Ontario Health
Cancer Care Ontario

Human Papillomavirus (HPV) Testing Frequently Asked Questions (FAQs) for Providers Offering Cervical Screening.

About the human papillomavirus test and why it has been introduced into the Ontario Cervical Screening Program.

1. Why is the cervical screening test changing from the cytology test (also known as the Pap test) to the human papillomavirus (HPV) test?

- There are several advantages to using HPV testing for cervical screening instead of cytology testing.
    - Providers can be more confident that people with a negative HPV test do not have a cervical pre-cancer than people with a negative cytology test because the HPV test is a more sensitive screening test, as shown in Table 1.
    - The improved performance of HPV testing over cytology testing allows for longer intervals between screens for people who test negative for HPV.
    - HPV testing is objective, which means results are highly consistent and reproducible. In contrast, cytology testing relies on subjective interpretation of results, which may identify cell changes that are not linked to cervical cancer and therefore do not need to be followed up with further testing.
    - Randomized controlled trials conducted in organized screening programs have shown that the HPV test can reduce the incidence of invasive squamous cell carcinoma and adenocarcinomas in the cervix[1]. Cervical screening with HPV testing results in a significant reduction in adenocarcinoma of the cervix compared to screening with cytology testing alone. The HPV test is also better at preventing cervical adenocarcinomas than a cytology test because the HPV test can more effectively identify people with a glandular pre-cancer[2, 3].

- HPV testing detects oncogenic types of HPV (i.e., strains containing oncogenic RNA or DNA). HPV testing does not detect low-risk (non-oncogenic) HPV types, such as those that cause genital warts. Therefore, a positive HPV test result means that oncogenic types of HPV were detected and a negative HPV test result means that oncogenic types of HPV were not detected.
- HPV testing in the Ontario Cervical Screening Program (OCSP) includes partial genotyping, which identifies the type of oncogenic HPV infection as 16, 18, 45 or other. Partial genotyping allows people with oncogenic types of HPV to be managed appropriately.
- Cytology testing will be used alongside HPV testing in the OCSP as a reflex test for results that are positive for oncogenic types of HPV or as a co-test in colposcopy. The OCSP is combining cytology testing with HPV testing as using the two tests has a higher chance of correctly identifying whether a cervical pre-cancer or cancer exists than HPV testing alone. The reflex cytology test will be performed on the same specimen that is submitted to the laboratory for HPV testing.
- Primary screening with the HPV test is increasingly considered to be the standard of care for organized cervical screening programs internationally and many jurisdictions have already transitioned from cytology testing to HPV testing[4, 5, 6, 7].

Table 1. Selected characteristics of the HPV test and the cytology test for cervical screening

Characteristic	HPV test	Cytology test
One-time sensitivity[a] in detecting cervical pre-cancer and cancer (defined in the study as cervical intraepithelial neoplasia 2+ [CIN2+])	96%[8, b]	53%[8, b]
One-time specificity[c] in detecting cervical pre-cancer and cancer (defined in the study as CIN2+)	91%[8, b]	96%[8, b]
What it detects	Oncogenic types of HPV in the cervix	Abnormal cell changes in the cervix
Interpretation of test[9]	Objective and reproducible[9]	Subjective[9]

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

[b] Sensitivity and specificity estimates shown here are drawn from performance data in the context of cervical screening programs across Europe and North America. However, specific estimates are expected to vary according to the test used and the screening population.

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

2. When will human papillomavirus (HPV) testing be available in screening and colposcopy as part of the Ontario Cervical Screening Program (OCSP)?

- Ontario Health (Cancer Care Ontario) is working with the Ministry of Health on changes to the OCSP that are required before implementing HPV testing. Once these changes are complete, HPV testing with reflex cytology testing (also known as Pap testing) will replace cytology testing as the primary cervical screening test in Ontario. In the colposcopy setting, HPV and cytology co-testing will be used instead of standalone cytology testing.
- When they are available, additional details, including the launch date, will be communicated to providers offering cervical screening and/or colposcopy.
- To ensure providers are well prepared for the launch of HPV testing, additional resources and supports will be provided on the HPV testing implementation resource hub at ontariohealth.ca/hpvhub

Changes to the Ontario Cervical Screening Program and screening recommendations.

3. Who is eligible for the Ontario Cervical Screening Program (OCSP)?

- Someone is eligible for cervical screening as part of the OCSP if they:
  - Have a cervix[a], including women, Two-Spirit people, transmasculine people and nonbinary people, as well as people who have undergone a subtotal hysterectomy and retained their cervix;
  - Are age 25 to 69 (some people may screen until age 74)[b];
  - Have ever been sexually active[c];
  - Have Ontario Health Insurance Plan (OHIP) coverage[d]; and
  - Have no symptoms suggestive of cervical cancer, such as abnormal vaginal bleeding or discharge, bleeding after sexual activity[c] and pelvic pain.
- People immunized for human papillomavirus (HPV), pregnant people and menopausal people who meet the OCSP eligibility criteria listed above still require cervical screening.

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[a] 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. Routine screening is not recommended for people who have had their cervix removed as a result of hysterectomy; for more information refer to the OCSP's Vaginal Vault Testing Guidance.

[b] People with one negative HPV test result from age 65 to 69 can stop cervical screening, with a few exceptions. The following people should screen until age 74: people who were not screened from age 65 to 69, immunocompromised populations, and people who have been discharged from colposcopy, but who have not yet met the criteria to return to routine cervical screening by age 69.

[c] Sexual activity is defined as any sexual contact with another person's genitals (private parts). This contact can be with the hands, mouth or genitals, and includes the sharing of sex toys. 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.

[d] To help someone get OHIP coverage, visit ontario.ca/page/apply-ohip-and-get-health-card, call Service Ontario toll-free at 1-800-267-8097 or text toll-free TYY at 1-800-268-7095 for more information.

4. What are the cervical screening recommendations for people who are immunocompromised?

- Most cases of cervical cancer are caused by persistent infection with oncogenic types of human papillomavirus (HPV). Immunosuppression may impair someone's ability to clear an HPV infection. In addition, it may enhance the speed that cervical cellular changes occur and the progression to cervical cancer. Therefore, people who are immunocompromised may be at higher risk of pre-cancer and cervical cancer[10].
- There is limited evidence available to inform age of initiation and interval for screening people who are immunocompromised. Therefore, the recommendations for people who are immunocompromised are based on expert opinion, practices in other jurisdictions and the precautionary principle (i.e., when there are potential harms, scientific uncertainty must be resolved in favour of prevention of harms).
- The Ontario Cervical Screening Program (OCSP) recommends that people who are immunocompromised screen at an interval of three years (as long as their HPV testing results are negative), which is more often than the five-year interval for people in the general screening population.
- The OCSP screening recommendations for people who are immunocompromised apply to people who meet the program eligibility criteria and the OCSP's definition of being immunocompromised. People who are immunocompromised include:
    - Those who are living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), regardless of CD4 cell count;
    - Those with congenital (primary) immunodeficiency;
    - Those who have received transplants (solid organ or allogeneic stem cell transplants);
    - Those requiring treatment (either continuously or at frequent intervals) with medications that cause immune suppression for three or more years;
    - Those who are living with systemic lupus erythematosus, regardless of whether they are receiving immunosuppressant treatment; and
    - Those who are living with renal failure and require dialysis.

5. How will cervical screening intervals change with human papillomavirus (HPV) testing?

- Before the launch of HPV testing, the Ontario Cervical Screening Program (OCSP) recommended cervical screening with cytology testing (also known as Pap testing) three years after each normal cytology test result.
- The OCSP now recommends that most eligible people screen with an HPV test five years after each negative HPV test result.

- There are a few exceptions:
    - **People who are immunocompromised.**
        - The screening interval for people who are immunocompromised is three years after a negative HPV test result.
    - **People who are HPV-positive (other high-risk types) with normal or low-grade reflex cytology test results.**
        - People who are positive for oncogenic types of HPV other than types 16, 18 and 45 (i.e., HPV-positive [other high-risk types]) with normal or low-grade reflex cytology test results should return to screening in two years.
        - If they remain HPV-positive at their subsequent screening test, they should be referred directly to colposcopy, regardless of their HPV type or reflex cytology test result.
    - **People who have been discharged from colposcopy.**
        - People who have been discharged from colposcopy should screen in two years, three years or five years, depending on their cytology test results at referral, immune status, histology and cytology test results, HPV status at discharge and whether treatment was required before discharge from colposcopy.
        - Refer to the Ontario Cervical Screening Program colposcopy pathways and post-discharge table for details, which can be found on the HPV testing implementation resource hub at ontariohealth.ca/hpvhub

6. Why is the screening interval increasing from three to five years for people with negative human papillomavirus (HPV) test results?

- Because it takes many years for cervical cancer to develop, someone has a very low risk of developing pre-cancer and cervical cancer if they get an oncogenic HPV infection in the five years after a negative HPV test result[11, 12, 13, 14, 15, 16, 17]. Furthermore, providers can be confident that a negative HPV test result correctly identifies people without a pre-cancer or cancer (i.e., the HPV test has a high negative predictive value)[18, 19].
- Published evidence shows that the risk of high-grade abnormal cervical cell changes five years after a negative HPV test result is lower than the risk three years after a normal cytology test (also known as a Pap test) result, which provides reassurance that the five-year cervical screening interval will not result in additional cancers[20].
- More frequent screening with the HPV test is not supported by evidence, which shows that the potential harms of shorter screening intervals outweigh the benefits[21]. More frequent screening can result in greater detection of false-positives and more referrals to colposcopy[22], which causes unnecessary anxiety, discomfort and pain[23].
- The five-year screening interval has been widely adopted internationally among populations that are similar to Ontario.

7. Do people with a history of abnormal cervical cell changes who have had a hysterectomy need to have vaginal vault testing?

- Only people in the following two groups should have vaginal vault testing with an human papillomavirus (HPV) test after a hysterectomy[a]:
    - People with evidence of any of the following histologies in their cervix at hysterectomy (i.e., in the hysterectomy specimen), regardless of margin status or known HPV status:
        - Low-grade squamous intraepithelial lesion (LSIL)
        - High-grade squamous intraepithelial lesion (HSIL)
        - Adenocarcinoma in situ (AIS)
    - People with a history of early cervical cancer (microinvasive cervical cancer, stage 1A1 only), regardless of whether there is still evidence of cancer or pre-cancer at hysterectomy (i.e., may have been excised with a LEEP or cone prior to hysterectomy).
- If the **first** vaginal vault HPV test is negative, no more HPV tests are needed.
- If someone's HPV test is positive, refer them directly to colposcopy, regardless of HPV type or reflex cytology test result.
- For details, refer to the *Ontario Cervical Screening Program Guidance for Vaginal Vault Testing* document available on the HPV testing implementation resource hub at ontariohealth.ca/hpvhub

Launching human papillomavirus testing.

8. What is the recommended timing for someone's next screening test if they are under age 25 with a normal cytology test (also known as a Pap test) result before human papillomavirus (HPV) testing was implemented?

- People with normal cytology test results who are under age 25 and immunocompetent should delay their next screen until age 25, or three years after their last test, whichever comes later.
- People with a normal cytology test result who are under age 25 and immunocompromised should delay their next screening test to age 25, or 12 months after their last test, whichever comes later.

[a] The use of the HPV test is approved by Health Canada for health care provider-collected cervical samples but has not been reviewed or authorized by Health Canada for use in the vaginal vault. HPV test performance has not been specifically evaluated for detecting vaginal precancer/cancer in relevant populations, therefore risks to the patient may include, but are not limited to, a decrease in testing accuracy. The Ontario Cervical Screening Program Guidance for Vaginal Vault Testing has been developed by Ontario Health in consultation with a multidisciplinary, international expert panel. Other Canadian and international jurisdictions also provide guidance on using the HPV test in the vaginal vault. The information provided by Ontario Health is not intended to serve as a substitute for a clinician's professional experience, independent judgment and decision making. Ontario Health assumes no liability whatsoever for any errors or omissions associated with the information provided herein and furthermore assumes no liability for any decision or action taken by the clinician or others in reliance on the information contained in these materials.

9. What is the recommended timing for someone's next screening test if they are under age 25 with an abnormal cytology test (also known as a Pap test) result before human papillomavirus (HPV) testing was implemented?

- For people under age 25 who had an abnormal cytology test result before HPV testing implementation, recommendations for next steps vary based on their cytology test results, screening history and immune status.
- For immunocompetent people who had a first-time, low-grade cytology test result before the launch of HPV testing, re-screening with an HPV test should be delayed until they reach age 25.
    - This recommendation is based on the evidence that HPV infections and related cell changes in the cervix are likely to go away on their own in people under age 25[24].
    - However, if someone chooses not to delay screening after a discussion with their provider about the limited benefits and potential harms of re-screening before age 25, they have the option to re-screen with an HPV test in 12 months.
    - Follow-up for people who choose to re-screen before age 25 should be based on the HPV testing recommendations.
- For immunocompromised[a] people who had a first-time, low-grade cytology test result before the launch of HPV testing, re-screening with an HPV test should be performed 12 months after their low-grade result, regardless of age.
    - Most cases of cervical cancer are caused by persistent infection with oncogenic types of HPV. Immunosuppression may impair someone's ability to clear an HPV infection.
    - In addition, immunosuppression may increase the speed of the cervical cellular changes caused by an HPV infection, including the progression to cervical cancer.
    - Therefore, people who are immunocompromised with known cervical abnormalities should not delay re-screening to age 25.
- People who had two consecutive low-grade cytology test results and people with high-grade cytology test results before the launch of HPV testing should be referred directly to colposcopy, regardless of immune status.

[a] The Ontario Cervical Screening Program includes the following groups in its definition of immunocompromised: 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.

10. What is the recommended timing for someone's next screening test if they are under age 25 with an unsatisfactory cytology test (also known as a Pap test) result before human papillomavirus (HPV) testing was implemented?

- The Ontario Cervical Screening Program (OCSP) recommends delaying re-screening until age 25 if someone under age 25 had an unsatisfactory cytology test result before HPV testing was implemented.
- Unsatisfactory cytology occurs due to specimen collection and processing errors, and not due to an increase in the risk of pre-cancer and cervical cancer.
- Waiting until age 25 to re-screen is appropriate because the incidence of cervical cancer in people under age 25 is extremely low[25]. The risk is lower in this age group because abnormal cervical cell changes in people under age 25 tend to be transient and are less likely to progress to pre-cancer and cervical cancer[26].
- Given the long natural history of cervical cancer, instances of progression to pre-cancer and cancer are likely to be detected through regular screening after age 25.
- Allowing time for transient abnormal cervical cell changes to resolve in people under age 25 also helps to avoid unnecessary follow-up investigation or treatment in colposcopy, which has associated potential harms.
- Therefore, screening in people under age 25 has no significant benefit and has potential for harm.
- The evidence supports waiting until age 25 to re-screen. However, if after a discussion with their provider about the benefits and risks, someone wants to screen again sooner, the OCSP recommends re-screening with an HPV test at their earliest convenience.

Ordering the human papillomavirus test and collecting the specimen.

11. Will there be a new Ontario Cervical Screening Program (OCSP) requisition form for human papillomavirus (HPV) testing and cytology testing (also known as Pap testing) for screening?

- Yes. There will be a new OCSP-specific screening requisition form for ordering an HPV test with reflex cytology, standalone cytology (where appropriate) or vaginal vault testing (*HPV and Cytology Tests Requisition – For Cervical Screening*).
- Providers will not be able to order OCSP-funded testing using any other requisition.

12. Where can providers find the new Ontario Cervical Screening Program (OCSP) requisition form for human papillomavirus (HPV) testing and cytology testing (also known as Pap testing) for screening?

- Leading up to the launch of HPV testing, the *HPV and Cytology Tests Requisition – For Cervical* Screening will be available on the HPV testing implementation resource hub at ontariohealth.ca/hpvhub and as part of an information package sent to providers offering cervical screening.
- In addition, Ontario Health (Cancer Care Ontario) is working with OntarioMD (OMD) to make the requisition form available through certified electronic medical records (EMRs).
- Providers can contact their EMR vendor closer to the launch of HPV testing implementation to explore how the requisition form will be made available in their EMRs.

Changes to the Ontario Cervical Screening Program's colposcopy recommendations.

13. What happens when someone has been discharged from colposcopy back to primary care?

- Providers offering colposcopy are strongly encouraged to send discharge letters to the referring provider when a patient is discharged back to primary care. The discharge letter should indicate whether the person required treatment and when they should return to screening.
- The OCSP is revising the current discharge letter templates for the launch of HPV testing, which will be available on the HPV testing implementation resource hub at ontariohealth.ca/hpvhub.
- Primary care providers are responsible for ensuring that participants screen at the appropriate time. People that are discharged from colposcopy for screening sooner than 5 years will not be sent a recall letter by Ontario Health (Cancer Care Ontario). Screening recommendations after discharge from colposcopy are available on the HPV testing implementation resource hub at ontariohealth.ca/hpvhub.

Education, resources and communications

14. Will there be educational opportunities for providers offering cervical screening to support the implementation of human papillomavirus (HPV) testing in the Ontario Cervical Screening Program (OCSP)?

- Yes. For providers who perform cervical screening, Ontario Health (Cancer Care Ontario) will offer an accredited continuing professional development module on the implementation of HPV testing and the new OCSP cervical screening recommendations. This module will be available regionally through face-to-face and virtual presentations

hosted by regional clinical leads. This module will also be available on the HPV testing implementation resource hub at ontariohealth.ca/hpvhub.

- To learn more about the accredited continuing professional development module presentations, providers should contact their Regional Cancer Program. A list of Regional Cancer Programs can be found at cancercareontario.ca/en/cancer-care-ontario/programs/regional-cancer-programs
- Closer to the launch of HPV testing, Ontario Health (Cancer Care Ontario) will also offer provincial webinars with details on HPV testing implementation. The webinars will be accessible to providers across Ontario.

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