BC Cancer Cervix Screening Program Program Overview

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Program Overview
Cervix Screening Program

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About BC Cancer

BC Cancer provides a comprehensive cancer control program for the people of BC. BC Cancer is committed to providing all patients with access to a full range of quality cancer services, regardless of where in BC they live.

Vision

A world free from cancer

Mission

To reduce the burden of cancer in British Columbia.

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Key Definitions and Abbreviations

The term…	Refers to…
AIS	Adenocarcinoma in situ.
CIN 2	Cervical intraepithelial neoplasia affecting one-third to two- thirds of the thickness of the epithelium; classified as a high- grade pathology result.
CIN 3	Cervical intraepithelial neoplasia affecting more than two-thirds of the thickness of the epithelium; classified as a high-grade pathology result.
Cisgender	People who have a gender identity that matches the sex they were assigned at birth.
Cotest	When a provider-collected (liquid based cytology method) sample undergoes both HPV and cytology testing.
Cytology High grade	• Atypical Squamous Cells Cannot Exclude High Grade Lesion (ASC-H), • High-Grade Squamous Intraepithelial Lesion (HSIL), moderate dysplasia • High-Grade Squamous Intraepithelial Lesion (HSIL), severe dysplasia • Potential Invasive Squamous Cell Carcinoma • Other Malignant Neoplasms
Cytology Glandular	• Atypical Glandular Cells other Otherwise Specified (AGC-NOS) • Atypical Endocervical Glandular Cells Not Otherwise Specified (AGC EC-NOS). • Atypical Endocervical Glandular Cells Favour Neoplasia (AGC – FN) • Endocervical Adenocarcinoma In Situ (AIS) • Atypical Endometrial Cells, Not otherwise specified • Atypical Endometrial Cells, Favour Neoplastic • Endometrial adenocarcinoma • Atypical Glandular Cells, Favour Neoplastic • Potential Endocervical Adenocarcinoma • Adenocarcinoma, Not otherwise specified
Eligible people	People with a cervix (including women and TTGD individuals), ages 25-69 who are or have been sexually active, who are due and eligible for cervix screening.
Gender diverse	Gender roles and/or gender expression that do not match social and cultural expectations; also referred to as non-confirming, gender variant.
HPV Test	When the sample is assessed for high-risk (oncogenic) HPV genotypes. HPV testing for cervix screening is not for detection of low-risk HPV types.
Hr-HPV Types	High-risk HPV genotypes.

LBC (Liquid-based cytology) – always provider-collected	A collection method used by health care providers to collect a cervical sample. Cells from the cervix are collected using a spatula and/or cytobrush, which are then transferred into a container containing an alcohol-based fixative. The liquid-based sample is submitted to the laboratory for testing and can be used for cytology, HPV testing or both, depending on the indication and testing algorithm.
Linked Clinic	A clinic that has been pre-identified by the Divisions of Family Practice to support follow-up care for unattached patients with positive cervix self-screening results, including performing a follow-up Pap test or supporting patients referred for colposcopy.
lr-HPV Types	Low-risk HPV genotypes.
Non-binary	An umbrella term to refer to diverse people whose gender identity is neither male or female.
Pap Test	Cytology testing conducted on a provider-collected (LBC method) sample.
Provider-Collected (LBC Method) Sample	When the provider collects the cervical screening sample for the patient.
Reflex Test	When the result of the primary screening test necessitates further testing. For example, when a sample was first assessed for hr-HPV and, due to an HPV-positive test result, is then sent for reflex cytology assessment.
Self-screening	When a patient collects their own sample vaginally using the Self-Screening Kit for HPV testing.
Self-Screening Kit	A kit that has everything a patient needs to collect a sample from their vagina for HPV testing. It includes a dry swab, instructions, brochure about cervix self-screening, plastic bag and pre-paid envelope.
TTGD	Two-Spirit, transgender, and gender-diverse.
Transgender	People who identify with a gender that is different from the sex they were assigned at birth.
Two-Spirit	A term used within some Indigenous communities, encompassing cultural, spiritual, sexual and gender identity.
Unattached Patient	A patient who does not have a primary care provider.
VAIN 2	Vaginal intraepithelial neoplasia 2
VAIN 3	Vaginal intraepithelial neoplasia 3

1. Introduction

BC has been the pioneer in population-based cervix screening since the launch of the Cervix Screening Program in 1955 – the first such program in the world. The BC Cervix Screening Program is an organized, population-based screening program with the goal to reduce cervical cancer incidence and mortality by identifying and treating pre-cancerous lesions and early cancers. Cervix screening with conventional cytology has reduced the incidence and mortality of cervical cancer by over 70% in BC [1] [2]. Prior to the availability of cervix screening, 28.4 per 100,000 women were diagnosed with cervical cancer. Today, 5.8 per 100,000 women are diagnosed with cervical cancer [2]. In BC, 66% of patients with squamous carcinoma and 46% of patients with adenocarcinoma had no screening history or were screened more than 5 years ago [3].

Follow-up management for cervical dysplasia is provided through the Regional Health Authorities (colposcopy, treatment and pathology reporting).

Cervix screening tests have a potential for false negative and false positive results. If your patient has any clinically suspicious lesions, abnormal bleeding or other relevant symptoms, further evaluation is required even if a screening test result is normal, see section 4.14.

Screening is recommended for people with a cervix (including women and Two-Spirit, transgender and gender diverse individuals), ages 25-69 who are or have ever been sexually active. When used in this document “people”, “participants” or “patients” is intended to refer to all people who are eligible for cervix screening.

2. Cervix Screening Roles

2.1 BC Cancer

BC Cancer provides medical and operational leadership for the Cervix Screening Program and is responsible for the development of provincial policies, standards and procedures for the primary screening test, follow-up testing, recall and surveillance reminders to providers and program performance and outcome monitoring.

Data is collected and analyzed on an ongoing basis for program evaluation and to identify areas for improvement.

The program publishes program results annually [4].

2.2 Cervical Cancer Screening Laboratory

Screening tests are analyzed and results are provided by the Cervical Cancer Screening Laboratory (CCSL), which is operated by PHSA's Provincial Laboratory Medicine Services. CCSL processes and interprets approximately 350,000 cervix screening tests annually, including cervical cytology and HPV tests. At times, to improve timeliness, some supportive services are provided by external laboratories in Canada and the United States. The laboratory distributes cervix screening test sampling supplies to health care providers at no cost.

CCSL demonstrates an ongoing commitment to providing quality patient care by following internationally recognized standards of excellence in laboratory practices. The laboratory is accredited by the College of American Pathologists and by the College of Physicians and Surgeons of BC Diagnostic Accreditation Program (ISO 15189).

Please visit the laboratory website for further information: http://www.bccancer.bc.ca/health-professionals/clinical-resources/laboratory-services/cervical-cancer-screening [5].

2.3 Health Care Providers

The following licensed health care providers are able to submit provider-collected (LBC) cervical samples for screening in BC:

- Members of the BC College of Physicians and Surgeons,
- Members of the BC College of Nurses and Midwives: Professionals who meets the additional competency criteria for pelvic exams and cervix screening,
- Members of the Association of Naturopathic Physicians of BC.

For information on how to register as a provider, obtain supplies and submit test samples please visit the Cervical Cancer Screening Laboratory website.

Physicians, nurse practitioners, midwives and registered nurses who possess the competencies required to appropriately assess patient eligibility for cervix screening and to support patients with recommended follow-up care, can order self-screening devices.

Health care providers are expected to review eligibility requirements and previous screening test results and recommendations prior to completing a provider-collected sample or providing a self-screening device to a patient to ensure patients are due to screen.

Health care providers play a key role in:

- Identifying individuals eligible for cervix screening.
- Educating patients about the benefits and limitations of screening.
- Educating patients about the importance of regular cervix screening.
- Informing patients of the signs and symptoms of cervical cancer.
- Providing and supporting recommended screening follow-up.

Health care providers are accountable for ensuring that a report is received for each cervix-screening test submitted and are responsible for:

- Informing screening participants of screening test results.
- Ensuring screening participants are referred for specialist assessment and investigation when required, and that ongoing care is coordinated. As no screening test has perfect sensitivity, investigation should occur regardless of a negative screening result for participants with signs or symptoms of cervical cancer, see section 4.14.
- Ensuring that participants are recalled at recommended intervals for routine screening.
- Identifying and ensuring recall of participants who need more frequent screening due to high-risk clinical conditions, such as immunocompromised.

The Cervix Screening Program supports primary care providers by notifying participants when they are due for screening and facilitating referral to the nearest colposcopy clinic when colposcopy is recommended. Ensuring continuing care and appropriate referral remains the responsibility of the ordering provider or the clinic/provider unattached patients are linked to for follow-up care/support.

For information on how to register as a provider, obtain supplies and submit test samples please visit the Cervical Cancer Screening Laboratory website.

2.4 Recruitment and Retention

The program notifies screening participants when they are due, reminds health care providers when their patients are due for screening and invites never screened people, those who are new to BC or who age into screening to participate in cervix screening.

2.5 Colposcopy Services

In BC, colposcopy is a non-core competence for gynecologists and gynecological oncologists. Credentialing and privileging for colposcopy occurs at the Health Authority level for those who provide this service at a BC hospital. Gynecologists interested in providing colposcopy are encouraged to participate in the BC Colposcopy Training program facilitated by BC Cancer. Training includes course work with an exam and participation in mentored colposcopy clinics with a trained colposcopist. An annual education event is provided for colposcopists in BC and participation in ongoing education activities, submission of quality indicator data and meeting indicator benchmarks is expected. For more information on how to apply for Colposcopy Training visit

http://www.bccancer.bc.ca/screening/Documents/Colposcopy-Standards.pdf or email CervicalScreeningQuality@bccancer.bc.ca

If recommended, patients should be referred promptly for colposcopy to investigate abnormal screening results. The BC Cancer Cervix Screening Program has implemented a facilitated referral process for cervix screening participants who have abnormal screening results and are recommended to have colposcopy follow-up. Under the facilitated referral process, BC Cancer Cervix Screening Program will send a notice to the colposcopy clinic with certified colposcopists nearest the patient's location to initiate colposcopy follow-up when that has been recommended. Patients will receive an abnormal result letter from BC Cancer advising that follow-up is needed and providers will be notified of the referral made on their behalf. The facilitated referral process will support program wait time standards for abnormal screening management and adherence to follow-up, by ensuring patients are referred for colposcopy promptly.

Colposcopy clinics will see patients for:

- Follow-up and management of abnormal screening test results
- Ongoing surveillance of higher than average risk patients
- Clinical abnormalities identified by a primary care provider

2.6 Colposcopy Clinics

Most colposcopy services in BC are provided in hospitals operated by the regional Health Authorities. Some colposcopy procedures are provided out of private offices.

2.7 Pathology Laboratories

Pathology laboratories in each Health Authority are responsible for reporting results on cervix related biopsy and excisional samples. Laboratories are encouraged to endorse and implement the standards for pathology processing and reporting as documented in the provincial cervix screening pathology standards document.

3. Screening Tests

3.1 Screening Tests

Human Papillomavirus (HPV) testing and cytology are both currently used in BC as primary screening tests. HPV testing does not require a sample of cells from the squamous columnar junction of the cervix. HPV-based screening can be performed by a provider (vaginal or cervical (LBC) collection) or by the screening participants themselves (vaginal collection self-screening).

Cervix self-screening with a patient-collected vaginal swab is available to all age eligible cervix screening participants. Provider-collected liquid based cytology (LBC) sampling is also available. Provider-collected samples are triaged at the laboratory to either HPV testing or cytology, based on the patient's screening history and age. A step down approach to phase out primary cytology screening is in process. The current patient age for primary HPV screening for provider-collected specimens is available on the program and laboratory websites: www.screeningbc.ca/health-professionals.

See Appendix A for the screening triage and follow-up algorithm.

The majority (99%) of cervical cancers are caused by a persistent infection with a high-risk genotype of human papillomavirus (HPV) [6]. Persistent infections with high-risk HPV may progress to pre-cancer and eventually to cervical cancer if left undetected and/or untreated. It takes approximately 15 to 20 years for an HPV infection to lead to cervical pre-cancer or cancer in people who are immunocompetent [7].

Cervical cytology detects abnormal cervical cell changes that have already occurred as a result of an HPV infection. HPV testing is more sensitive, and has a higher negative predictive value than cervical cytology for the detection of CIN 2 and CIN 3 and more severe abnormalities [8] [9] [10] [11]. As a result, the interval between negative screens can safely be extended. When compared to HPV screening, cytology misses eight times more pre-cancerous lesions [12].

	HPV test	Cytology
One-time sensitivity in detecting CIN 2 or worse	96.1% (94.2–97.4%)	53.0% (48.6–57.4%)
One-time specificity in detecting CIN 2 or worse	90.7% (90.4–91.1%)	96.3% (96.1–96.5%)

[13]

In a combined analysis of four European randomized trials, a negative HPV result at baseline decreased the risk of subsequent invasive carcinoma by 70% with a rate ratio of 0.3 (95% CI: 0.15 – 0.60). The HPV testing arms showed an overall reduction in invasive carcinoma of all participants of 40% with a rate ratio of 0.60 (95% CI: 0.40 – 0.89), compared to the control group which was offered cytology-based screening [14]. In the BC HPV FOCAL Trial, those who were HPV-negative had a significantly lower cumulative incidence of CIN 3 or worse at 48 months than cytology-negative women (CIN 3+ incidence rate, 1.4/1000 [95% CI, 0.8-2.4]; CIN 3+ risk ratio, 0.25 [95% CI, 0.13-0.48]) [8]

3.2 Cervical Cytology Testing

The CCSL classifies results according to the 2014 Bethesda System [15]. Cervix screening using cytology will still be used until the entire population has been converted to primary HPV testing. In addition, cervical cytology testing is performed after a positive HPV test. This is done as a reflex test in the laboratory for provider-collected specimens or as a follow-up test for self-collected HPV tests. Limited cytology testing is also utilized in the screening of patients exposed to DES in utero and in the follow-up of patients previously treated for high-grade cervical dysplasia.

A short 2-week course of vaginal estrogen therapy can be considered in those experiencing vaginal dryness (e.g., post-menopausal, on gender affirming hormone therapy, etc.) who opt for a provider-collected sample or who are recommended for cytology after a positive HPV self-screening test, prior to collecting the sample. This can reduce discomfort and improve the diagnostic accuracy of cytology.

3.3 Human Papillomavirus Testing

In BC, the Roche Cobas instrument is used for HPV testing for self-screening samples and for provider-collected specimens undergoing HPV testing. The result will detect if high-risk HPV DNA is present or absent.

3.4 Management of Participants Who Test Positive for HPV

Although HPV testing has higher sensitivity, it has a lower specificity, since not all those with HPV detected will have cervical dysplasia. As a result, secondary testing is recommended in some cases to minimize unnecessary colposcopy referral and treatment of those who are HPV positive.

Published research with long-term follow-up have predominantly utilized cervical cytology, partial genotyping and repeat HPV and/or cytology testing on a reduced follow-up schedule to adequately stratify risk of subsequent CIN 3 or worse and to help guide management [16] [17] [18]. Partial genotyping determines if a person has an HPV genotype that is more likely to cause cervical cancer (testing in BC will report HPV subtypes 16,18 or a group of other high-risk types. The other types that are grouped include 31, 33, 35 39, 51, 52, 56, 58, 59, 66 and 68. Reflex cytology is when cytology testing is performed automatically by the laboratory on provider-collected samples that test positive for HPV. Cytology may be the recommended follow-up test after a self-collected HPV positive result. The Cervix Screening Program will use a combination of partial genotyping and cytology on those who test positive for HPV to help guide subsequent management.

Population wide cervix screening based on HPV testing has been fully implemented in Australia, the Netherlands, the United Kingdom and Turkey with partial implementation in Italy, Finland and Sweden [19]. Initial results of the Dutch, Australian and Turkish screening programs are published [20] [21] [22]. The World Health Organization [23] and the Canadian Partnership Against Cancer [24] have both recommended HPV testing as the primary screening method for cervical cancer prevention.

4. Screening Program Guidelines

4.1 Screening Program Eligibility

Screening seeks to balance the benefits of screening while limiting the potential harms. The current Cervix Screening Program policy was implemented in 2024 and, for average risk screening, is based on the BC Lifetime Prevention Schedule. In addition, recommendations and guidelines for non-average risk screening and follow-up were developed considering evidence from review of the literature, the Canadian Preventative Services Taskforce, the Society of Canadian Colposcopists, Cancer Care Ontario, screening and colposcopy recommendations from other jurisdictions and expert opinion [25] [26].

Screening is recommended for people with a cervix (including women and Two-Spirit, transgender and gender diverse individuals), ages 25-69 who are or have been sexually active. When used in this document "people", "participants" or "patients" is intended to refer to all people who are eligible for cervix screening. Sexual activity includes intercourse, as well as digital or oral sexual activity involving the genital area with a partner of any gender. In this document, "people" refers to individuals who are eligible for cervix screening.

For individuals with significant co-morbidities that are likely to limit life expectancy, the need for screening should be assessed on an individual basis and discussed with the individual.

4.2 Provider-Collected Cervical Samples versus Self-Collected Vaginal Samples for HPV Testing

HPV DNA can be detected in vaginal secretions, therefore, it is possible to test for HPV in self-collected vaginal samples. HPV-based self-collection has been shown to overcome many barriers to cervix screening that some people have experienced [27] as a result of the traditional approach with provider-collected cervical cytology. Providing HPV self-collection kits to never screened and under-screened people has been shown to improve screening participation in international studies [28]. In the BC pilot, never and under screened participants offered self-screening returned screening samples up to 26% of the time. In addition, the WHO and Canadian Partnership Against Cancer calls for elimination of cervical cancer indicate that innovative approaches for screening (e.g.: self-collection) are required to improve equitable access to screening [24] [23].

In a meta-analysis of 56 accuracy studies, the clinical sensitivity of self-collected HPV samples was equivalent to clinician-collected samples for detection of CIN 2+ and CIN 3+, for polymerase chain reaction (PCR) based assays. The pooled sensitivity ratio for CIN 2+ detection as 0.99 (95% CI: 0.97-1.02) and for CIN 3+ 0.99 (95% CI 0.96-1.02) [29]. Table 1 summarizes the results for relative sensitivity, specificity, test positivity rate and positive predictive value (PPV) for PCR based assays. These results were confirmed in a subsequent randomized trial-comparing physician collected to patient collected samples [30]. Comparison of the 7643 women in the self-sampling group and the 6282 women in the clinician-based sampling group showed similar sensitivity and specificity for CIN 2+ and for CIN 3+. Relative sensitivity for CIN 2+ was reported as 0.96 (95% CI 0.90-1.03 and relative specificity was 1·00 (95% CI 0·99-1·01). For CIN 3+, relative sensitivity was 0·99 (95% CI 0·91-1·08) and relative specificity was 1·00 (95% CI 0·99-1·01) [30]. This large body of evidence shows no difference in the diagnostic accuracy of HPV

testing between using self-collected and clinician-collected samples as long as a PCR based assay is used [31].

Based on the evidence, self-collected vaginal samples are deemed equivalent to health care provider-collected cervical samples undergoing HPV testing and both are options in BC's Cervix Screening Program. All eligible people have a choice in screening collection method: self-screening or provider-collected sample. As The Canadian Task Force on Preventive Health Care recommends not performing a screening pelvic examination to screen for noncervical cancer, pelvic inflammatory disease, or other gynecological conditions in asymptomatic women [32], self-screening is an important option to increase access to and improve participation in screening for eligible people in BC.

Table 1: Comparison of Physician Collected to Self-Collected HPV Samples

	Ratio (95% CI)			
	Sensitivity	Specificity	PPV	Test positivity
CIN 2+	0.99(0.97-1.02)	0.98 (0.97-0.99)	0.97 (0.90-1.04)	1.00 (0.94-1.06)
CIN 3+	0.99 (0.96-1.02)	0.98 (0.97-0.99)	0.90 (0.78-1.05)	

Table adapted from Arbyn et. al. 2018. CIN 2+ results based on 17 studies and CIN 3+ results on 8 studies [29]

The following patients are eligible for self-screening:

- Is due for screening
- Has ever had any sexual contact
- Has not been recommended for a cotest (HPV and cytology testing) as their next screen
- Not pregnant
- No pessary
- No AIS ever

The following patients should have a provider-collected specimen (LBC method).

- Will undergo a speculum exam anyways
- Has a disability, mobility challenge or body habitus that makes self-screening difficult*
- Requires a cotest (HPV and cytology testing) due to their clinical history, see section 5.3
- Has difficulty getting to the office (distance, time off work, ect…) and has come in for an appointment*
- Does not regularly interact with the health system and has come in for an appointment*

*Taking a provider-collected (LBC method) specimen may prevent the patient from needing another in-person visit to collect cytology should they complete self-screening and have a positive HPV test result. The provider-collected specimen can be reflexed to secondary screening if the primary screen is positive.

4.3 Frequency of Screening for Average Risk Individuals

Average risk individuals are those who are not immunocompromised, who have not been exposed in utero to DES and who have not had a CIN 2, CIN 3, AIS or cervical cancer diagnosis.

Guideline:

Screen by a Human Papillomavirus test every five years or cytology every three years.

Rationale:

The majority of cervical cancers are caused by high-risk human papillomavirus (HPV) [6]. Testing for HPV is more sensitive than cervical cytology and therefore can detect CIN 2 and CIN 3 and more severe abnormalities earlier and better [8] [9] [10] [11]. Screening using HPV testing has the potential to improve identification of adenocarcinoma and its precursors [9] [14] [33]. The increased sensitivity allows for an extended screening interval because those in whom HPV types are not detected are at very low risk of CIN 3 or cancer for at least 5 years (5 year risk of CIN 3+ after a negative HPV test of 0.25% (95% confidence interval [CI]: 0.12% to 0.41%) [34].

Based on the risk of detecting CIN 3 or a more severe abnormality, a screening interval of 5 years is recommended for HPV-based screening by the Society of Canadian Colposcopists and the Society of Obstetricians and Gynecologists of Canada [35] as well as the US Preventative Services Taskforce and the American Society of Colposcopy and Cervical Pathology (ASCCP) [36] [37]. Screening every five years by HPV testing is also recommended by the Australian National Cervical Screening Program, the first national population-based screening program to utilize HPV testing in cervix screening [38]. An evidence review by a health technology expert panel of the Canadian Agency for Drugs and Technologies in Health (CADTH) did not specifically recommend for or against HPV primary screening but suggested a five yearly screening interval if HPV testing is adopted [39]. The BC Lifetime Prevention Schedule found that HPV based screening would lead to a reduction of 55% in the incidence of cervical cancer, compared to cytology based screening [40].

The current Canadian Task Force on Preventative Health Care Cervical Cancer screening guidelines recommends a three year screening interval, for primary cytology screening, as the best balance between the small incremental benefit from shorter intervals against the potential harm of overtreatment because of more frequent screening [25]. Screening every three years with cervical cytology is also recommended as an acceptable strategy for cervical cancer prevention by the United States Preventative Services Task Force [41]. Modeling data from eight countries (1,381 people with squamous cell carcinoma of the cervix and 2,259 age-matched controls), estimated the effect of different screening intervals on cervical cancer rates in people ages 20-64 (see table below) [42]. Annual screening from ages 20-64 produced the greatest reduction in cervical cancer incidence (93%). Screening every three years was only marginally less protective at 91%, or 90% if screening commences at age 25 [42]. Many cervical abnormalities regress within two years of diagnosis [43] [44] [45], and therefore a three year screening interval limits over diagnosis while still providing almost identical protection. A modeling study of 938,576 people with biopsy proven cervical neoplasia estimated the excess risk of progression to cervical carcinoma to 3 per 100,000 in people who were screened every three years compared to those screened annually [46].

4.4 Age to Start Screening

Guideline:

Initiate screening at age 25. Cervical screening is not recommended for those who have never had any sexual activity.

Rationale:

The recommendation to initiate screening at age 25 is based on several factors.

- Cervical cancer is rare in people under age 25. Analysis of BC data of cervical cancers diagnosed between 1986 and 2009 showed an incidence of 0.5 per 100,000 in women at age 20 and 1.35 per 100,000 in women aged 20 to 24 [47]. This incidence is the same as the incidence of breast cancer in men.
- Cervix screening appears to be less effective in younger people. A case control study from the United Kingdom showed no significant difference in cervical cancer incidence in women aged 25 to 29 who were screened at ages 20 to 21 or ages 22 to 24 versus women of the same age who were not so screened [48].
- Comparisons of cancer incidence in jurisdictions with different screening commencement ages did not show significant differences in outcomes [49].
- Only a small subset of cervical cancers in this age group is detected by a screening test, even in jurisdictions where routine organized screening is offered from age 20. In a population-based study, only 26% of cervical cancers in women between ages 20 and 25 were detected with a screening test, while 38% were detected as a result of symptoms [50].
- The target abnormalities of cervical screening often undergo spontaneous resolution in young women. Approximately 60 to 70% of biopsy proven cervical intraepithelial neoplasia grade 2 (CIN 2) will regress in younger women over a period of 1 to 3 years [43] [44] [51] [52].
- BC began a voluntary school-based HPV immunization program in 2008, with uptake rates of approximately 70%. HPV vaccination leads to a substantial decrease in cervical pre-cancer among young people. Data showed that people who received a complete series of vaccine on schedule between age 9 and 14 years had an adjusted RR = 0.42 (95% confidence interval [CI], 0.31-0.57) for CIN 2 or worse compared to those who are unvaccinated [53]. Through a combination of primary prevention with vaccination and herd immunity, people under age 25 in BC will have good protection against high-risk HPV.
- Most oncogenic HPV infections in younger people are transient and resolve spontaneously and as a result, screening in this population can lead to unnecessary colposcopy and treatments, which have associated risks. (see Table 2 and 3) [54] [55].

Table 2: Reproductive Risk of Excisional Treatments.

	Anticipated Absolute effects		Relative Risk
	Risk (per 1000) [Comparison]	Risk (per 1000) [Intervention] (95% CI)	Intervention/comparison (95% CI)
Pre term birth (<37 weeks)	54	95 (85 - 106)	1.75 (1.57 - 1.96)
Pre term birth (<37 to 34 weeks)	14	32 (26 - 40)	2.25 (1.79 - 2.82)
Pre term birth (<28 to 30 weeks)	3	7 (5 - 11)	2.23 (1.55 - 3.22)
Low birth weight (<2500 gram)	37	66 (58 - 76)	1.81 (1.58 - 2.07)
Perinatal mortality	7	11 (8 - 14)	1.51(1.13 - 2.03)

Table adapted from Kyrgiou et. al. 2017. [54]

Table 3: Risk of Preterm Birth Associated with Treatment for CIN.

	Untreated	Treated	RR(995% CI)
<37 Weeks gestation	5.43%	10.73%	1.78 (1.60- 1.98)
<32-34 Weeks gestation	1.43%	3.47%	2.40 (1.92- 2.99)
<28-30 Weeks gestation	0.33%	1.03%	2.54 (1.77- 3.63)
<37 Weeks gestation by single vs. repeat treatment			
Single treatment	4.17%	7.48%	1.75 (1.49- 2.06)
Repeat treatment	4.11%	13.25%	3.78 (2.65- 5.39)
<37 Weeks gestation by cone depth			
Cone depth ≤10-12mm	3.42%	7.14%	1.54 (1.09- 2.18)
Cone depth ≥10-12mm	3.42%	9.77%	1.93 (1.62- 2.31)
Cone depth ≥15-17mm	3.40%	10.05%	2.77 (1.95- 3.93)
Cone depth ≥20mm	3.40%	10.22%	4.91 (2.06- 11.68)
<37 Weeks gestation by treatment modality			
Laser ablation	6.68%	7.25%	1.27 (0.67- 2.40)
Loop Electrosurgical Excision Procedure (LEEP)	4.66%	7.59%	1.69 (1.46- 1.97)
Laser conisation	7.12%	14.17%	2.39 (1.24- 4.61)
Cold knife conisation	6.12%	15.90%	3.28 (2.44- 4.42)

Table adapted from Kyrgiou et. al. 2016. [55]

4.5 Cessation of Cervical Screening

Guideline:

Average Risk: Stop screening at age 69, provided that there has been a negative HPV screening test between the ages of 65 and 69 and under no active surveillance of CIN 2, CIN 3 or AIS.

Immunocompromised: Stop screening at age 74 provided there has been a negative HPV screening test between the ages of 69 and 74 and under no active surveillance of CIN 2, CIN 3 or AIS.

Those who have been discharged from colposcopy after treatment of CIN 2, CIN 3 or AIS, but have not yet completed the post discharge 12 month cotest (HPV and cytology) before age 69 (not immunocompromised) or 74 (immunocompromised), should have a cotest. After a negative cotest, screening can be discontinued.

Rationale:

The decision to stop screening is informed by the data on cervical cancer incidence in this age group, the duration of protection against cervical cancer due to prior screening and the life expectancy at the age of discontinuing screening. Most published guidelines recommend cessation of screening between ages 60 and 70 years of age, provided that there has been adequate screening in the past [20] [56]. The Canadian Taskforce for Preventative Health care issued a strong recommendation to continue cervix screening till age 69 and a weak recommendation to discontinue screening at age 70 [25]. The evidence for screening until at least age 60 is strong. Cervical cancer incidence rates in BC are highest in the age group 40 to 59 (12.2/100,000 in 2015) [57]. Screening is very effective in preventing cervical cancer in women in this age group [48] [58]. Studies have shown that a single negative HPV test after age 50 is associated with a 5 year risk of developing CIN 3 of 0.06 (95% CI 0.05-0.07) and 0.03 (95% CI of 0.02-0.04) [59] [60]. After age 65 cervical cancer and pre-cancer incidence rates decrease and most women who develop cervical cancer after age 65 have not effectively participated in screening [2] [3].

Because of the high negative predictive value of an HPV test, screening can be discontinued at age 69 given there has been a single negative HPV test between the ages of 65 and 69 and the patient is not under active surveillance for cervical cancer or pre-cursor abnormalities. Those who are 69 years or older who have never had a cervical screening test, or have not had one in the previous five years, may request a test and should be screened.

4.5.1 Management of those over age 69 with HPV Positive Results

Guideline:

Those with a positive HPV result after the age of 69, regardless of HPV genotype or cytology result should be referred to colposcopy directly. If colposcopic evaluation is negative, they can be discharged to primary care for a repeat HPV test in 12 months. If patients continue to be HPV positive they should be referred back to and followed in colposcopy until they are HPV negative or age 79. At age 79, if the colposcopic examination is negative, HPV positive patients can be discharged with no further need for screening.

Rationale:

As people get older, it is generally accepted that the benefits of screening begin to diminish and the risks of additional testing and intervention become higher. When developing eligibility criteria for cervical screening, one must weigh the potential benefits of screening and diagnostic tests against the harms. The natural history of cervical cancer is long, typically taking 15-20 years from HPV infection through development of cervical intraepithelial neoplasia and eventually to invasive cancer [61]. After reviewing BC data on the rates of cervical cancer in patients over the age of 79, a panel of clinicians and HPV experts agreed that screening and colposcopic evaluation should stop at the age of 79 provided there are no clinical or pathological abnormalities of the cervix. This approach is aligned with other cervical screening programs around the world.

4.6 Screening of Immunocompromised Participants

Guideline:

1. *Immunocompromised patients should initiate cervix screening with an HPV test starting at age 25 if they are or have ever been sexually active.*
2. *Immunocompromised patients who are HPV negative should be screened every 3 years with an HPV test.*
3. *Immunocompromised patients can stop screening at age 74, provided that there has been a negative HPV screening test between the ages of 69 and 74 and they are under no active surveillance of pre-cursor abnormalities.*
4. *Immunocompromised patients who are positive for HPV, regardless of genotype or cytology results, should be directly referred to colposcopy.*

The criteria for immunocompromised patients is based on BC's COVID-19 Vaccine Eligibility [62]. For the purposes of cervix screening, immunocompromised is based on the definition of moderate to severely immunocompromised, as defined in Appendix B.

Rationale:

Women who are immunosuppressed experience higher rates of HPV infections, cervical pre-cancer and cervical cancer due to impaired ability to clear HPV [63]. As a result, there is a need for increased screening and surveillance in this population.

Review of the literature as well as international guidelines was undertaken and it is recommended that screening in immunocompromised patients begin at age 25. A 3-year interval for screening is recommended and the age of screening cessation is 74. This is supported by the WHO guidelines [64].

4.7 Screening of Two-Spirit, Transgender and Gender-Diverse People

The screening strategy for Two-Spirit, transgender and gender diverse (TTGD) people is based on the anatomy present and is summarized below. See further information for supporting cervix screening for TTGD people in section 6 [65] [66].

Anatomy	Cervix Screening Recommendation
Cervix Present	• Follow the recommendations for average risk screening. Commence screening at age 25 with an HPV test and screen every five years until age 69. • Those with a prior high-grade cervical abnormality (i.e. CIN 2, CIN 3, or AIS) are recommended to follow the guidelines outlined in section 3.1.
Cervix Removed	• Individuals who have had their cervix removed and with no prior high-grade cervical abnormality (i.e. CIN 2, CIN 3, AIS) do not need to be screened. • People who have had a total hysterectomy with previous CIN 2, CIN 3 or AIS diagnosis should have a cotest on a sample from the vaginal vault at 12 months post hysterectomy. If HPV is negative and cytology is NILM, LSIL or ASCUS they can discontinue screening. If at the 12 month cotest, HPV is positive or if cytology shows ASC-H, HSIL or AGC they should be re-referred to colposcopy [36].
NeoVagina, No Cervix	• Individuals who had a vaginoplasty or surgically created vagina, screening is not recommended [67]. The ectocervix is composed of stratified squamous epithelium, whereas the endocervix is formed of columnar epithelium. Between these two kinds of epithelia, a transition zone is present, composed of metaplastic stratified squamous epithelium. The transition zone is the most common site of HPV-associated cancers. This transition zone has atypical epithelial organization where viral gene expression becomes dysregulated, resulting in precancerous alterations in cell phenotype, and ultimately in the development of invasive cancer [68]. As these patients do not have a transition zone, screening is not recommended. •

Testosterone induces genital atrophy, which can make visualizing the squamocolumnar junction and obtaining a sample more difficult. Topical local estrogen for two weeks can bring down the squamocolumnar junction and make it a more comfortable exam for the patient as well as increasing the diagnostic accuracy of cytology. HPV-based self-collection should be considered for people with difficulty obtaining provider-collected samples.

4.8 Screening of DES-Exposed Participants

Guideline:

Participants who were exposed to DES in utero should have annual colposcopic examination of both the cervix and vagina, including annual cotest (HPV and cytology testing), until age 69.

Rationale:

Diethylstilbestrol (DES) was prescribed in Canada from 1948 to 1971 to prevent miscarriage or premature birth by stimulating production of estrogen and progesterone in the placenta. In utero exposure to DES increases the risk of clear cell carcinoma of the vagina and cervix [69] [70]. In utero exposure to DES causes a significantly increased risk of clear cell adenocarcinoma of the cervix and vagina at a younger age [71] [72] [73]. There is also evidence for an increase in high-grade squamous intraepithelial lesions of the cervix [74]. Recent evidence shows that the risk of DES related malignancies are rare in those older than 50 with no cases of cervical or vaginal cancers related to DES seen after age 65 [75]. Annual colposcopy with screening by cotesting (HPV and cytology) is recommended until 69 years old.

- *Exposure to DES while pregnant:* Exposure to DES while pregnant does not appear to cause an excess of cervical and vaginal cancers and pre-cursors. Please follow routine screening recommendations.
- *Offspring of DES exposed individuals (third generation):* These individuals do not appear to have any increased risk of cervical or vaginal cancer and pre-cursors [74]. Please follow routine screening recommendations.

4.9 Screening in Pregnancy

Guideline:

Cervix screening is not necessary as a routine part of pre-natal care for those who are up to date with cervix screening, and likely to attend for regular cervix screening. Screening can be delayed until after pregnancy is complete. With the extended interval for HPV-based cervical screening (every five years) and with opportunities for self-collection, it is likely that cervix screening will be less likely to be part of routine prenatal care. However, prenatal care can still be used as an opportunity to offer screening to those who have never been screened, or are overdue and have limited contact with the health system.

Although self-collection is not contraindicated in pregnancy, BC Cancer currently recommends that screening in the prenatal setting should be a provider-collected so that both HPV and cytology can be assessed if needed. The endocervical cytobrush should not be used.

Rationale:

Approximately 5% of pregnant women will have abnormal cervical cytology [76], however the incidence of cervical cancer in pregnancy is low, ranging from 3.3 to 26 cases per 100,000 births [77] [78]. It is recommended that cervical screening using an HPV test be included in routine antenatal care in scenarios where it may be the only opportunity to engage a patient in cervix screening. This will help to increase participation and retention within the cervix screening program.

4.10 Screening after Hysterectomy

Guideline:

People who have had a total hysterectomy (i.e. cervix removed and with no past or present high-grade cervical abnormality (i.e. CIN 2, CIN 3, AIS or cervical carcinoma) can discontinue screening.

People who have had a subtotal hysterectomy with conservation of the cervix and with no past or present high-grade cervical abnormality (i.e. CIN 2, CIN 3, AIS or cervical carcinoma) should continue to follow average risk guidelines.

People who have had a total hysterectomy with previous CIN 2, CIN 3 or AIS diagnosis should have a cotest on a sample from the vaginal vault at 12 months post hysterectomy. If HPV is negative and cytology is NILM, LSIL or ASCUS they can discontinue screening. If at the 12 month cotest, HPV is positive or if cytology shows ASC-H, HSIL or AGC they should be re-referred to colposcopy [36].

Rationale:

In the absence of a history of CIN 2, CIN 3, AIS or invasive carcinoma, the risk of vaginal abnormalities or vaginal cancer is low after total hysterectomy. In a large cohort study of 10,595 vaginal smears from 6,265 people after hysterectomy, a total of 0.5% of all vaginal cytology results showed atypical squamous cells of undetermined significance, 0.5% showed low grade squamous intraepithelial lesion and 0.1% showed high grade squamous intraepithelial lesion (HSIL). Subsequent biopsies revealed high grade vaginal intraepithelial neoplasia (VAIN 2 or VAIN 3) in three instances (0.05%) and no vaginal carcinomas [79].

In contrast, the risk of invasive squamous carcinoma of the vaginal vault remains elevated for up to 20 years after treatment for CIN 2 or CIN 3 and this risk is increased, even after hysterectomy [47]. CIN 2+ prior to or at the time of total hysterectomy, is a risk factor for the development of secondary VAIN, with recurrence rates of 0.9–7.4% [80]. For this reason, these patients warrant some form of surveillance.

Similar to the development of cervical intraepithelial neoplasia and cervical cancer, the persistence of HPV is associated with VAIN and vaginal cancer with over 90% of people with VAIN testing positive for HPV [81] [82] [83] [84]. After a positive HPV test, the risk of VAIN or vaginal SCC is elevated to up to 35% in those with abnormal reflex cytology. However, after a negative cotest (negative HPV and negative cytology), the incidence of VAIN is 0.1% [85] highlighting the sensitivity of HPV testing in this scenario.

Previous BC Guidelines recommended ongoing vaginal vault cytology following a hysterectomy for those who had a previous history of CIN 2, CIN 3, AIS or invasive carcinoma, however that recommendation was made prior to the availability of HPV testing. The decision to discontinue screening after one negative cotest (HPV and cytology testing) is based on the high negative predictive value of cotesting in identifying patients at risk of recurrence as well as the rarity of vaginal cancer.

4.11 Screening after Excisional Treatment for CIN 2 or CIN 3

Guideline:

After discharge from colposcopy, the patient should undergo a cotest (HPV and cytology testing) at 12 months through a primary care provider. If HPV is negative and cytology is NILM, LSIL or ASCUS they can transition back to HPV-based screening at 3 year intervals (average risk) and 1 year interval (immunocompromised). If at the 12 month cotest, HPV is positive or if cytology shows ASC-H, HSIL or AGC they should be re-referred to colposcopy [36]*. Screening can be discontinued at age 69 (average risk) or 74 (immunocompromised) provided the patient has had a negative cotest*.

If a patient does not attend for colposcopy to obtain one cotest (HPV and cytology testing) prior to discharge, a second cotest should be completed in the community setting.

For patients who have been discharged from colposcopy and are currently undergoing annual cytology screening (first 5 years after treatment), a cotest is recommended. If HPV is negative and cytology is NILM, LSIL or ASCUS they can transition back to HPV-based screening at 3 year intervals (average risk) and 1 year interval (immunocompromised). Patients who have completed annual cytology for 5 years can transition to HPV based screening at 3 year intervals (average risk) and 1 year interval (immunocompromised), no cotest required.

Rationale:
In patients who have been treated for a CIN 2 or CIN 3 the risk of recurrence and of invasive cervical cancer remains elevated for up to 25 years [86] [87]. This highlights the importance of increased surveillance post-treatment in order to identify residual or recurrent disease.

Studies have looked at the risk of recurrent CIN 2 or worse following treatment. Katki et al. estimated the 5-year risk of recurrent CIN 2 or worse following two negative cotests was 1.5% [95% CI: 0.3 to 7.2] [61]. A second study found the 5-year cumulative risk of CIN 2 or worse was 1.0 (0.2–4.6) and of CIN 3 or worse was 0.0 (0.0–2.9) following a negative cotest at 6 and 24 months [88]. Review of the literature shows that two negative cotests (HPV and cytology testing) identifies people with the lowest five-year risk of HSIL recurrence. Based on this, patients who have been treated for CIN 2 or CIN 3 and have been discharged from colposcopy should have a cotest (HPV and cytology testing) at 12 months. If HPV is positive or if cytology shows ASC-H, HSIL or AGC they should be re-referred to colposcopy [36]. If the cotest (HPV and cytology testing) is negative, patients can return to routine screening every 3 years. Screening for HPV negative patients can be discontinued at age 69 (average risk) or 74 (immunocompromised).

4.12 Screening after Excisional Treatment for Endocervical Adenocarcinoma in Situ (AIS)

Guideline:
After discharge from colposcopy, the patient should undergo a cotest (HPV and cytology testing) at 12 months through a primary care provider. If HPV is negative and cytology is NILM, LSIL or ASCUS they continue with cotesting (HPV and cytology testing) at 3 year intervals (not immunocompromised) and 1 year interval (immunocompromised). If at any cotest, HPV is positive (any genotype) or if cytology shows ASC-H, HSIL or AGC they should be re-referred to colposcopy [36]*. Screening can be discontinued at age 69 (not immunocompromised) or 74 (immunocompromised) provided the patient has had a negative cotest*.

Rationale:
There are no randomized or pseudorandomized controlled trials to guide management decisions after treatment for AIS. Cohort studies report a risk of recurrent AIS or progression to invasive, or micro invasive adenocarcinoma in 12% to 40% of patients [89] [90]. The best predictors of risk were, completeness of excision and HPV status [89] [90]. Patients should continue with colposcopy follow up unless the AIS has been excised with clear margins and the post treatment HPV test is negative.

HPV status is highly predictive of recurrent AIS [90] [91]. A study by Costa et al. found that HPV testing predicted persistence/clearance of AIS at 6-month post treatment follow up [90]. In this study, cotest (HPV and cytology testing) had a negative predictive value of 88.9% at 6 months and 100% at 12 months.

HPV testing and cytology testing independently assist in the detection of recurrent AIS however cotesting (HPV and cytology testing) appears to be more sensitive. A study that provided data on the performance

of HPV and cytology tests in AIS detection found that of 118 patients diagnosed with AIS , 78% of patients were HPV-positive and had high-grade cytology results, 12.75% were HPV-positive and had normal cytology results and 9.3% of patients were HPV-negative and had high-grade cytology results [92]. The results of this study suggests that cotesting (HPV and cytology testing) improves the detection of AIS and cervical cancer compared to HPV testing or cytology testing alone. For this reason, the Cervix Screening Program recommends cotesting every 3 years for the follow up of patients with AIS treated with an excisional procedure.

The data on the need for long-term follow up are sparse. In the absence of safety data for stopping screening we recommend HPV cotesting (HPV and cytology testing) until age 69 (74 for immunocompromised). The need for ongoing screening should be considered in conjunction with the overall medical condition of the patient.

4.13 Screening after Cervical Cancer Treated with Surgery or Radiation

Guideline:

The patient's colposcopist or oncologist is responsible for outlining the post-treatment follow-up of a patient diagnosed with cervical cancer for the first 5 years. Once discharged from the care of the colposcopist/ oncologist, the patient's follow up is no longer within the purview of the screening program as this patient is now undergoing surveillance for recurrence as opposed to screening for a new diagnosis.

Rationale:

Studies evaluating the use of HR-HPV testing for the detection of recurrent disease are sparse with most recommendations made through expert opinion. In individuals treated for cervical cancer with radiation, vaginal cytology should not be performed, as radiation will induce changes to the tissue that make cytology unreliable [93]. Aryasomayajula looked at the whether the presence of hr-HPV infection after cervical cancer treatment is associated with recurrent disease and found that positive hr-HPV testing in the surveillance setting was not associated with cervical cancer recurrence but did lead to additional studies and procedures. Their findings do not support the routine use of hr-HPV testing for the evaluation of cervical cancer recurrence [94].

Taking a thorough history, performing a thorough examination including a pelvic exam, and educating survivors about concerning symptoms are the most effective methods for the detection of cervical cancer recurrence. A systematic review found that 89 to 99% of local recurrences of cervical cancer after curative intent treatment occurred in the first five years [95] and as a result, this is a critical time for enhanced surveillance. There is currently no evidence that routine cytology or HPV testing improves the ability to detect cervical cancer recurrences that will impact cure or response rates to salvage therapy [96].

For patients who have not had their entire cervix removed as part of their cancer treatment, it is reasonable to follow the recommendations from section 4.11 and perform an HPV test every 3 years after discharge from the oncologist. Patients who have had a hysterectomy do not require HPV testing, and patients who have had radiation should not have HPV testing performed.

Please note, once a patient has a cervical cancer diagnosis, they will no longer be recalled as part of BC's Cervix Screening Program. Please ensure that your patient receives the appropriate follow up. Refer to follow up recommendations as laid out by BC Cancer's Gynecology Tumor Group.

4.14 Cervical Evaluation in those Exhibiting Signs and Symptoms of Cervical Cancer

Cervix screening is only appropriate for those who are age eligible and asymptomatic.

People who have symptoms, including post coital bleeding, persistent abnormal bleeding and/or a persistent vaginal discharge that cannot be explained by benign causes, such as infection, should have a speculum examination by someone with experience in gynecologic exam. If any suspicious abnormality is noticed during speculum examination, a referral should be made for colposcopic evaluation. Referral to a Colposcopist is appropriate and may be expedited if the clinical suspicion is high. A screening test is not required for referral. If a test is performed, a cotest (HPV and cytology testing) is the recommended test as the presence of blood can increase the false negative rate of an HPV test. HPV self-screening is not appropriate in this scenario.,

Cotest (HPV and cytology testing) results are not required for referral and referral should not be delayed pending results.

Contact bleeding at the time of sample collection, in the absence of other concerning symptoms need not be referred [97].

4.15 Unscheduled Screening

Unless a person is otherwise due for screening, a screening test should not be collected in association with pregnancy (pre- or postpartum), when an intrauterine device is placed or removed, or when oral contraceptive is initiated.

Health care providers play a vital role to prevent over-screening which may lead to screening related harms. There is no reason to commence screening earlier or to screen more frequently as a result of diagnosis of genital warts, multiple sexual partners, new sexual partners, heavy smoking or hormone replacement therapy (HRT).

Patients with symptoms or abnormal appearance of the cervix should be referred to a colposcopy clinic for evaluation. A cotest (HPV and cytology testing) is not required and referral to colposcopy should be arranged as soon as possible, regardless of any test result, see section 4.14.

4.16 Withdrawal from Screening

The decision to participate in cervix screening is an informed choice and participants may choose to voluntarily discontinue screening. Apart from informed personal choice, there may be appropriate medical reasons to discontinue screening, such as severe illness that renders screening of limited or no additional health benefit, severe discomfort and or anatomic impediment to obtaining a satisfactory sample. In the latter instance, a gynecological referral to directly view the cervix and/or to obtain a screening sample should be offered.

It is important to make sure that screening participants are offered the opportunity to be informed of the benefits of screening and the risk of cervical cancer, before the decision is made to discontinue screening.

5. Cervix Screening Results

5.1 Result Reports

Self-screening samples can only be tested for HPV. A single result laboratory report will be issued.

Provider-collected samples will be triaged to either primary HPV testing or primary cytology depending on the clinical history of the patient and the age of the patient at the time of screening. Negative screening results will be issued as a single result laboratory report. Patient samples with positive screen test results will be reflexed by the laboratory to the alternate test and both cytology and HPV results will be reported.

Please refer to the CCSL website and documentation for further information regarding reporting format and terminology. Please contact CCSL for any laboratory report questions or concerns [5].

See Appendix A for the screening triage and follow-up algorithm.

5.2 Rejected, Unsatisfactory and Invalid

Unless a cotest (HPV and cytology testing) was recommended for the patient, if the Cervix Screening Program receives a rejected or unsuitable for testing result from the laboratory, the patient will automatically be sent a self-screening kit to repeat screening. If a cotest (HPV and cytology testing) was recommended, the patient will be sent a result letter indicating that repeat testing is required and to book an appointment with a provider for a Pap test.

5.2.1 Rejected Samples

In accordance with international accreditation standards, CCSL has strict specimen labeling requirements and will not process specimens if specimen identification cannot be confirmed or lacks at least two patient identifiers. Samples that are received by the lab that cannot be tested will be rejected and information will be provided in the report regarding the reason for the sample being unsuitable for testing. Samples which are inadequate for interpretation due to poor preservation or obscuring elements will be reported as unsatisfactory for interpretation and should be repeated as soon as possible.

Unless a cotest (HPV and cytology testing) was recommended for the patient, the Cervix Screening Program will automatically send a self-screening kit to the patient to repeat screening if a rejected or unsuitable for testing result is received from the laboratory – regardless of whether the reject/unsuitable test was provider-collected or self-screening. If a cotest (HPV and cytology testing) was previously recommended, the patient will be sent a result letter indicating that repeat testing is required and to book an appointment with a provider for a Pap test.

5.2.2 Unsatisfactory Cytology Results

Samples which are inadequate for interpretation due to inadequate cellularity, poor preservation or obscuring elements will be reported as unsatisfactory for interpretation and should be repeated.

5.2.3 Invalid HPV Test Results

The HPV assay utilizes human beta-globin DNA as an internal control to confirm sample adequacy and monitor sample preparation and polymerase chain reaction (PCR) processes. Invalid HPV tests are most commonly due to insufficient sampling indicated by an absence of beta-globin but may also rarely

indicate a test process or interference error. For patients that have 2 invalid self-screening HPV test results, a provider collected sample is recommended with the aim of obtaining a successful screen. Patients who continue to have an invalid result with 3 separate tests, regardless of collection method, will be referred to colposcopy.

5.3 COTESTING (HPV AND CYTOLOGY TESTING)

The following patients are recommended for cotesting (HPV and cytology testing). If cotesting has been recommended, both cytology and HPV testing will be completed on the sample.

- Post CIN 2 or CIN 3 excisional treatment and discharged from colposcopy, patient should have 1 negative cotest prior to returning to HPV screening every 3 years
- Post AIS excisional treatment and discharged from colposcopy, patient should have a cotest every 3 years until age 69
- Post AIS excisional treatment and immunocompromised and discharged from colposcopy, patient should have a cotest every year until age 74
- Post total hysterectomy and a history of CIN 2, CIN 3 or AIS, patient should have a negative cotest prior to discontinuing cervix screening

5.3.1 HPV Positive for any high risk types

Since the presence of HPV can signal a significant risk for CIN 2, CIN 3, AIS and cancer, immediate colposcopy referral is recommended regardless of the result of cytology.

5.3.2 HPV Negative and Cytology ASCUS or LSIL

5.3.2.1 Average risk

HPV screening in 5 years.

5.3.2.2 History of CIN 2 or CIN 3

HPV screening in 3 years.

If the patient is immunocompromised, repeat HPV screening in 1 year.

5.3.2.3 History of AIS

Cotest (HPV and cytology testing) in 3 years.

If the patient is immunocompromised, cotest (HPV and cytology testing) in 12 months.

5.3.3 HPV Negative and Cytology High Grade or Glandular

Colposcopy is recommended.

5.4 HPV PRIMARY SCREENING

5.4.1 Negative for HPV

Primary screening test results reported as negative for HPV would generally receive a recommendation to repeat cervix screening in 5 years. Shorter screening intervals are recommended for individuals who are immunocompromised, in active follow-up after a previous HPV other positive test but normal or low

grade cytology result and after treatment for CIN 2, CIN 3 or AIS. Provider-collected samples triaged to HPV primary screening and reported as negative will not have cytology testing performed.

5.4.2 Positive for HPV Types 16 and/or 18

Since the presence of HPV types 16 and/or 18 signal a significant risk for CIN 2, CIN 3, AIS and cancer, immediate colposcopy referral is recommended regardless of the result of cytology. If screening was by provider-collected sample, a cytological evaluation and report will also be performed by the CCSL. This cytology result will not influence the colposcopy referral recommendation but may aid the colposcopist's management decisions. If the screening test was obtained by self-sampling, the colposcopist will collect a cytology sample at the time of colposcopy to aid with follow-up management decisions.

5.4.3 Positive for HPV Types Other than 16 and/or 18

Unless immunocompromised, over age 69 or 12 month follow-up HPV testing for persistent infection, patients with HPV other high risk positive screening test results will require cytology triage to determine if colposcopy is recommended.

For average risk patients:

5.4.3.1 Cytology Results Unknown or Unsatisfactory.

Patients who participated in self-screening and those who had a provider-collected samples where cytology was unsatisfactory will be recommended to see a provider for a follow-up Pap test to obtain a cytology result.

A provider-collected sample should be obtained within 6 weeks of the HPV Other positive test result.

If repeated cervical cytology samples are reported as unsatisfactory on two different occasions, colposcopy referral is recommended.

5.4.3.1 Cytology Negative for Intraepithelial Lesion or Malignancy (NILM), ASCUS or LSIL.

When the results are positive for high risk HPV types other than 16 and/or 18 and there is a NILM, ASCUS or LSIL cytology interpretation, a follow-up HPV test is recommended in 12 months to see if the HPV infection persists.

A self-screening HPV test will be sent to the patient for their 12 month follow-up HPV test.

Patients who test negative at the 12 month follow-up HPV test can return to their regular screening interval (e.g every 5 years for average risk or every 3 years for those who are immunocompromised). Patients who are persistently positive at 12 months are recommended for colposcopy. If the HPV sample is a provider-collected sample, a cytology interpretation will be added to the report by the CCSL. The cytology interpretation will not influence the colposcopy referral decision but may be used by the colposcopist to guide follow up. If the screening test was obtained by self-sampling, the colposcopist will collect a cytology sample at the time of colposcopy to aid with follow-up management decisions.

It is important to allow 12 months from initial positive HPV test result to determine the persistence of an HPV infection. A positive follow-up HPV tests result completed too early will need to be repeated at 12 months after the initial HPV positive test result.

5.4.3.2 Cytology High Grade or Glandular

When the results are positive for high risk HPV types other than 16 and/or 18 and there is a high grade cytology result, colposcopy is recommended. If the HPV sample is a provider-collected sample, a cytology interpretation will be added to the report by the CCSL. The cytology interpretation will not influence the colposcopy referral decision but may be used by the colposcopist to guide follow up. If the screening test was obtained by self-sampling, the colposcopist will collect a cytology sample at the time of colposcopy to aid with follow-up management decisions. High grade cytology results are:

- Atypical Squamous Cells Cannot Exclude High Grade Lesion (ASC-H),
- High-Grade Squamous Intraepithelial Lesion (HSIL), moderate dysplasia
- High-Grade Squamous Intraepithelial Lesion (HSIL), severe dysplasia
- Atypical Glandular Cells other Otherwise Specified (AGC-NOS)
- Atypical Endocervical Glandular Cells Not Otherwise Specified (AGC EC-NOS).
- Atypical Endocervical Glandular Cells Favour Neoplasia (AGC –FN) and Endocervical Adenocarcinoma In Situ (AIS)
- Potential Invasive Squamous Cell Carcinoma and Potential Endocervical Adenocarcinoma
- Atypical Endometrial Cells, Not otherwise specified
- Atypical Endometrial Cells, Favour Neoplastic
- Endometrial adenocarcinoma
- Atypical Glandular Cells, Favour Neoplastic
- Adenocarcinoma, Not otherwise specified
- Other Malignant Neoplasms

5.5 CYTOLOGY PRIMARY SCREENING

5.5.1 Negative for Intraepithelial Lesions or Malignancy

Primary cytology screening test results with an interpretation of NILM will not have reflex HPV testing performed and generally receive a recommendation to re-screening 3 years. Shorter screening intervals are recommended for individuals who are immunocompromised and after treatment for CIN 2, CIN 3 or AIS.

5.5.2 Low Grade Cytology Results

Primary cytology screening tests with low grade cytology results (e.g. Atypical Squamous Cells of Uncertain significance (ASCUS) and low grade squamous intraepithelial lesion (LSIL)) will have HPV testing performed.

5.5.2.1 HPV Negative

Patients with a low grade cytology result who are HPV negative would generally receive a recommendation to repeat cervix screening in 5 years. Shorter screening intervals are recommended for individuals with immunosuppression or a history of CIN 2, CIN 3 or AIS.

5.5.2.2 HPV Positive for high risk types 16 and/or 18

Since the presence of HPV types 16 and/or 18 signal a significant risk for CIN 2, CIN 3, AIS and cancer, immediate colposcopy referral is recommended. The cytology result will not influence the colposcopy referral recommendation but may aid in the colposcopist's management decisions.

5.5.2.3 HPV Positive for high risk types other than 16 and/or 18

See section 5.4.1.

5.5.2.4 Invalid HPV Test

HPV testing is recommended. The patient will be sent a self-screening kit to complete screening. In lieu of self-screening, a provider-collected sample can also be completed.

5.5.3 Cytology High Grade or Glandular

Colposcopy is recommended. Primary cytology screening tests with high grade cytology results will have HPV testing performed. The HPV test result will not influence the colposcopy referral recommendation but may aid with the colposcopist's management decisions. High grade cytology results are:

- Atypical Squamous Cells Cannot Exclude High Grade Lesion (ASC-H),
- High-Grade Squamous Intraepithelial Lesion (HSIL), moderate dysplasia
- High-Grade Squamous Intraepithelial Lesion (HSIL), severe dysplasia
- Atypical Glandular Cells other Otherwise Specified (AGC-NOS)
- Atypical Endocervical Glandular Cells Not Otherwise Specified (AGC EC-NOS).
- Atypical Endocervical Glandular Cells Favour Neoplasia (AGC –FN) and Endocervical Adenocarcinoma In Situ (AIS)
- Potential Invasive Squamous Cell Carcinoma and Potential Endocervical Adenocarcinoma
- Atypical Endometrial Cells, Not otherwise specified
- Atypical Endometrial Cells, Favour Neoplastic
- Endometrial adenocarcinoma
- Atypical Glandular Cells, Favour Neoplastic
- Adenocarcinoma, Not otherwise specified
- Other Malignant Neoplasms

5.5.4 Other Primary Screening Cytology Results

5.5.4.1 Benign Endometrial Cells in Cervical Samples

Benign endometrial cells may be identified in cytology samples collected from participants who are HPV positive. Benign endometrial cells are a normal finding in the first half of the menstrual cycle. Finding benign appearing endometrial cells in the second half of the menstrual cycle may indicate dysfunctional endometrial bleeding, especially if accompanied by abnormal bleeding. Endometrial carcinoma is rare before the age of 45 years, as such; endometrial biopsy or referral for further investigation is generally reserved for those over the 45 years of age. ***The need for referral should be based on a general assessment of endometrial carcinoma risk inclusive of cytological findings and clinical signs and symptoms. Cervical cytology examination has poor sensitivity for endometrial carcinoma and should not be used as a screening test to either rule in or rule out an endometrial abnormality.***

5.5.4.2 Atypical Endometrial Cells or Endometrial Carcinoma

Atypical Endometrial cells or endometrial carcinoma may be identified in in cytology samples collected from participants who are HPV positive.

Patients with these findings should be referred to colposcopy or a general gynecologist for further evaluation which should include an endometrial biopsy. Cervical cytology examination has poor sensitivity

for endometrial carcinoma and should not be used as a screening test to either rule in or rule out an endometrial abnormality.

5.5.4.3 Possible Extrauterine Carcinoma or Rare Malignancies

Features of possible extrauterine carcinoma or rare malignancies may be identified in cytology samples collected from participants who are HPV positive.

These should be dealt with on a case-by-case basis and may need a multidisciplinary team approach for management. Contact the Cervical Cancer Screening Laboratory for clarification of the results if needed.

6. Underserved and Vulnerable Populations

Participation in cervix screening is not evenly distributed across populations or cultures. There are known populations that are less likely to screen and keep up-to-date with screening. Factors contributing to the inequity in care are multifactorial and barriers are both personal and systemic. Within a primary care practice, these populations may need additional services and support to be safely encouraged to participate in screening. Conversations with patients and community service providers who regularly support these populations are needed to assess barriers and determine what approach may be required to engage and support the person for regular screening. Cervix screening rates are known or suspected to be lower for the following populations [98] [99] [100] [101] [102] [103] [104]:

- Low-income
- Immigrant
- Indigenous (First Nations, Métis and Inuit)
- Transgender, gender diverse and non-binary
- Not attached to a primary care provider
- Rural and remote communities
- Those less familiar with the BC Health Care System
- Those who do not speak the language in which service information is available
- History of trauma and/or violence

In BC, cervical cancer incidence is higher amongst First Nations people compared to the non-First Nations population [22] [104].

Some people may prefer a female provider to complete their screening. The Cervix Screening Program maintains a list of providers across BC who are willing to see people for cervix screening and includes information on language spoken at the clinic and whether a female provider is available. Ongoing follow-up and care can continue with a person's usual provider. See the Clinic Locator at www.screeningbc.ca.

For transgender, gender-diverse and non-binary people, Trans Care BC has developed several educational resources for providers and patients and are an excellent source for guidance and advice for these populations in BC Resources include a document for sexual health screening and pelvic exam.

The current trend is an increasing role for the primary care provider in the health care of trans people, rather than solely specialist care. This will be facilitated by familiarity with the below terminology, and adoption of pronouns and names used by the patient, which may differ from their identification and medical chart. Provider knowledge of gender-affirming terminology and language can contribute to greater access to services, increased uptake in screening and better health outcomes for trans and gender diverse individuals. Cervix self-screening was well supported and accepted by many TTGD people during the BC Cervix Self-Screening Pilot.

For more information, please visit Trans Care BC: www.phsa.ca/transcarebc

Definitions	
Transgender	People who identify with a gender that is different from the sex they were assigned at birth.
Cisgender	People who have a gender identify that matches the sex they were assigned at birth.
Non-binary	An umbrella term to refer to diverse people whose gender identify is neither male or female.
Gender diverse	Gender roles and/or gender expression that do not match social and cultural expectations; gender non-conforming; gender variant.
Two-Spirit	A term used within some Indigenous communities, encompassing cultural, spiritual, sexual and gender identity.

7. Overview Table

Summary Screening Recommendations	
Age to Start Screening	• Initiate screening at age 25. Cervical screening is not recommended for those over age 25 who have never been sexually active.
Cessation of Cervical Screening	• **Average Risk:** Stop screening at age 69, provided that there has been a negative HPV screening test between the ages of 65 and 69 and under no active surveillance of pre-cursor abnormalities. • **Immunocompromised:** Stop screening at age 74 provided there has been a negative HPV screening test between the ages of 65 and 69 and under no active surveillance of pre-cursor abnormalities. • Those who have been discharged from colposcopy, but have not yet completed the post discharge 12 month cotest (HPV and cytology testing) before age 69 (average risk) or 74 (immunocompromised), should continue with screening until they have had a negative cotest. After this, screening can be discontinued.
Management of Those over age 69 with HPV Positive Results	• Refer to colposcopy directly. • If colposcopic evaluation is negative, discharge to primary care for a repeat HPV test in 12 months. If patients continue to be HPV positive, refer back to and follow in colposcopy until HPV negative or aged 79. • At age 79 and the colposcopic examination is negative, HPV positive patients can be discharged with no further need for screening.

Screening of Immunosuppressed	• Immunosuppressed patients to initiate cervix screening with an HPV test starting at age 25 if they are or have ever been sexually active. • Immunosuppressed patients who are HPV negative to screen every 3 years with an HPV test. • Immunosuppressed patients can stop screening at age 74, provided that there has been a negative HPV screening test between the ages of 69 and 74 and they are under no active surveillance of pre-cursor abnormalities. • Immunosuppressed patients who are positive for high risk HPV, regardless of genotype or cytology results, refer directly to colposcopy.
Screening of Transgender, Gender-Diverse and Non-Binary People	Cervix Present • Follow the recommendations for average risk screening for cervix screening. Cervix Removed • No prior CIN 2, CIN 3 or AIS, cervix screening not recommended. People who have had a total hysterectomy with history of CIN 2, CIN 3 or AIS should have a cotest (HPV and cytology testing) on a sample from the vaginal vault at 12 months post hysterectomy. Any positive HPV test or a high grade or glandular cytology result should be referred directly to colposcopy. After a negative cotest, screening can be discontinued. Neovagina, No Cervix • Individuals who had a vaginoplasty or surgically created vagina, screening is not recommended.
Screening of DES-Exposed Patients	• Annual colposcopic examination of both the cervix and vagina with cotest (HPV and cytology testing) is recommended until age 69.

Screening in Pregnancy	• Screening is not necessary as a routine part of pre-natal screening for those who are up to date with screening. Screening can be delayed in patients who are expected to continue to engage with the health system until they are postpartum. • Provider-collected cervix screening can be offered during pregnancy if screening is due or overdue. • Use prenatal care as an opportunity to engage under or never screened patients in the screening program.
Screening after Hysterectomy	• People who had a total hysterectomy (i.e. cervix removed and with no past or present high-grade cervical abnormality (i.e. CIN 2, CIN 3, AIS or cervical carcinoma) can discontinue screening. • People who had a subtotal hysterectomy with conservation of the cervix and with no past or present high-grade cervical abnormality (i.e. CIN 2, CIN 3, AIS or cervical carcinoma) should continue to follow average risk guidelines. • People who have had a total hysterectomy with current or past high-grade cervical abnormality (i.e. CIN 2, CIN 3 or AIS) should have a cotest (HPV and cytology testing) on a sample from the vaginal vault at 12 months post hysterectomy. Any positive HPV test or if cytology shows ASC-H, HSIL or AGC, refer to colposcopy. If HPV is negative and cytology is NILM, ASCUS or LSIL, screening can be discontinued.
Screening after Excisional Treatment for High Grade Cervical Intraepithelial Neoplasia (CIN)	• After discharge from colposcopy, cotest (HPV and cytology testing) at 12 months through their primary care provider. • If HPV is negative and cytology is NILM, ASCUS or LSIL they can transition back to routine HPV-based screening at 3 year intervals (average risk) or 1 year interval (immunocompromised). • If at the 12 months cotest (HPV and cytology testing), high risk HPV is positive or if cytology shows ASC-H, HSIL or AGC, re-refer to colposcopy. • Screening can be discontinued at age 69 (average risk) or 74 (immunocompromised) provided the patient has had a negative cotest (HPV and cytology testing) and they are under no active surveillance of pre-cursor abnormalities.

Screening after Excisional Treatment for Endocervical Adenocarcinoma in Situ (AIS)	• After discharge from colposcopy, cotest (HPV and cytology testing) at 12 months through their primary care provider. • If HPV is negative and cytology is NILM, ASCUS or LSIL they can transition back to a cotest (HPV and cytology testing) at 3 year intervals (average risk) or 1 year interval (immunocompromised). • If High risk HPV is positive or if cytology shows ASC-H, HSIL or AGC, re-refer to colposcopy. • Screening for HPV negative patients can be discontinued at age 69 (average risk) or 74 (immunocompromised) provided that there has been a negative cotest (HPV and cytology testing) at last screen, and they are under no active surveillance of pre-cursor abnormalities.
Screening after Cervical Cancer Treated with Surgery or Radiation	• The patient's colposcopist or oncologist is responsible for outlining the post-treatment follow-up of a patient diagnosed with cervical cancer for the first 5 years. • Once discharged from the care of the colposcopist/oncologist, screening is no longer recommended. Ongoing surveillance for recurrence by someone experienced in cervical disease is recommended.
Cervical Evaluation in Those Exhibiting Signs and Symptoms of Cervical Cancer	• Cervix screening is only appropriate for those who are age eligible and asymptomatic. • People with symptoms eg. post coital bleeding, abnormal bleeding and/or a persistent vaginal discharge should have a speculum examination by someone with experience in gynecologic exams. • Providers can perform a cotest (HPV and cytology testing) and referral to a colposcopist is appropriate and may be expedited if the clinical suspicion is high. • A cotest (HPV and cytology testing) is not required for referral and referral should not be delayed pending results of the cotest.

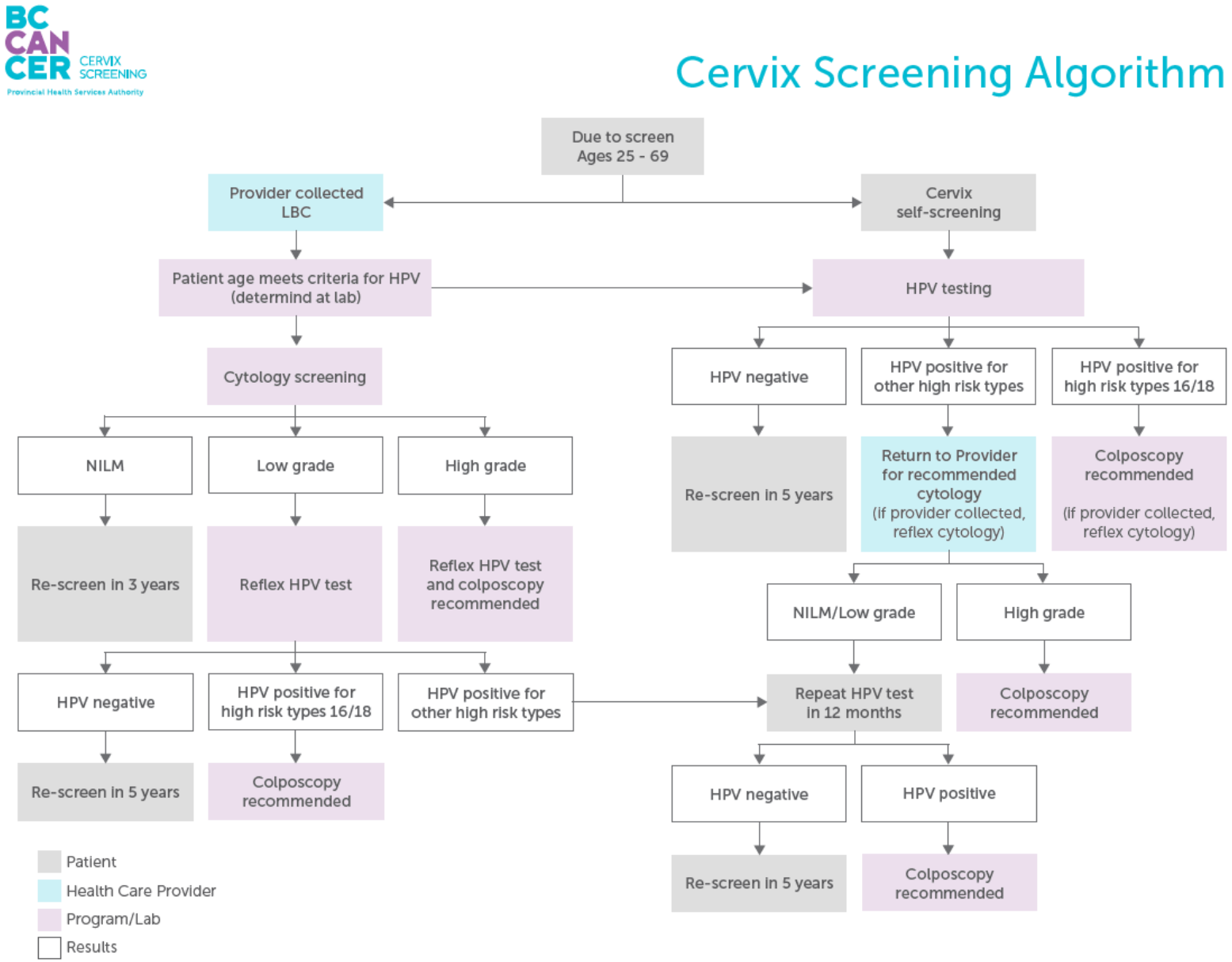
Cervix Screening Results	
HPV Invalid	• Repeat HPV testing. Unless a cotest (HPV and cytology testing) was recommended, a self-screening test will be sent to the patient at the time of the invalid result notification. • For patients that have 2 invalid self-screening HPV test results, a provider collected sample is recommended with the aim of obtaining a successful screen. • Patients who continue to have an invalid result with 3 separate tests, regardless of collection method, will be referred to colposcopy.
Rejected Samples	• CCSL will reject and will not process specimens if specimen identification cannot be confirmed. • Unless a cotest (HPV and cytology testing) was recommended, a self-screening test will be sent to the patient at the time of the invalid result notification.
Unsatisfactory Samples	• Samples which are inadequate for interpretation due to poor preservation or obscuring elements. • Unless a cotest (HPV and cytology testing) was recommended, a self-screening test will be sent to the patient at the time of the invalid result notification.
High Risk HPV Negative	• Repeat cervical screening in 5 years. • Shorter screening interval recommendation for immunocompromised patients and after treatment for CIN 2, CIN 3 or AIS.
High Risk HPV 16/18 Positive	• Refer to colposcopy. • If screening is performed with a provider-collected sample, the CCSL will perform a cytological evaluation to aid in the colposcopist's decision. • If screening is performed by self-sampling, colposcopist will collect a cytology sample to aid with management decisions.
High Risk HPV Other Positive with ASC-H, HSIL or AGC Cytology	• Refer to colposcopy.

High Risk HPV Other Positive with Unknown or Unsatisfactory Cytology Result	• Follow-up cervical screening with primary care provider. • If cytology samples are reported as unsatisfactory on two different occasions, colposcopy referral is recommended.
High Risk HPV Other Positive with Cytology Negative (NILM), ASCUS or LSIL	• Repeat HPV in 12 months. • If repeat HPV test is negative, return to routine screening (e.g. every 5 years for average risk patients). • If repeat HPV test is positive for any HPV type; refer to colposcopy. o If screening is performed with a provider-collected sample, the CCSL will perform a cytological evaluation to aid with colposcopist's decision. o If screening is performed by self-screening, colposcopist will collect a cytology sample at the time of colposcopy to aid with management decisions.
ASCUS and LSIL	• Pap test will be triaged by reflex HPV testing. o If HPV test is positive for HPV other than 16 or 18; HPV testing is recommended in 12 months. o If HPV test is positive for HPV 16 or 18; colposcopy referral is recommended. o If HPV test is negative; return to routine screening (e.g. every 5 years for average risk patients).
ASC-H, HSIL, Moderate Dysplasia and Severe Dysplasia	• Refer to colposcopy.
Atypical Glandular Cells	• Refer to colposcopy.
Benign Endometrial Cells in Cervical Sample	• Cervical cytology examination has poor sensitivity for endometrial carcinoma and should not be used as a screening test to either rule in or rule out an endometrial abnormality.
Atypical Endometrial Cells or Endometrial Carcinoma	• Refer to colposcopy or a general gynecologist for further evaluation which should include an endometrial biopsy.

Possible Extrauterine Carcinoma or Rare Malignancies	• Features of possible extrauterine carcinoma or rare malignancies may be identified in cytology samples collected from participants who are HPV positive. • These should be dealt with on a case-by-case basis and may need a multidisciplinary team approach for management. Contact the CCSL for clarification of the results if needed.

8. Appendix

8.1 Appendix A



8.2 APPENDIX B: CRITERIA FOR IMMUNOSUPPRESSED

BC Centre for Disease Control, Communicable Disease Control Manual, Chapter 2: Immunizations, http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%202%20-%20Imms/Part4/COVID-19-vaccine-eligibility.pdf [62].

BC Centre for Disease Control
Provincial Health Services Authority

COVID-19 Vaccine Eligibility

Appendices

Appendix A

For those 12 years of age and older, moderately to severely immunosuppressed includes those who:

- Have had a solid organ transplant and are taking immunosuppressive therapy (heart, lung, liver, kidney, pancreas or islet cells, bowel or combination organ transplant).
- Will have, are having, or are on active treatment for solid tumour or haematologic malignancies (like myeloma or leukemia):
  - Will have, are having, or in the last 12 months have received systemic treatment for a haematological malignancy, or in the last 24 months have received anti-CD20 or other B-cell depleting therapies for a haematological malignancy.
  - Will have, are having, or in the last 24 months have had a bone marrow, stem cell transplant or CAR-T [G] or who are still taking immunosuppressive drugs.
  - Will have, are having, or in the last 6 months have received anti-cancer systemic therapy for solid tumours (including but not limited to cytotoxic chemotherapy; molecular targeted therapy; immunotherapy; monoclonal antibodies; bone modifying agents used in the setting of metastatic disease; high dose steroids e.g., equivalent to > 20 mg/day for more than 1 month but excluding patients only receiving hormonal or bone modifying therapy in the adjuvant setting).
  - Are planned for radiation, are having or will have had radiation in the last 3 months.
  - Have a diagnosis of CLL/SLL, myeloma/plasmacytoma, or low grade lymphoma.
- Prior AIDS defining illness or prior CD4 count ≤ 200/mm³ or prior CD4 fraction ≤ 15% or any detectable plasma viral load since January 2021 or HIV infection and ≥ 65 years old or perinatally acquired HIV infection.
- Are on active treatment with the following categories of immunosuppressive therapies:
  - In the last 2 years, been treated with anti-CD20 agents, B-cell depleting agents or similar therapeutic agents.
  - In the last 3 months, been treated with biologic agents that are significantly immunosuppresive, oral immune-suppressing drugs, steroids (orally or by injection >14 days), immune-suppressing infusions/injections or intermittent high dose steroids administered as immune suppression prior to intravenous enzyme replacement treatment.
- Have combined immune deficiencies affecting T-cells, immune dysregulation (particularly familial hemophagocytic lymphohistiocytosis) or those with type 1 interferon defects (caused by a genetic primary immunodeficiency disorder or secondary to anti-interferon autoantibodies).
- Have a moderate to severe primary immunodeficiency which has been diagnosed by an adult or pediatric immunologist and requires ongoing immunoglobulin replacement therapy (IVIG or SCIG) or the primary immunodeficiency has a confirmed genetic cause (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- On dialysis (hemodialysis or peritoneal dialysis) or have stage 5 chronic kidney disease (eGFR <15 mL/min) or have glomerulonephritis and receiving steroid treatment.

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