages 21 to 24. This guidance is for people who started screening before the OCSP formally changed the recommended age of initiation to age 25, which occurred when human papillomavirus (HPV) testing was implemented in the OCSP.

Important notes:

- People ages 21 to 24 with squamous cell carcinoma (SCC), adenocarcinoma (ACC), endocervical adenocarcinoma (ACC-E) or poorly differentiated carcinoma (PDC) cytology results should follow Colposcopy pathway 5: Investigation and management for people referred with HPV-positive and SCC, ACC, ACC-E or PDC cytology in the OCSP's Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document.

Table 1: Cervical screening guidance for people ages 21 to 24 who started screening before HPV testing was implemented in the OCSP

Cytology-based screening result before HPV testing implementation	**Recommended next step after HPV testing implementation for people who are immunocompetent**	**Recommended next step after HPV testing implementation for people who are immunocompromised[a]**
Normal	Delay next screening test to age 25 or in 3 years, whichever comes **later**	Delay next screening test to age 25 or in 12 months, whichever comes **later**
Unsatisfactory	Delay next screening test to age 25 or, if requested, repeat the test at the patient's earliest convenience	Delay next screening test to age 25 or, if requested, repeat the test at the patient's earliest convenience
Low-grade (ASCUS, LSIL) x1	Delay next screening test to age 25 (repeat screening optional[b])	Repeat screening in 12 months
Low-grade (ASCUS, LSIL) x2	Refer to colposcopy	Refer to colposcopy
High-grade (ASC-H, LSIL-H, HSIL, AGC[c], AIS)	Refer to colposcopy	Refer to colposcopy
High-grade (SCC, ACC, ACC-E, PDC)	Refer to colposcopy or consider referral to gynecologic oncology centre if an obvious lesion is seen in the cervix	Refer to colposcopy or consider referral to gynecologic oncology centre if an obvious lesion is seen in the cervix

ACC: adenocarcinoma; ACC-E: endocervical adenocarcinoma; 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-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL; LSIL: low-grade squamous intraepithelial lesion; PDC: poorly differentiated carcinoma; SCC: squamous cell carcinoma

[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.

[b]People who choose not to delay after a discussion with their health care provider about the limited benefits and potential risks of screening before the age of 25, can screen with an HPV test in **12 months**. The result of the repeat test should be managed according to the HPV-based cervical screening recommendations. For further details, refer to the Risk-based screening recommendations section of the OCSP's Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document.

[c] 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)

Screening test

Recommendation

HPV testing is the recommended cervical screening test for people ages 21 to 24. Reflex cytology will automatically be performed on specimens that are HPV positive (i.e., the health care provider will not need to order a second test).

Key evidence

HPV testing in this population was supported by the expert panel because it aligns with the guiding principles regarding feasibility of implementation and acceptability for health care providers and the public.

Screening interval

Repeat screening after a normal cytology result

Recommendation

People ages 21 to 24 who are **immunocompetent** with normal cytology results should delay their next screening test until age 25 or three years after their last normal cytology result, whichever comes **later**.

People ages 21 to 24 who are **immunocompromised** with normal cytology results should delay their next screening test to age 25 or 12 months after a normal cytology result, whichever comes **later.**

Key evidence

Cervical cancer in people under age 25 is extremely uncommon. In Ontario, from 2016 to 2020, only 29 new cases of cervical cancer were diagnosed in people under age 25 (2). 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 (1). As a result, screening in this population can lead to unnecessary colposcopy, which has associated risks.

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 (3). 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.

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 (1).

Repeat screening after a first time low-grade or unsatisfactory cytology result

Immunocompetent populations

Recommendation

People ages 21 to 24 who are immunocompetent with first time low-grade (i.e., atypical squamous cells of undetermined significance [ASCUS] or low-grade squamous intraepithelial lesion ([LSIL]) or unsatisfactory cytology results should delay screening until age 25.

People who choose not to delay after a discussion with their health care provider about the limited benefits and potential risks of screening before age 25, can repeat screening with an HPV test in 12 months (for people with a first time low-grade) or at the patient's earliest convenience (for people with unsatisfactory results).

Results of repeat testing should be managed according to the OCSP's HPV-based cervical screening recommendations. For further details, refer to the risk-based screening recommendations section of the OCSP's Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document.

Key evidence

Based on Ontario data, people under age 30 with a first time ASCUS or LSIL result have a five-year risk of high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS) histology and cervical cancer (defined in the analysis as cervical intraepithelial neoplasia 3+ [CIN3+]) of 2.9% and 5.6%, respectively (4). This risk falls below the OCSP's criteria for referral to colposcopy (i.e., immediate risk of HSIL or AIS histology and cervical cancer ≥ 6%). Therefore, it is safe for people ages 21 to 24 who are immunocompetent with first time low-grade cytology results to delay re-screening to age 25. At age 25, people in this population can re-start screening according to the OCSP's HPV-based cervical screening recommendations. For further details, refer to the Risk-based screening recommendations section of the OCSP's Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document.

There is no risk data available for people with unsatisfactory results. However, the expert panel advised that delayed screening would also be safe for people with unsatisfactory screening results given the low incidence of cervical cancer in this population.

Although the evidence and/or expert panel input supports waiting until age 25 to re-screen in people ages 21 to 24 who are immunocompetent with first time low-grade or unsatisfactory cytology results, the expert panel felt that it was important to provide the option for people to re-screen sooner. The expert panel felt providing an option to re-screen was more person centred because people in this population may be expecting to be re-screened based on the OCSP's prior cytology-based screening recommendations. As a result, the OCSP recommends that health care providers have a fulsome discussion of potential benefits and risks of screening under age 25 with people who wish to re-screen. If, after that discussion, the person still wishes to re-screen, the option is available to re-screen at 12 months.

An interval for repeat screening was selected based on the natural history of HPV infections and Ontario data. Another Ontario study examining appropriate follow-up for low-grade cytology found that 68.2% of ASCUS results

and 48.3% of LSIL results resolve on their own within 24 months (5). Although these data are not specific to a younger age cohort, they suggest that many low-grade cytologic changes are transient and do not progress to cervical cancer. Ontario data also show that the five-year risk of developing HSIL or AIS histology and cervical cancer (defined in the analysis as CIN3+) for people with first time ASCUS or LSIL results is very low in people under age 30 (2.9% and 5.6%, respectively) (4).

Ontario data and the published literature show that the risk of cervical cancer remains low for many years following a first-time low-grade cytology result. A 12-month interval was ultimately selected because it is the same as the OCSP's prior cytology-based screening recommendations for people with low-grade cytology results. Maintaining the 12-month interval is in alignment with the guiding principles regarding feasibility of implementation and acceptability for health care providers and the public.

Immunocompromised populations

Recommendation

People ages 21 to 24 who are immunocompromised with first time low-grade (i.e., atypical squamous cells of undetermined significance [ASCUS] or low-grade squamous intraepithelial lesion ([LSIL]) should repeat screening with an HPV test in 12 months.

People ages 21 to 24 who are immunocompromised with unsatisfactory result should delay next screening test to age 25. People with unsatisfactory results who choose not to delay after a discussion with their health care provider about the limited benefits and potential risks of screening before age 25, can repeat screening with an HPV test at their earliest convenience.

Results of repeat testing should be managed according to OCSP's HPV-based cervical screening recommendations. For further details, refer to the risk-based screening recommendations section of the OCSP's Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document.

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. 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 **with known cervical abnormalities** should not delay re-screening to age 25.

A 12-month re-screening interval was ultimately selected because it is the same as the OCSP's prior cytology-based screening recommendations for people with low-grade cytology results. Maintaining the 12-month interval is in alignment with the guiding principles regarding feasibility of implementation and acceptability for health care providers and the public.

There is no risk data available for people with unsatisfactory results. However, delayed screening is presumed to be safe for people with unsatisfactory screening results given the low incidence of cervical cancer in this population.

Re-screening after two consecutive low-grade cytology results or a high-grade cytology result

Recommendation

People ages 21 to 24 with the following cytology results require referral to colposcopy:

- Two consecutive low-grade cytology results
- High grade cytology results, including:
    - ASC-H: atypical squamous cells, cannot exclude HSIL,
    - LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL,

- HSIL: high-grade squamous intraepithelial lesion,
- AGC: atypical glandular cells, or
- AIS: adenocarcinoma in situ.

Key evidence

When cytology testing was used as the primary test for cervical screening, the OCSP recommended referral to colposcopy for people with two consecutive low-grade cytology results or high-grade cytology results. Maintaining this recommendation is in alignment with the guiding principles regarding feasibility of implementation and acceptability for health care providers and the public.

Interim guidance: Colposcopy for people ages 21 to 24

Pathway A: Investigation and management for people ages 21 to 24 referred with two consecutive low-grade cytology results or ASC-H, LSIL-H, HSIL, AGC or AIS

This pathway applies to people ages 21 to 24 with the following cytology results who are referred to colposcopy:

- Two consecutive low-grade cytology results (i.e., atypical squamous cells of undetermined significance [ASCUS] or low-grade squamous intraepithelial lesion ([LSIL])
- High grade cytology results, including:
  - ASC-H: atypical squamous cells, cannot exclude HSIL,
  - LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude HSIL,
  - HSIL: high-grade squamous intraepithelial lesion,
  - AGC: atypical glandular cells, or
  - AIS: adenocarcinoma in situ.

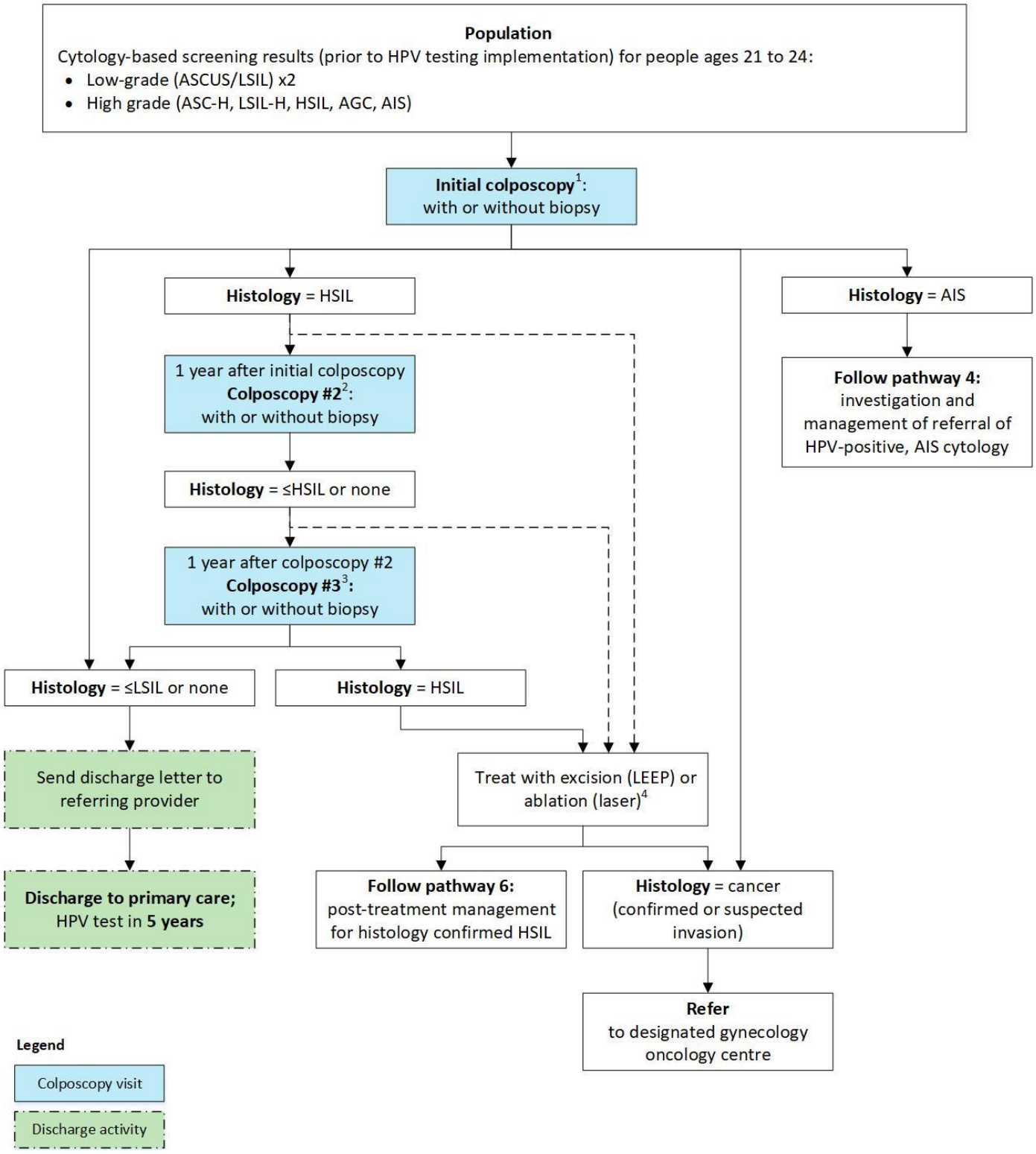
Recommendation

For people ages 21 to 24 referred to colposcopy with two consecutive low-grade cytology results or ASC-H, LSIL-H, HSIL, AGC or AIS 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 five years (immunocompetent people) or three years (immunocompromised people) with an human papillomavirus (HPV) test.

If HSIL histology is detected at the initial colposcopy visit, the patient should be managed conservatively in colposcopy (see Figure 1). If AIS is detected at the initial colposcopy visit, the patient should follow Colposcopy pathway 4: Investigation and management for people referred with HPV-positive and AIS cytology results in the Ontario Cervical Screening Program's (OCSP's) Recommendations for Cervical Screening and Colposcopy with Human Papillomavirus Testing in Ontario document. If cancer is detected or invasive disease cannot be ruled out at the initial colposcopy visit, the patient should be referred to a gynecologic oncology centre.

The full recommendations for investigation and management in colposcopy are summarized in Figure 1.

Figure 1: Investigation and management for people ages 21 to 24 referred with two consecutive low-grade cytology results or ASC-H, LSIL-H, HSIL, AGC, AIS



AGC: atypical glandular cells; AIS: adenocarcinoma in situ; 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; LEEP: loop electrosurgical excision procedure; LSIL: low-grade squamous intraepithelial lesion, LSIL-H: low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion

Footnotes:

1. 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.
2. After initial colposcopy, conservative management with two follow-up colposcopy visits 12 months apart is recommended. Conservative management can include visual inspection and/or biopsies without treatment (i.e., no diagnostic excisional procedures such as loop electrosurgical excision procedure).
3. If HSIL persists after two years, treatment is recommended. However, colposcopists may choose to treat HSIL during the two-year period of conservative management in some cases.
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 colposcopists.

Key evidence

Most of the guidance for colposcopy for people ages 21 to 24 is based on the OCSP colposcopy best practice pathways first released in 2016. The 2016 colposcopy pathways for people under age 25 were developed based on a rapid review of peer-reviewed studies and guidelines published from January 2000 to December 2016 on management of people under 25 in colposcopy as well as expert opinion.

One study was identified in the rapid review, which informed the pathway for people with LSIL detected at colposcopy. This study found that 12% of people with LSIL (defined in the study as cervical intraepithelial neoplasia 1 [CIN 1]) detected at their initial colposcopy progressed to CIN 2 or CIN 3 over a mean of 4.1 years (2.0 to 7.4 years) and no one developed cancer. Given the low rate of progression and the potential harms associated with colposcopy and overtreatment, the OCSP recommends that people ages 21 to 24 who are immunocompetent with LSIL detected at their initial colposcopy be discharged to primary care to resume screening in five years (or three years if immunocompromised) with an HPV test.

Several studies were identified in the rapid review, which informed the pathway for people with HSIL detected at colposcopy; key findings from these studies are summarized below.

- Five of the studies reported on disease persistence, progression or regression for people under 25 years of age with HSIL detected at colposcopy (defined in the studies as CIN2 or CIN2/3) (6–10).
    - The observed rate of disease regression ranged from 29% to 68% over 0.3 to 3.9 years of follow-up.
    - The observed rate of disease recurrence or persistence ranged from 4% to 24% over 0.3 to 10.0 years of follow-up.
    - The observed rate of disease progression ranged from 4% to 24% over 0.3 to 7.7 years of follow-up.
    - Only one cancer was observed during follow up (follow range: 0.3–10 years). This cancer was detected in an individual who had a recurrence after treatment for LSIL or HSIL. No cancers were reported for untreated people with LSIL or HSIL at their initial colposcopy.

- Five studies reported follow-up for people with HSIL (defined in the studies as CIN2 or CIN2/3) who were not treated (6–10).
    - Disease regression was observed in 29% to 68% of people under age 25 over 0.3 to 3.9 years of follow-up.
    - Persistence of disease was observed in 17% to 24% of people under age 25 over 0.3 to 7.0 years of follow-up.
    - Progression of disease was observed in 15% to 24% of people under age 25 over 0.3 to 7.0 years of follow-up; however, no cancers were reported in untreated people with available follow-up data.

Overall, these findings show that conservative management is appropriate for people ages 21 to 24 who have HSIL histology detected at their initial colposcopy visit. In the 2016 pathway, the interval between colposcopy visits for conservative management was six months. However, based on published evidence on the natural history of HPV (5), the expert panel felt that six months was inadequate for most people to clear their infection and any associated cervical cell changes. As a result, the OCSP has extended the time between the two conservative management colposcopy visits from six to 12 months.

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