CANADIAN PARTNERSHIP AGAINST CANCER

Cervical Cancer:

HPV PRIMARY SCREENING AND ABNORMAL SCREEN FOLLOW-UP ENVIRONMENTAL SCAN

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This environmental scan is a component of the Canadian Partnership Against Cancer's broader efforts toward bringing greater equity and accessibility to cervical cancer prevention, screening, treatment and care. This resource amongst others provides a base of evidence to support addressing the priorities, targets and actions set out in the Action Plan for the Elimination of Cervical Cancer in Canada (2020-2030), which engages partners across the country in work to eliminate cervical cancer by 2040. The Action Plan and associated knowledge products, including this environmental scan, advance a top priority of the Canadian Strategy for Cancer Control 2019-2029 (the Strategy), which is to decrease the risk of people getting cancer, including cervical cancer. The Strategy is a 10-year roadmap to improve equity in the cancer system and to deliver world-class cancer care to everyone in Canada, while focusing on a sustainable health care system for the future.

Executive Summary

INTRODUCTION

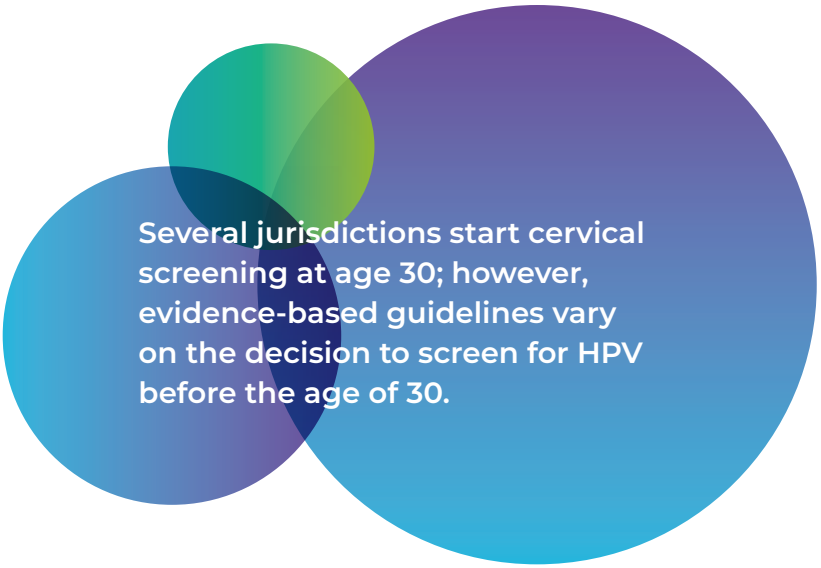
Cervical cancer screening programs have the opportunity to embrace a screening approach that is expected to help eliminate cervical cancer in our lifetime.[1] Advances in technology and understanding have established the link between Human Papillomavirus (HPV) and cervical cancer and enabled the development of effective tests to screen for the presence of HPV. In this new paradigm, HPV primary screening identifies cervical pre-cancer earlier and results in a significantly lower likelihood of cervical cancer compared to screening with the Pap test, the current primary method for cervical cancer screening in *Canada*.[2] HPV testing improves cervical cancer outcomes and also allows other cervical screening enablers to work, such as self-sampling that improves access to screening but cannot be done with the Pap test.

The evidence for transitioning to HPV primary screening has continued to advance in the last few years and countries have started to implement this new approach. The *Netherlands* and *Australia* implemented it nationwide in 2017 while the *United Kingdom (UK)* finished implementation in 2020. While the scientific evidence for the effectiveness of HPV primary screening is established, the first countries to implement faced unknowns about what impacts HPV primary screening would have on the health system, which screening processes would be effective, and what challenges they would face in implementation. Today, learnings from other countries that have implemented HPV primary screening are available to enable successful implementation in *Canada*.

This environmental scan focuses on learnings from other countries about how to effectively implement HPV primary screening. First, it describes the pathway from an organized screening program to follow-up of abnormal results. Then it describes implementation considerations including those related to equity, self-sampling, health system resources, and change management.

APPROACH

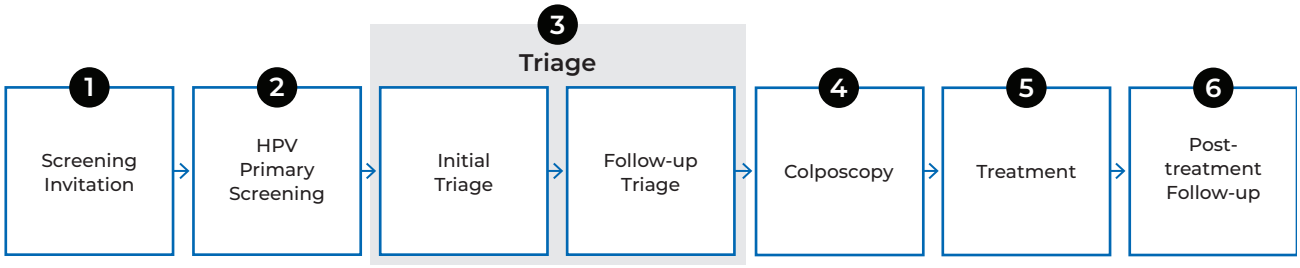
A mixed methods approach was used, including a literature review and interviews with five jurisdictions. The aim of the environmental scan was to identify informative and practical answers to the research questions, drawing from international jurisdictions that have transitioned existing cervical screening programs to an HPV Primary Screening Program. The five jurisdictions were: *Australia*, the *Netherlands*, the *UK*, the *United States of America*, and *Finland*. This review also drew findings from select research studies in Canada, specifically, findings from the HPV FOCAL Randomized Clinical Trial in British Columbia and a randomized controlled trial for cervical screening self-sampling in Newfoundland.



HPV PRIMARY SCREENING PATHWAYS

Care pathways are a foundational component to enable implementation of HPV primary screening and follow-up of abnormal screening results. Care pathways identify how a person moves through a screening program and what follow-up tests or procedures they require if results are abnormal. When the pathways are viewed at a higher level, commonalities are seen. There are six common pathway steps which are illustrated in the following diagram.

Figure 1: Common Pathway Steps



Within these steps, the actual pathway of each jurisdiction examined varies. There are, however, common considerations around which jurisdictions design their pathways. The design considerations relate to the common pathway steps and include:

Screening Ages and Intervals (Step 1): Several jurisdictions start cervical screening at age 30; however, evidence-based guidelines vary on the decision to screen for HPV before the age of 30. This is because HPV is often present in younger people and resolves without treatment, the implication being that screening in younger people may result in unnecessary monitoring and overtreatment, which has risks of its own. The screening programs typically end at age 65; however, invitations to screening are extended if the person did not participate in earlier screening and in *Australia*, there is a final program exit test between ages 70-74. Screening intervals are typically 5 years and at times extend to 10 years. Balancing these aspects allows screening programs to avoid screening for HPV too early when HPV infections have a higher likelihood of resolving without treatment, ensure that older people have sufficient screening coverage that corresponds to their risk of cervical cancer, and maintain screening efficacy for patients while decreasing health system resource requirements with longer screening intervals.

Screening Invitations and Results Communication (Step 1, 2 & 3): Centrally organized invitations from screening programs are sent by a variety of channels including mail and electronic communication. Invitations and results are sent to the individual and/or primary care provider depending on the jurisdiction and result. There are several techniques to improve communication with screening participants and clinicians that have been demonstrated to improve participation rates in screening programs.

Self-Sampling (Step 2): With increasing evidence pointing towards the accuracy of detecting high-risk HPV (hrHPV) through self-sampling, jurisdictions are leaning towards expanding its use. In the past there were greater concerns about the sensitivity of self-sampling being lower than clinician-collected samples. While some of these concerns continue, advances in technology and further studies are showing reasonably high diagnostic accuracy and performance.[3] Self-sampling is typically seen as an approach that complements clinician-collected samples. In the past, self-sampling has been offered only to people from groups who are typically under- or never-screened, however, some jurisdictions are moving towards allowing anyone participating in screening to use self-sampling.

Self-sampling can be done either in a clinician's office or at home. When self-sampling kits are mailed to the person's home, carefully considered aspects around communication can overcome concerns related to privacy. "Opt-in" approaches conserve resources while "opt-out" approaches better improve participation, and advanced communication with an "opt-out" approach is one way to help balance advantages and disadvantages of these approaches. While implementation of self-sampling does present several challenges, ways to mitigate these challenges are available.

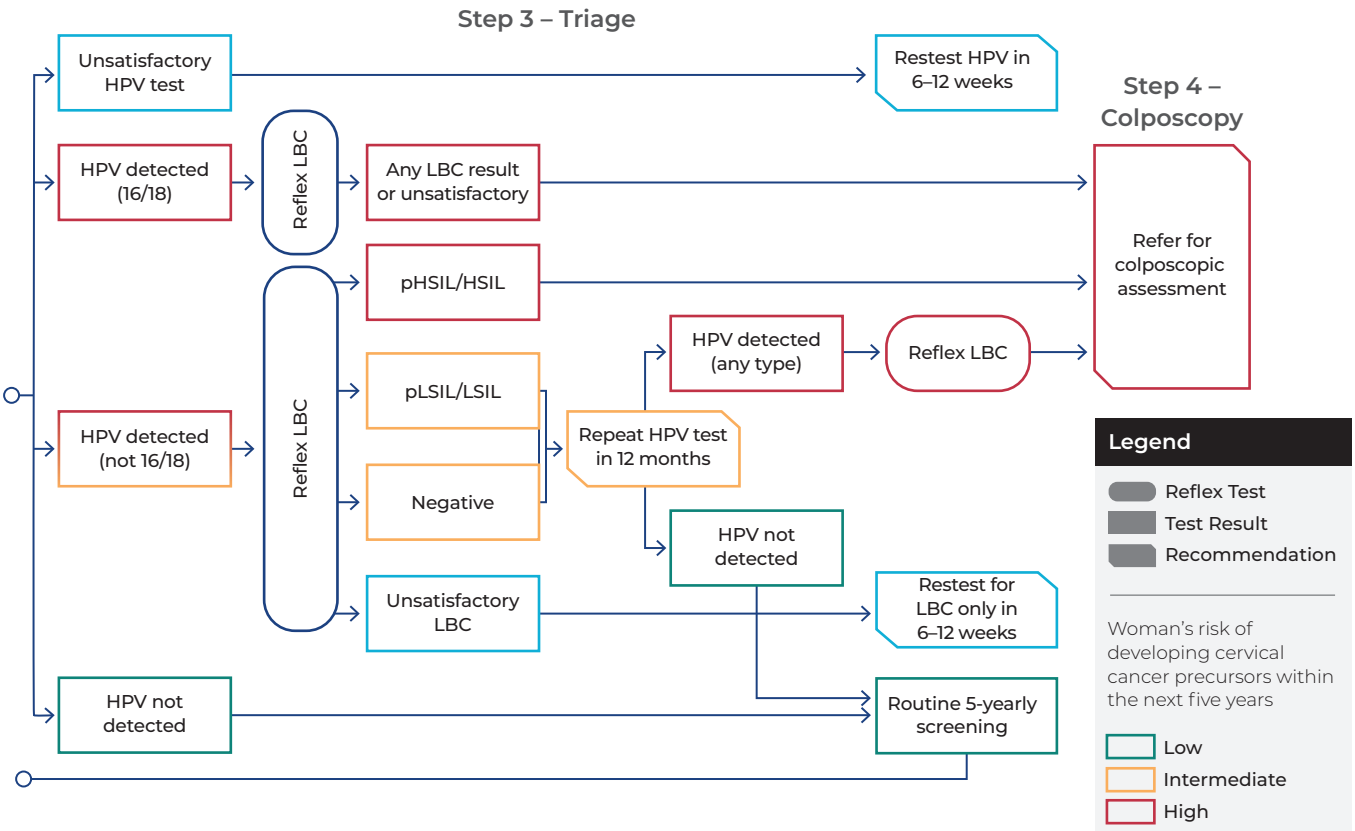
Other enablers of implementation of self-sampling include clear pathways, advance planning for any regulatory considerations, realistic processes for distribution and retrieval of self-collection device that are tailored to the local environment, good communication with patients and providers, and support for primary care providers. Self-sampling helps to improve equity, can be more comfortable for the person being screened, and increases participation in cervical screening programs.

Test Types (Step 2 & 3): Since HPV is the primary cause of cervical cancer and certain types of HPV are known to be higher-risk, HPV partial genotyping (especially for HPV+ 16/18) can be used to identify when hrHPV is present. Ongoing research is exploring links between different HPV types and increased risk for cervical cancer and highlighting the benefit to understanding which types of HPV a person has. Genotyping can be used in the future to identify what types of HPV a patient has and identify that person's related risk of developing cellular abnormalities or cancer, however, consideration is also needed for how cases that do not include high-risk HPV types will be sufficiently screened. While cytology is commonly used for triage, better triage tests are being studied for the future.

Triage Design (Step 3): HPV testing is more sensitive and currently less specific than the Pap test. It should be noted that test specificity is expected to improve as a higher proportion of people being screened have been immunized against HPV. Higher HPV test sensitivity means that the test is effective in identifying the presence of HPV, while higher HPV test specificity means that the test is effective in accurately identifying when HPV is not present. Until the specificity of HPV testing improves, a triage process is needed to increase specificity, avoid false-positive test results and negative patient outcomes, and steward health system resources. Triage design typically involves identifying high-risk types of HPV through genotyping, using cytology, and periods of waiting and retesting for HPV to avoid unnecessary referrals to colposcopy. Partial genotyping to determine which types of HPV are present is used in some jurisdictions for triage and research continues to provide additional insights into how genotyping can be used most effectively. For example, HPV+ 16/18 is of greater concern for younger people while cervical cell abnormalities in older people are associated more with other types of HPV or types that are not considered high-risk. Partial genotyping can be used in the design of triage pathways to provide care specific to the patient, shape the way health system resources are used, and provide better care for patients.

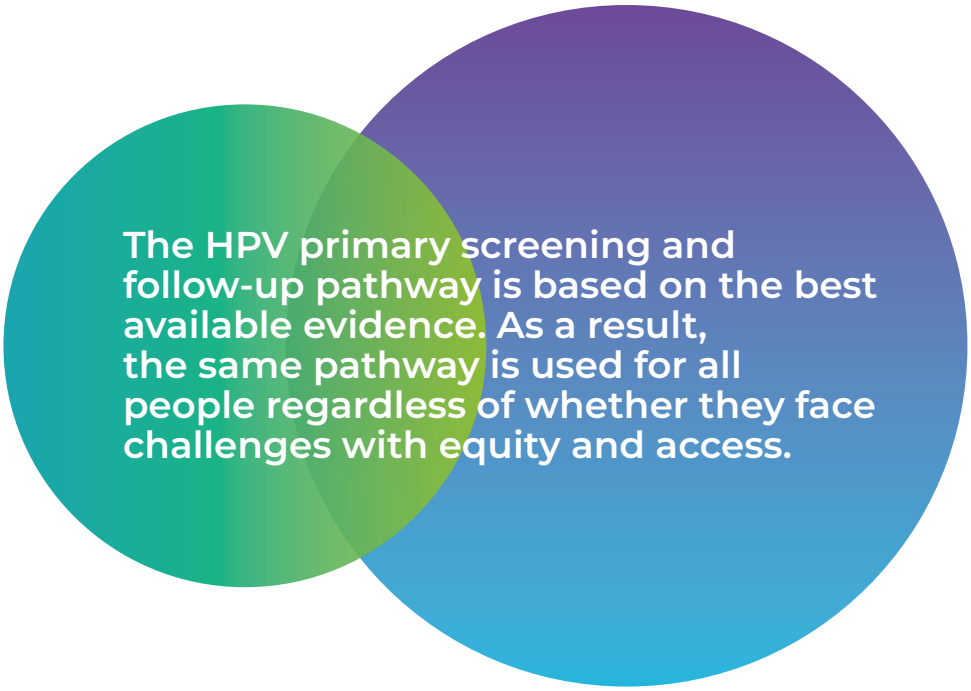
A sample of a triage pathway from *Australia* that uses partial genotyping to direct the patient's path is shown in the diagram below.

Figure 2: HPV Primary Screening Triage Pathway in Australia



Acronyms: LBC- Liquid-based cytology; pLSIL- possible Low grade squamous intraepithelial lesion; LSIL- Low grade squamous intraepithelial lesion; HSIL- High grade squamous intraepithelial lesion.

Source: Cancer Council Australia, Clinical Guidelines Network website



Abnormal Screen Follow-up (Step 4, 5 & 6): Follow-up on abnormal screening results is essential, as screening without following up on abnormal results will not lead to better outcomes. There is a lot of variation in the abnormal result follow-up steps (Steps 4, 5, & 6), however, ensuring there is a good "hand-off" from abnormal screening result to follow-up is seen as impowrtant across all jurisdictions. Communication and reminders from the screening program to the patient and clinician enables proper follow-up and referrals. Across jurisdictions, the HPV primary screening and abnormal result follow-up pathways at Colposcopy (Step 4) and Post-Treatment Follow-up (Step 6) generally provide clinicians with decision-making direction, while Treatment (Step 5) is generally left to a greater degree to physician discretion.

Equity and Access (All Steps): The HPV primary screening and follow-up pathway is based on the best available evidence and as a result the same pathway is used for all people regardless of whether they face challenges with equity and access. There are several tactics that can be taken which help to improve equity, including:

- **Engaging with the Community:** Program implementation is tailored to the community of focus based on the needs identified by the community. Communities that experience inequity have different needs, social or cultural expectations, and practical implementation considerations, so different approaches are needed for different communities, with co-design seen as a leading approach to identify how the program should be tailored.
- **Conducting Research:** Understanding areas and causes of inequity and who is impacted.

- **Developing Community-Specific Materials and Approaches:** Aspects of implementation that are modified to increase equitable access include screening and follow-up access frequency and channels, communications approaches and materials, and community-program relationship development. The communication materials help to identify and build awareness about culturally competent ways to engage with different communities and enhance participation.
- **Self-Sampling:** Self-sampling addresses several barriers to participation in screening including those related to geographic distance and transportation, social and cultural acceptability, and avoidance due to a history of trauma or other reasons.

Together, these approaches help to improve equity in a culturally competent manner.

Risk and Health System Resource Use (All Steps): Triage pathways are designed based on scientific evidence; however, the pathways can also be influenced by jurisdictional preferences such as the amount of resources dedicated to the health system, the scope of clinician practice, and focus on patient experience. Societal risk tolerance and resource availability may impact aspects of pathway design especially when those aspects are expected to have limited impact on outcomes. Ways to modify and balance health system resources include using different health professionals to conduct clinical activities (e.g. nurses rather than gynecologists to perform colposcopy) and making decisions related to scientific evidence and societal risk-tolerance (e.g. the ages at which people will be eligible to participate in screening; clinical pathway decisions about when people are referred to colposcopy). Robust monitoring of outcomes enables better use of health system resources since different approaches can be monitored for the degree to which they impact risk of cellular abnormalities and cancer. These factors can be considered during planning to balance population and community needs and resources.

Pathway Complexity (All Steps): A simpler pathway design is easier for clinicians and patients to understand and supports implementation, as a simpler pathway is easier to understand and remember. However, slightly more complex pathways may limit the impact of apparent false-positives on individuals and the system. Technology can be used to make these longer pathways user-friendly by taking the patient specific inputs and identifying the suggested next step. These factors related to clear communication of the pathway can be considered in implementation planning to enable support and buy-in for HPV primary screening.

IMPLEMENTATION CONSIDERATIONS

In addition to pathway design, jurisdictions identified several other considerations for successful implementation. These include systems and information, people and teams, plans, and communication and engagement, as briefly described below.

Systems and Information: Information systems are foundational for successful HPV primary screening program implementation. In particular, a registry is needed to identify those that are eligible and due for screening, track invitations and participation, and ensure over-screening is prevented. The amount of time to implement these systems is dependent on the suitability of underlying IT systems and larger IT system changes or implementations can take several years. A well-designed and implemented system provides a number of benefits including, but not limited to: sending timely invitations and reminders to the right people, tracking screening and result history, identifying where proper hand-offs to follow-up care are necessary, and monitoring quality.

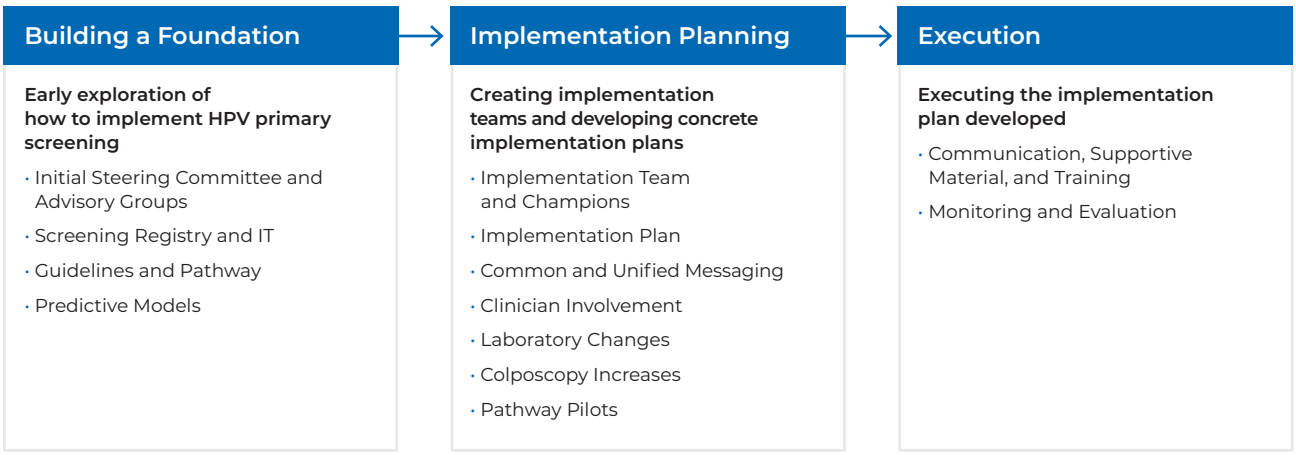
People and Teams: The right teams and people provide guidance and advice, develop plans, and drive forward and monitor implementation initiatives. These people include health system leaders, clinicians, laboratory staff representatives, respected individuals (i.e. champions) in relevant groups, program managers, and relevant government decision-makers. Representatives of those people that will use and be impacted by the program are also included with special focus on engaging with and involving communities that experience inequity. Dedicated teams and groups that meet regularly are established. Health care human resources are impacted in different ways and resources are shifted to match need through tactics such as retraining, modifications to roles (e.g. non-clinical roles providing basic education on HPV primary screening process instead of primary care clinicians), and advance notice to professionals to allow them to shift their areas of focus.

Plans: Plans are developed for several aspects of implementation, including pathway design, implementation guidance, and specific implementation plans. Predictive models are used to understand health system costs and resource impacts, such as demand for laboratory services and colposcopy, when developing implementation plans. Special attention is paid to the impacts on colposcopy referrals, supply, and wait times, as well as the impact to lab facility and human resource supply and demand. Actions are identified that minimize negative impacts, such as increasing supply of colposcopy, adjusting pathway design or implementation timelines, and retraining of cytologists for work in similar areas of practice. For example, in *Australia*, cytotechnologists were retrained within the labs while in *Finland* this role already had broader training. Pilot programs help to identify if assumptions are correct and allow for adjustments as needed ahead of full implementation. Monitoring and evaluation plans are made to ensure progress and outcomes are as expected and allow for adjustment if there are unexpected results. Development of the plans takes varying amounts of time depending on the type of plan and jurisdiction. Creating pathways and guidelines were reported to take a longer duration and in one jurisdiction ranged from 18 months to 5 years. Together these plans allow health system planners to envision and adjust implementation plans to suit local needs and resources, create documents that clearly describe the program to be implemented, and enhance the chance of implementation going according to plan.

Communication and Engagement: Throughout planning and implementation clinicians, other health related professionals, and the public are engaged and communicated with. Professionals are engaged to share evidence about the efficacy of HPV primary screening, gather considerations for implementation planning, and provide advice when they have operational questions during implementation. The public is engaged to share evidence about the efficacy, experience, and process of HPV primary screening and abnormal screen follow-up so that psychological barriers to participation are reduced.

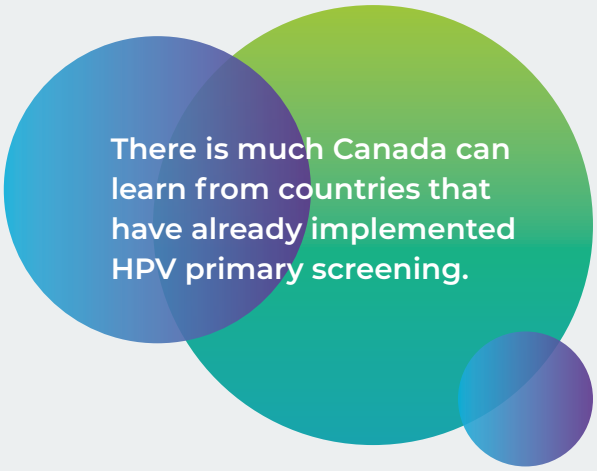
Attention is paid to what concerns the public may have and ensuring simple and relatable information is available through multiple channels. Clearer communication and high levels of engagement help to prevent implementation challenges and inform and convince people of the benefits of implementing and participating in HPV primary screening. The above considerations can be organized in a sequence according to the phase of planning and implementation, as illustrated in the following diagram.

Figure 3: Implementation Phases



Weblinks to sample tools and resources from other jurisdictions can be found in Key Weblinks, section 6.4.1.

Summary of Lessons Learned



There is much to learn from other jurisdictions and several themes emerged through this scan. The following list provides a synthesized summary of key lessons learned from the findings:

1. Tailor programs to communities experiencing inequity in screening to increase participation

Inequity is faced by some communities leading to decreased participation in screening (i.e. being under- or never-screened) and poorer outcomes. Tactics used to increase equity include community engagement and co-design, research, ongoing relationships, tailored communication, and self-sampling.

2. Develop a Care Pathway Early

A foundational element is forging agreement on what the care pathway will be and since development involves numerous stakeholders and advisors, it should be started early in the process.

3. Balance Risk with Resources

Pathway design has impacts on health system resources use, clinician practice, and patient experience. While the development of pathways must be firmly rooted in the evidence, system leaders and the people designing the pathway also need to make value and risk judgements (e.g. what degree of cytology abnormality triggers a referral to colposcopy) while closely monitoring the impact of these decisions on patient outcomes.

4. Focus on Participation Rates as a Key Mechanism to Decrease Cervical Cancer

Ways to improve screening participation include, but are not limited to:

- Self-sampling, especially for populations with barriers to screening;
- Good relationships between the patient and a clinician, typically in primary care, that is supportive of HPV primary screening; and
- Communications materials, especially when tailored to the target audience.

5. Consider How Self-Sampling Can Be Used to Increase Participation in Cervical Screening Programs

Self-sampling is seen as a promising method to enable participation in screening for under- or never-screened populations.

6. Consider the Extent to Which the Screening Program is Involved in Follow-Up of Abnormal Results

The transition between an abnormal result and follow-up care can be a step where people get "lost" in the care pathway. The organized screening program can create mechanisms to maximize the likelihood that patients participate in abnormal screen follow-up.

7. Create A Plan to Limit and Manage the Temporary Increase in Demand for Colposcopy

There is often a 2-3 times increase in referral to colposcopy when HPV primary screening is introduced, however, ways to smooth demand include pathway design, screening age and interval, and test types used. It is important to note that the increase is temporary.

8. Engage with Clinicians and the Public to Communicate the Superiority of HPV Primary Screening

There is need to educate and reinforce for clinicians and patients why HPV primary screening is superior to the prior screening approach.

9. Monitor Advancements in Cervical Screening Technologies and Approaches

HPV primary screening science and technology is advancing quickly and new studies and technology can be routinely scanned to ensure cervical screening practices are using the best evidence.

1 Introduction

Cervical cancer is a frequently occurring gynecological cancer and it is estimated that in 2020, 1,350 Canadians will be diagnosed with the disease.[4] Cervical cancer screening is conducted in many countries, including Canada, and allows for detection of abnormalities and potential cervical cancer so that monitoring and treatment can be provided. Due to advances in technology, the approach to cervical cancer screening is undergoing a significant change

The Pap test, developed in the 1940s, was incorporated into cervical cancer screening programs in the 1960s and 1970s. The Pap test was initially met with skepticism, though it gained acceptance overtime and until recently was seen as foundational to preventing cervical cancer.[5] In a Pap test, the primary care physician, nurse, or gynecologist collects a sample of cells from the cervix and sends them to the laboratory for cytology. Cytology involves examining cells for evidence of abnormality and categorizing the degrees and types of abnormalities.

Fast forward almost 50 years to today when cervical cancer screening is once again seeing revolutionary change. Human Papillomavirus (HPV) testing is now seen as the leading approach to primary cervical cancer screening. Additional scientific understanding has established the link between the persistent presence of HPV and the risk of developing cancer. HPV primary screening is advantageous as it identifies cervical pre-cancer earlier and results in a significantly lower likelihood of cervical cancer compared with Pap test screening.[2] Technological advances have provided a testing approach that is sensitive to detecting the virus along with mechanisms to prevent false-positives and over-treatment of cases that are not likely to develop into cancer. Some of the pioneering work to establish that HPV primary screening is more effective than the Pap test was done in Canada through the FOCAL trial. This trial showed that using HPV primary screening resulted in lower risk of having high-grade cervical cancer compared with using cytology and that pre-cancer could be detected earlier, allowing for earlier treatment.[2,6]

HPV is a virus that is the primary cause of cervical cancer.[5] It is estimated that most HPV infections resolve naturally and without treatment in six months to two years.[7] Persistent HPV infections, however, can lead to the growth of abnormal cells on the surface of the cervix, also called cervical intraepithelial neoplasia (CIN), which can develop into cancer. Because of the link between HPV and cervical cancer, screening for HPV can identify elevated risk of cervical cancer early to reduce the number of people who get the disease. There are several types of HPV, and 12 of these types are

associated with a greater risk of developing cancer. These 12 types of HPV are classified as either oncogenic (i.e. cause cancer) or high-risk (hrHPV) and are responsible for 97% of cervical cancer cases. They include HPV16/18/31/35/39/45/51/52/56/58/66/68. HPV 16 and 18 are the most common types that are responsible for 70% of all the cervical cancer cases (about 50% are caused by a positive HPV 16 (HPV+ 16) and 20% HPV 18 (HPV+ 18)).[7] While the presence of high-risk types of HPV require greater attention and follow-up, the lower-risk types may also require attention.

Cervical screening involves a variety of people and professionals. For example, primary care physicians, gynecologists, and nurses are involved in collecting samples and following up on abnormal screening results. Laboratory professionals carry out the tests and provide reports on the cells to specialists, such as gynecologists, who are involved in abnormal result follow-up procedures, such as colposcopy (the visual examination of the cervix). Several types of organizations are also involved in various aspects of a cervical screening program. Governments are involved in approving and often funding cervical screening programs, while health system planning organizations are involved in screening program planning, implementation, and monitoring.

Like the Pap test, the shift to HPV primary screening is also being met with some initial skepticism; however, HPV primary screening has gained acceptance as the best approach to cervical cancer screening in many countries.[5] The switch to HPV primary screening and abnormal result follow-up does have challenges which can be overcome.

Today, using HPV as the primary screening approach has gained, and continues to gain, acceptance as a leading practice. Implementation of HPV as the primary screening method is at various stages around the world and is in early stages in Canada. The subsequent findings provide a collection of international implementation lessons to learn from.

2 Environmental Scan Objectives and Overview

The Canadian Partnership Against Cancer (the Partnership) is the steward for the Canadian Strategy for Cancer Control 2019-2029. The Strategy's vision is fewer Canadians developing cancer, more people surviving it, and those with cancer having a better quality of life.[8] This environmental scan contributes to the strategic priorities of decreasing the risk of people getting cancer by adopting proven practices and diagnosing cancer faster, accurately and at an earlier stage by strengthening existing screening efforts across Canada.[8] The strategy is further supported by the Action Plan for the Elimination of Cervical Cancer in Canada, 2020-2030 that plans to implement the above priorities.[9] This environmental scan also contributes to the Action Plan's priorities and actions, including identifying best practices from other jurisdictions that have implemented HPV primary screening.

This Environmental Scan had the following **objectives**:

- Identify lessons learned from leading international jurisdictions' HPV primary screening program implementation
- Provide input to inform implementation planning for Canadian jurisdictions planning on implementing HPV primary screening and abnormal result follow-up

The intended audiences for this environmental scan are health system administrators, cancer agencies and screening programs, and others that are planning to implement HPV primary screening. It is designed to provide practical information and lessons learned from select jurisdictions that have already implemented an HPV primary screening program and from jurisdictions that are advanced in their screening and follow-up pathways. It can be used to inform preliminary planning discussions and the development of guidance and plans for implementation of HPV primary screening and abnormal screen follow-up in Canada.

The document is divided into five sections and an Appendix. The early sections (sections 1-3) provide introductory information to orient the reader to the document and topic. Section 4, Findings, is further divided into 3 sub-sections and provides details on the findings. The three sub-sections are:

- HPV Primary Screening and Results Follow-up Pathways
- Pathway Design Similarities and Differences Across Jurisdictions
- Practical Considerations for Implementation

Throughout the document, examples from specific jurisdictions are provided to illustrate lessons learned. Examples were drawn from the literature and interviews.

3 Approach

A mixed methods approach was used, which included a literature review and interviews with five jurisdictions. A brief online scan was conducted to identify jurisdictions that appeared to have successfully implemented HPV primary testing within and organized cervical screening program.*

Of these, four jurisdictions that were anticipated to have implementation lessons most relevant to Canada were selected. A limited set of interviews with key informants from Newfoundland and Labrador and British Columbia were also conducted. Partway into the environmental scan process another jurisdiction (*Finland*) was added on recommendation that it would be beneficial to include interviews to learn about its experience. Selected jurisdictions include:

- *Australia*
- *The Netherlands*
- *The United Kingdom*
- *The United States of America*
- *Finland* (interviews only)

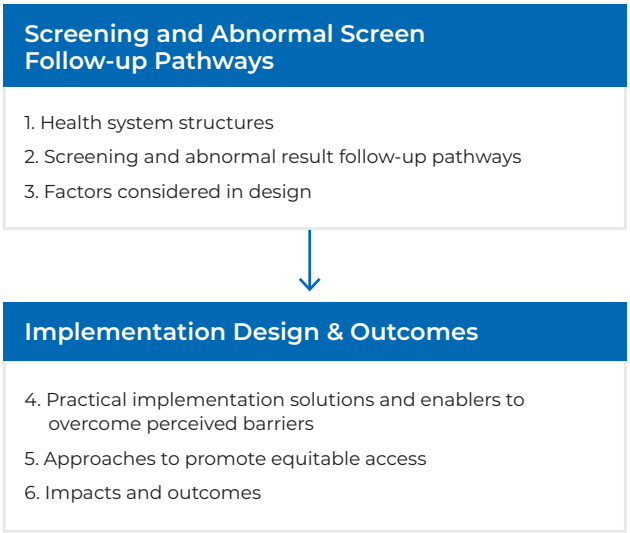
We would like to acknowledge all the key informants that contributed their time and input to this process. Their insights were valuable and provided information beyond that which is available in the literature.

The approach involved the following steps:

1. Develop Research Questions:

The research questions were developed by Optimus SBR and refined by the Partnership. The research questions pertained to two major research categories and six research topics. The categories and topics are listed below (see section 6.1 Appendix: Environmental Scan Research Questions for full list of questions).

Figure 4: Research Topics by Category



*The American Society for Colposcopy and Clinical Pathology (ASCCP) in the United States (US) is in the process of implementing HPV Primary Screening and the US was included due to the ASCCP's unique, risk-based approach to screening and abnormal screen follow-up. New guidelines were released during development of this document.

2. Conduct Literature Review:

The literature search used three sequential selection filters:

1. **Sources:** A range of indexed sources and grey literature were searched to answer the research questions, including research findings and published review articles.
2. **Key Words:** The Title, Abstract and Key Word fields in the indexed databases were searched with key words based on the research questions.
3. **Inclusion Criteria:** The inclusion criteria were the international jurisdictions, 2010 to 2020, and the English language. Four to seven (4-7) of the most relevant articles per jurisdiction were reviewed.

3. Conduct Interviews:

Eleven, 1-hour interviews were held subsequent to the literature review and included the following professionals from the aforementioned jurisdictions:

- Executive Director, Primary HPV Laboratory
- Directors, Cervical Screening
- Champion and former Steering Committee Chair for program implementation
- Gynecologic oncology surgeon
- Organization's champion of combined Pap/HPV testing
- President, European Federation for Colposcopy
- CEO, Cervical cancer charity
- Program Coordinator
- Program Manager
- Quality Assurance Manager
- HPV Implementation Lead

4 Findings

Successful implementation of HPV primary screening and abnormal screen follow-up requires a well-designed care pathway as well as an understanding of what enablers and barriers to implementation may exist. There are several pathway design elements to consider and numerous implementation considerations to plan for. These include considerations related to testing age, test type, and equitable access for the pathway design, and communications, information systems, and planning for the implementation approach. Fortunately, there are lessons from other jurisdictions to inform this planning.

Care pathways are a foundational component to enable implementation of HPV primary screening and proper follow-up of abnormal screening results.

Care pathways identify how a person moves through a screening program and what follow-up tests they require, if any. While the pathway is foundational for implementation, other factors also need to be considered for implementation of HPV primary screening to be effective. This section outlines what has been learned to date from other jurisdictions related to:

1. **HPV Primary Screening and Abnormal Result Follow-up Pathways;**
2. **Pathway Design Similarities and Differences Across Jurisdictions;**
3. **Additional Pathway Design Considerations; and**
4. **Practical Considerations for Implementation.**

4.1 HPV PRIMARY SCREENING AND ABNORMAL RESULT FOLLOW-UP PATHWAYS

Key findings:

- While there are some commonalities across jurisdictions, the screening and abnormal results follow-up care pathways vary significantly between jurisdictions.
- HPV primary screening and follow-up care pathways generally include the following steps:

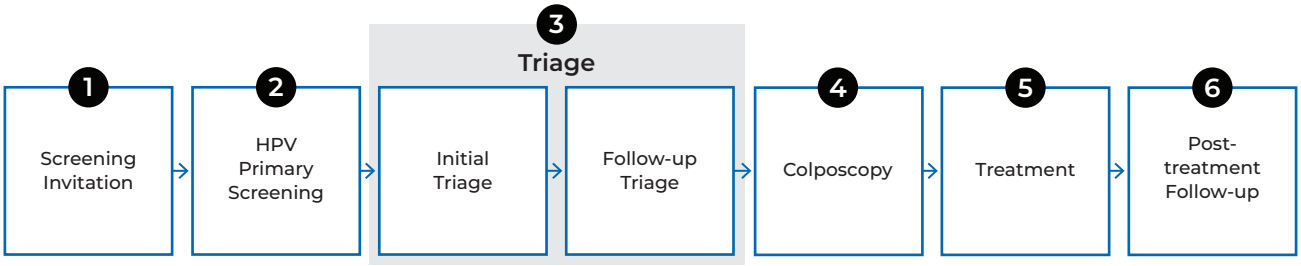
Step 1: Screening Invitation
Step 2: HPV Primary Screening
Step 3: Triage
Step 4: Colposcopy
Step 5: Treatment
Step 6: Post-Treatment Follow-up

Multiple countries are moving towards HPV primary screening. While there are common elements to the HPV primary screening and abnormal result follow-up pathways, the specific pathway steps vary significantly by jurisdiction.

4.1.1 Basic Overview of Pathway Steps

The following diagram provides an overview of the common steps of HPV primary screening and abnormal results follow-up care pathways across jurisdictions. The following steps are generalized here to illustrate the similarities across jurisdictions, while the actual pathways in each jurisdiction are more complex and vary significantly (see section 6.3 Appendix: Additional Pathways). The *Netherlands*, *Finland*, *Australia*, and the *United Kingdom* all have organized screening programs while the United States provides national guidelines.

Figure 5: Common Pathway Steps



Numerous health professional roles are involved in the steps including roles in primary care (e.g. primary care physician), laboratories (e.g. cytotechnician), and follow-up of abnormal results by a range of clinicians (e.g. gynecologist).

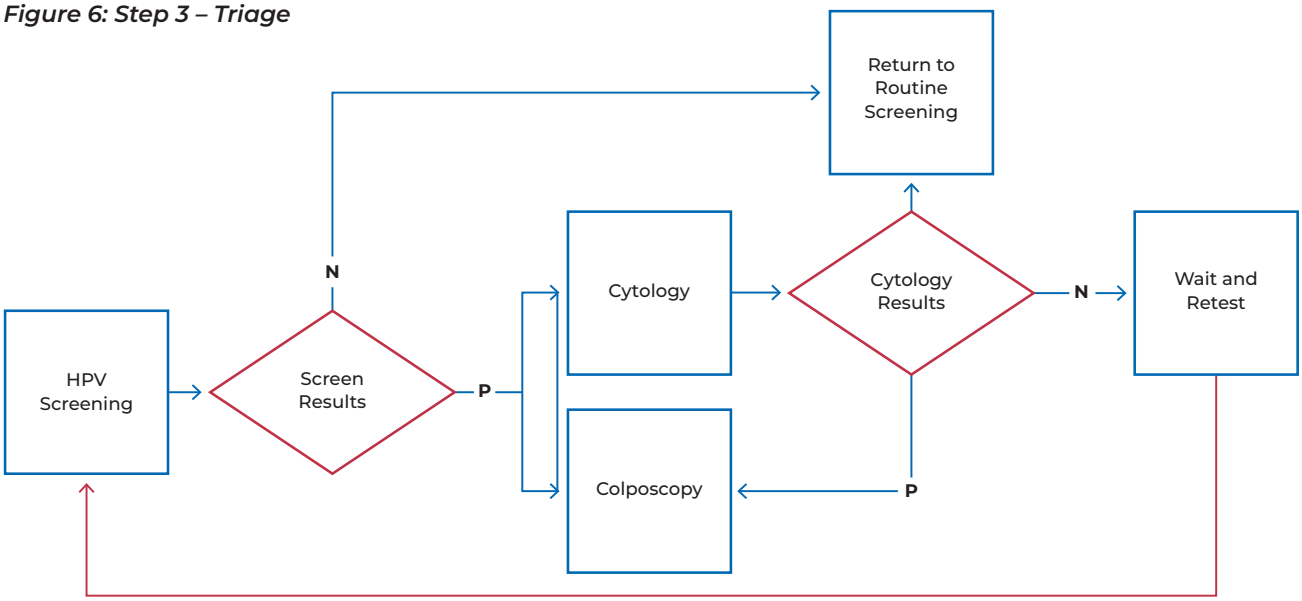
The individual steps are described below:

Step 1 – Screening Invitation: In the screening programs, a screening registry is used to store individuals' contact information and screening history and manage invitation and reminder notifications for individuals due for screening. Typically, this is done by mail. If needed, a reminder is sent.

Step 2 – HPV Primary Screening: The initial screening is conducted by taking a sample in a clinical setting or at home. The sample is taken by a clinician, often a general practitioner or nurse, or by the individual (if self-collection is permitted by the screening program) and sent to the lab for analysis. If screening results are normal at this step, the HPV negative result is communicated back to the person screened and the person returns to routine screening. This is typically done by mail through the registry.

Step 3 – Triage: Initial screens from Step 2 that are HPV positive require a triage process to avoid over-referral to colposcopy. While there are many types of HPV, partial genotyping is frequently used to identify if certain high-risk types of HPV are present. If presence of these high-risk types is detected, then the person advances faster to colposcopy. If the person is identified as having HPV but not a high-risk type, additional triage processes are used. While the specific triage processes differ across jurisdictions, they generally include variations of the following components illustrated in the following diagram.

Figure 6: Step 3 – Triage



Further to the diagram above:

Cytology: Cytology (usually liquid-based cytology) identifies if there are normal or atypical squamous cells and, if atypical, what grade (i.e. ASC-US+, LSIL, HSIL, etc. See section 6.4 Appendix: Glossary of Selected Terms for a description of terms). This cytology is often referred to as "reflex cytology" or "triage cytology" where the same sample is used to test for HPV and perform cytology.

Wait and Retest: One or more periods of waiting and retesting, often in 6-12 months, to see if the HPV infection resolves spontaneously.

Colposcopy: Referral to colposcopy for further assessment.

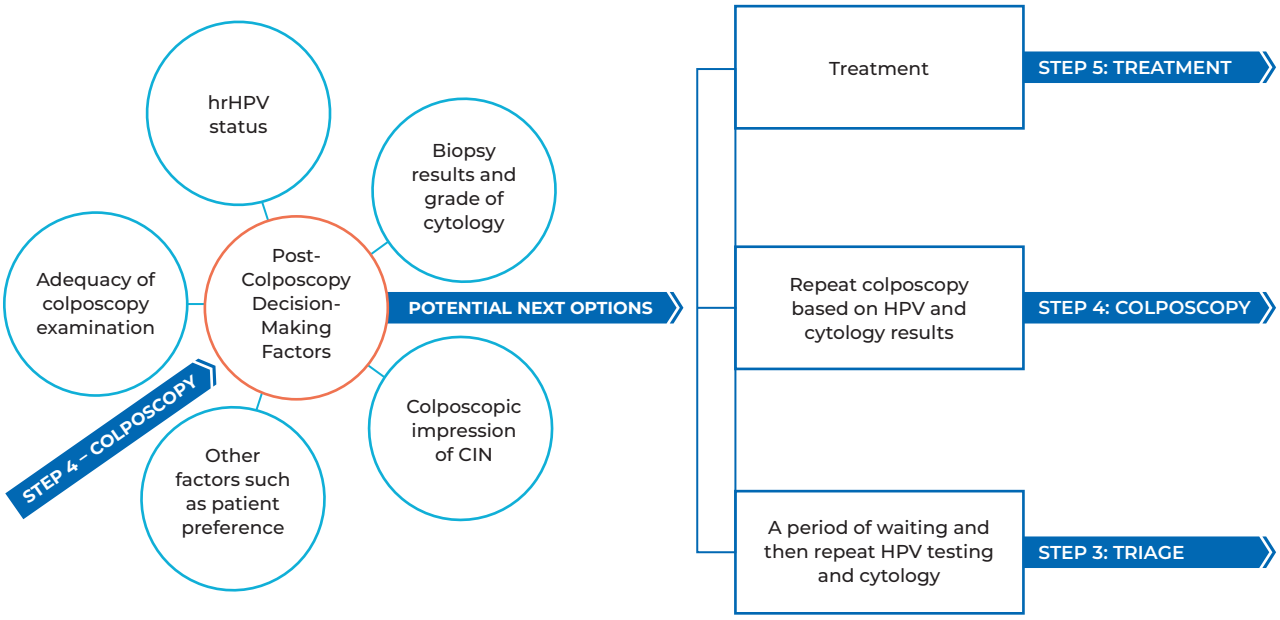
Release to regular screening: The person returns to routine screening.

While all the pathways across jurisdictions generally use these same components, the specific pathways vary in components used, order in which they are carried out, and when they are used. A case example is provided in the section 4.2.4.1 below. Variation likely occurs because the evidence is seen to be insufficient to determine the best approach for repeat testing which illustrates the need for "decision makers to consider the prevalence of HPV types... as well as quality of cytology."[7]

Results are communicated back to the patient (and primary care physician, depending on the jurisdiction), by mail or electronic means. For example, in the *Netherlands*, the screening program sends the results directly to the person screened except when there is moderate dysplasia (abnormal cells) or greater abnormality, in which case the primary care provider tries to contact the person in advance of the results; however, it is up to the patient to schedule follow-up with primary care for next steps and referral to colposcopy.[10]

Step 4 – Colposcopy: People are referred to colposcopy based on the outcomes of the triage tests. The colposcopist (a nurse or physician with specialized colposcopy training) conducts the colposcopy and may take a biopsy. Results are used to inform next steps and a treatment plan, if needed. Across the jurisdictions, next steps are dependent on several factors as illustrated in the following figure.

Figure 7: Step 4 – Colposcopy



Colposcopy can be a "bottleneck" in the overall pathway when patients have been referred to colposcopy but have long wait times for the colposcopy procedure. This predictably happens for a limited period of time in jurisdictions that have recently implemented HPV primary screening, as the screening participants that have been in a 3-year Pap test screening interval switch to a longer screening interval (typically a 5-year interval). In the first few years after HPV primary screening implementation, there are more referrals to colposcopy, since HPV primary testing identifies risk of cancer earlier. The impact of longer screening intervals are not seen until eligible people have been through their first round of HPV primary screening (for additional information see section 4.3 Practical Considerations for Implementation Planning). In these jurisdictions, the increased number of referrals and bottleneck decreases after a few years.

Step 5 – Treatment: There are multiple treatment options such as Large Loop Excision of the Transformation Zone (LLETZ), laser ablation, cryocautery, cone biopsy, and other excisions. More advanced cases may require hysterectomy, radiation, or chemotherapy. Treatment plans are developed between the physician and patient depending on the characteristics of the patient's case. Depending on the jurisdiction and pathways, a specific treatment may be recommended or recommended for exclusion, however, generally the treating physician is given discretion in developing the treatment plan.

Step 6 – Post-Treatment Follow-up:
After treatment, follow-up is needed to ensure treatment is successful. This may be done by hrHPV recall test, further cytology, and/or colposcopy. Some jurisdictions use an HPV test as the first step in post-treatment follow-up, while others require co-testing with cytology. In both cases, cytology is used if there is a positive HPV result. If HPV negative after sufficient cycles of retesting (jurisdiction dependent), the person returns to routine screening, however, timelines and the number of retesting cycles vary.[11,10]

Additional details about what occurs in each jurisdiction examined can be found in Appendix: Pathway Design Jurisdictional Comparison and Appendix: Additional Pathways.

4.1.2 Clinicians Involved in Pathway Steps

Each step in the pathway tends to have different clinicians involved. These include, but are not limited to:

Table 1: Clinicians Involved in the Pathway

STEP	CLINICIANS INVOLVED
1: Screening Invitation	· Primary care physician and nurse
2: HPV Primary Screening	
3: Triage	· Cytotechnician · Cytopathologist
4: Colposcopy	· Colposcopist (may be gynecologist or nurse) · Gynecologist · Nurse
5: Treatment	· Gynecologist · Gynecologic Oncologist · Radiation Oncologist · Medical Oncologist · Allied health
6: Post-Treatment Follow-up	

4.2 PATHWAY DESIGN SIMILARITIES AND DIFFERENCES ACROSS JURISDICTIONS

Key findings:

Similarities and differences exist at multiple areas of the pathways when comparing the pathways of different jurisdictions and these areas of variation relate to the basic pathway steps.

- **Screening Ages and Intervals:** Several jurisdictions start HPV primary screening at age 30; however, there are differing clinician opinions and guidelines on whether HPV primary screening should be used before the age of 30. This is because HPV is often present in younger people and often resolves without treatment, the implication being that screening in younger people could result in unnecessary monitoring and overtreatment, which has risks of its own. Screening intervals are typically 5 years and at times extend to 10 years.

- **Screening Invitations and Results:** Centrally organized invitations from the screening programs are sent by a variety of channels including mail and electronic communication. Invitations and results are sent to the individual and/or primary care provider depending on the jurisdiction and result.

- **Clinician-led versus Self-Sampling:** With increasing evidence pointing towards effectiveness of detecting hrHPV through self-sampling, jurisdictions are leaning towards expanding the use of self-sampling. In the past, self-sampling was offered only to people who are under-screened, however, some jurisdictions are moving towards allowing anyone participating in screening to choose self-sampling. Commercial HPV assays used in HPV testing in the laboratories do not have manufacturer validated claims for their use on samples collected by individuals, creating regulatory obstacles to implementing self-sampling. Regardless of this issue, some jurisdictions are exploring and piloting the use of self-sampling and identifying ways to overcome the regulatory obstacles, such as laboratories independently validating self-collection protocols.
  - Self-sampling is typically seen as one screening tool that complements clinician-collected samples.
  - Some jurisdictions are seeking to expand access to self-sampling to the general population rather than focusing its use on people who are under-screened.
  - Jurisdictions are exploring using self-sampling during COVID-19 to maintain screening.

- **Test Types:** HPV tests that identify certain types of hrHPV (i.e. HPV partial genotyping) are preferred as the primary screening test. Ongoing research is exploring links between different HPV types and increased risk for cervical cancer and highlighting the benefit to understanding which types of HPV a person has. While cytology is commonly used for triage, better triage tests are being studied for the future.

- **Triage Design:** HPV testing is a more sensitive and less specific test and so a triage process is needed to increase specificity, avoid false-positive test results and negative patient outcomes, and steward health system resources. Higher HPV test sensitivity means that the test is effective in identifying the presence of HPV, while higher HPV test specificity means that the test is effective in accurately identifying when HPV is not present.

- **Abnormal Result Follow-up:** There is a lot of variation in the abnormal result follow-up steps (Steps 4, 5, & 6). Across jurisdictions, colposcopy (Step 4) and post-treatment follow-up (Step 6) results generally provide clinicians with decision-making direction, while treatment (Step 5) decisions are generally left to a greater degree to the physician's discretion.

- **Equity and Access:** The technical aspects (i.e. which tests are used and in what order) of HPV primary screening and abnormal screen follow-up pathway is based on the best available evidence and as a result the pathway is not modified for certain groups to address inequity. To enable equity, program implementation is tailored to the community of focus based on the needs as identified by the community. Tailored aspects of implementation can include how screening and follow-up is accessed, communications approaches and materials, and community-program relationship development

- **Risk, Resources, and Outcomes:** While triage pathways are designed based on the evidence, values-based decisions also are needed as pathway design impacts health system resource use, clinician practice, and patient experience. Societal risk tolerance may impact aspects of pathway design especially when those aspects may have limited impact on outcomes.

- **Pathway Complexity:** A simpler pathway design is easier for clinicians and patients to understand and supports implementation and uptake. While variation exists across the pathways of different jurisdictions, there are common pathway design considerations. Pathway design impacts patient outcomes, patient experience, and the use of health system resources. A poorly designed pathway can lead to high resource use, over-treatment or under-treatment, and patients experiencing unnecessary stress, while a well-designed pathway can avoid these pitfalls. The following table identifies how the common pathway design consideration relate to the pathway steps outlined in section 4.1.1 above. For example, the Screening Ages and Intervals design consideration relates to Step 1: Screening Invitation in the pathway.

Table 2: Pathway Design Considerations in Relation to the Pathway Steps

PATHWAY DESIGN CONSIDERATIONS	STEP 1: SCREENING INVITATION	STEP 2: HPV PRIMARY SCREENING	STEP 3: TRIAGE	STEP 4: COLPOSCOPY	STEP 5: TREATMENT	STEP 6: POST-TREATMENT FOLLOW-UP
Screening Ages and Intervals	◆					
Screening Invitations and Results	◆					
Self-Sampling		◆				
Test Types		◆	◆	◆		
Triage			◆			
Abnormal Screen Follow-up				◆	◆	◆
Equity and Access	◆	◆	◆	◆	◆	◆
Risk and Health System Resource Use	◆	◆	◆	◆	◆	◆
Pathway Complexity	◆	◆	◆	◆	◆	◆

Each of these pathway design considerations are described below.

4.2.1 Screening Ages and Intervals (Step 1: Screening Invitation)

The age at which screening starts and ends varies across jurisdictions. It is also intertwined with the interval length between screenings.

Across the jurisdictions examined, the screening start ages range from 25-30, end ages range from 60-74, and intervals range from 3-10 years depending on the jurisdiction and the age group. Screening at an age older than the end age may occur if the person did not participate or had an HPV+ result during their last screening invitation.

There are variations in the start age. Some jurisdictions start at age 25, while others start at age 30. Before age 30, HPV infections commonly resolve on their own and so screening could lead to over-treatment of HPV that would otherwise resolve naturally. It was noted that outside the jurisdictions examined, some screening programs start at age 20, however, due to the same concern about overtreatment most programs start no earlier than age 25.

The last screen in a program is typically called the 'exit test.' This is the last test for older individuals participating in the program. Older individuals are still susceptible to HPV and need to be screened. The age at which screening stops varies by jurisdiction but is typically age 60-65. This variance is related to studies conducted in each jurisdiction. For example, the *Netherlands* reports that the majority of cervical cancer cases are in individuals between 30-60 years and *Australia* reports that the majority of cases are in individuals between 20-69 years. These ages are then reflected in their respective screening periods.[10,12] The exact age of the last screening test can be dependent on an individual's screening history and results, whether they were screened in the past under the new HPV primary screening program, or if they are under screened for the years leading up to the exit screen. Differing opinions about the exit age remain, however, and further research is needed. While the research shows the risk of persistent HPV infection and subsequent developing cancer is very low in older individuals, one recent study identified risk of cervical dysplasia for older

individuals and that 30% of cervical cancer cases were diagnosed in individuals older than age 60.[5]

Additional screening may happen for individuals older than the eligible screening program age range (e.g. older than 65 years) who didn't participate in screening during their last screening invitation or for individuals who received a recent HPV+ screening result.

Screening intervals are often 5 years and some jurisdictions are using or considering 10-year intervals.

The table below provides screening ages and interval lengths across jurisdictions.

Table 3: Screening Ages and Interval Lengths Across Jurisdictions

JURISDICTION	SCREENING AGE RANGE	INTERVAL LENGTH
Australia[12]	· **Start age:** 25 · **End age:** between 70-74 · Request for screening for 75+ years possible if they have never had a screening test or not had one in the previous 5 years	· Every 5 years
Netherlands[10]	· **Start age:** 30 · **End age:** 60 · Individuals aged 30, 35, 40, 50 and 60 are invited to participate. · Individuals aged 45 and 55 are invited if they did not participate five years previously, or if they were hrHPV positive five years ago. · Individuals aged 65 are invited if they were hrHPV positive five years ago	· Every 5 years (for ages 30-39 years) · Every 10 years (for ages 40 and 50) · All women who tested positive for hrHPV receive a new invitation after 5 years.
UK[13]	· **Start age:** 25 · **End age:** 64 · Individuals aged 65+ are invited if they never had a screening test or if one of their 3 last tests were abnormal	· Every 3 years (ages 25-49) · Every 5 years (ages 50-64) *Exploring extension to 10 years for >40 years of age*
US[14]	· **Start age:** 25 · **End age:** 65 · Discontinue screening for individuals who are >65 years and have had no history of ≥CIN2+ within past 25 years and have had adequate prior screening with negative results (i.e. 2 consecutive negative primary HPV tests)	· HPV-primary testing every 5 years is preferred; co-testing every 5 years or cytology every 3 years are acceptable

4.2.2 Screening Invitations and Results Communication (Steps 1: Screening Invitation, 2: HPV Primary Screening, & 3: Triage)

Invitations to participate in screening are managed by the screening program using a screening registry, which identifies when eligible individuals are due for screening. If the individual does not complete the HPV primary screening within a certain time period, a reminder is sent. There is variation in the channels through which invitations and reminders are sent to and target recipients, including:

- Mailed letters (to individual and/or primary care providers);
- Electronic prompts (to primary care providers through the health information system);
- Phone calls (to individual and/or primary care provider); and
- Text messages (to individuals).

A notable aspect of sending invitations in *Finland*, the invitation letter provides a location, date, and time for screening, and a prompt that the individual requests a different date and time if needed. People can change their provided date and time online or by phone. This practice of sending specific date and time is reported to increase participation by 6.6-9.4%.[15] This is similar to the European Guidelines that recommend a personal reminder letter that includes a scheduled appointment (date, time, and place) and a second invitation if no response is received to the initial reminder.[16]

There is some variation in how primary screening test results are received and who receives them. Results may be shared through the following channels:[11]

- Mailed letters (to individual and/or primary care provider);
- Electronic systems, such as the health information system (to primary care provider); and
- Phone calls (to individual and/or primary care provider).

For example, in the *Netherlands* results are mailed to the individual, however, if the HPV primary screening test result indicates a more significant abnormality, then the primary care physician calls the individual to share and explain the test result.[10] In *Australia*, the lab sends the results with a recommended next step of action after which the primary care physician reviews the results within 30 days and refers for colposcopy within 8 weeks when necessary.[17]

Reminders are an effective way to increase participation rates. It was reported that reminder letters increased participation by 8% and 10% in *Finland* and *Australia*, respectively. In general, for routine screening, reminders are sent between 6-24 months. Greater screening system resources are spent following-up on results that indicate higher risk for cancer. For example, in *Australia* reminder letters are sent for routine screening while reminders for results that indicate concerning cytology results are followed up with phone calls to the physician and manual reviews of the patient's information to ensure reminders were sent. In *Finland*, if there is no screening after 2 reminder letters, the person receives a phone call.

Sending invites or reminders by letter does present challenges to participation for transient and other populations, as they may not have a regular address or addresses may not be properly updated in the screening database. This continues to be a challenge in other jurisdictions such as *Australia*.[18]

4.2.3 Clinician-collected Samples Versus Patient-collected Samples (Step 2: HPV Primary Screening)

The use of self-sampling in HPV primary screening programs is gaining momentum for several reasons. First, the majority of cervical cancer cases occur in eligible individuals who are under- or never-screened (for example, 90% of cervical cancer cases in *Australia* are in under- or never-screened individuals).[12] Second, additional research has identified that self-sampling results are of comparable accuracy to clinician-collected samples in detecting CIN2+ or CIN3+.[19] Self-sampling has been typically offered only as an option to individuals who belong to groups who do not participate in screening with the same frequency as the rest of the population and who would have otherwise not participated in screening (i.e. under- or never-screened). Today, some jurisdictions are seeking to expand the use of self-sampling to anyone who is eligible for screening.[19] In particular:

- *Australia* and the *Netherlands* currently use self-sampling;
- The *UK* is currently testing self-sampling in pilot studies; and
- While clinician-collected sampling is recommended in the *US*, the US Preventive Services Task Force is calling for more testing with self-sampling, especially for under-screened individuals.[20,21]

In *Canada*, self-sampling is also being studied and there have been promising results with increased participation. Research findings also identified that digital health literacy and interest in online platforms is high in under-screened communities examined, and is a consideration for developing a screening program.[22]

Self-sampling shows promise to increase participation in under- and never-screened individuals when compared to individuals who are sent a reminder letter for a clinician-collected sample. In a randomized controlled trial in *Australia* the difference is just over 14% in the never-screened group (20.3% vs 6.0%) and 5.1% in the under-screened group (11.5% vs 6.4%).[24] This trial showed that the majority of the individuals with HPV detected also had the appropriate clinical follow-up (over 80%). The increased participation in under-screened individuals were also seen in studies in the *UK*, *Sweden* and *Finland*.[23,24] In *Finland* approximately 1/3 of the participants returned the self-collected sample in a pilot study and this was similar in *The Netherlands*.

Self-sampling can be done in a clinician's office or at home and may be targeted to under-screened people or made available for all people participating in screening. For example, *Australia*'s self-sampling happens in a clinical setting and focuses on under-screened people, while the *Netherlands* mails kits to the person's home if requested (more information on which groups were under-screened see section 4.2.7 Equity and Access (All Steps)).

As noted above, different jurisdictions are at different stages and contemplating different sets of offerings. The table below summarizes who can use self-sampling today and emerging developments under consideration in each jurisdiction.

Table 4: Self-Sampling Status Across Jurisdictions

SELF-SAMPLING ITEM	AUSTRALIA	FINLAND	NETHERLANDS	UK
Population Eligible for Self-Sampling	Under- and never-screened individuals (health care providers hand kits to individuals)	Individuals who are not participating in the screening program (mail self-sampling kits to individuals)	Individuals who refuse a clinician-collected sample (mail self-sampling kits to individuals)	N/A
Emerging Developments	Seeking to expand offering self-sampling to all eligible individuals to maintain equality in access to health care	Making the case to offer self-sampling to all eligible individuals to increase screening participation	Increasing self-sampling to all eligible individuals to opt-in when they do not attend a screening visit	Starting pilots for self-sampling

4.2.3.1 Benefits and Challenges of Self-Sampling

While there a several benefits to self-sampling, there are also challenges. Considerations on the use, benefits, implementation, and regulatory approaches continue to be examined.

Benefits: The benefits of self-sampling include increased screening participation, better patient experience with the collection of the sample, and increased convenience for some individuals.

Studies with self-sampling have seen higher participation in screening programs and over 80% in under-screened women in an *Australian* pilot study.[25,26] In *Australia*, self-sampling participation rates among under- and never-screened individuals were respectively triple and almost double those of their counterparts invited or reminded to go for a clinician-collected sample.[24] Patients in these studies have also expressed a better experience with self-sampling versus clinician-collected samples. The majority of participants in the *Netherland* studies noted that they would prefer self-sampling in future screening.[27,25] For some cultures it is a taboo to have a sample taken by a clinician and self-sampling avoids this taboo.[28] In some studies, it was reported that self-sampling is less embarrassing, stressful and painful than clinician sampling (it is particularly painful in older individuals as the physician speculum exam can be painful for post-menopausal individuals).[27,25]

In addition to being a better experience, some individuals also saw this approach as more convenient because it no longer requires scheduling an appointment with a health care provider for sample collection. A study in the *Netherlands* noted that barriers to participation in cervical screening include participants forgetting to book an appointment or having difficulties with arranging an appointment to fit in their busy work and home schedules.[29,27] Similarly, in an *Australian* study, it was discussed that there is a large advantage in offering self-sampling at home for individuals who have a difficulty in attending appointments, are experiencing trauma or anxiety and not wish to collect samples in a public setting.[26]

Challenges: While there are many benefits to self-sampling, including overall increases in primary screening participation, there are also some challenges. Approaches to overcome the challenges are described in the following section 4.2.3.2 Self-Sampling Implementation Considerations.

- It is reported that only a small percentage (approximately 1/3) of self-sampling kits are returned completed by people who received the self-sampling kit at home.[24]

- While the initial screen can be performed at home, a self-collected sample cannot be used for follow-up triage when there is an HPV+ result since it does not collect cervical cells for cytology. If the self-sample result is HPV+ it requires individuals to have a clinician-collected sample taken for cytology, or in some jurisdictions if HPV+ 16/18 is present have a referral directly to colposcopy.
- There were some concerns about packaging of mailed kits and privacy
- It may be challenging for screening programs to know whether mailed self-sample kits were received by the intended recipient or delivered to the correct address
- Self-sampling can be costly depending on the approach taken (i.e. "opt-out" approaches are more expensive. See the following self-sampling implementation considerations description below for further information)
- Over-screening can occur if the results of self-sampling are not integrated with the jurisdiction's screening registry
- Regulatory barriers sometimes exist

4.2.3.2 Self-Sampling Implementation Considerations

Self-sampling implementation considerations include:

1. Location and Packaging
2. Opting-in, Opting-out, and Requesting Kits
3. The Need for Links to Screening Registries
4. Public Concerns About Sample Collection and Validity
5. Cost
6. Regulatory Barriers
7. Pilot Programs
8. Maintenance of Self-Sampling During COVID-19
9. Public and Health Care Provider Education
10. The Role of Primary Care Relationships in Supporting Participation
11. The Use of Community Campaigns

Details of these elements are described below.

1. **Location and Packaging:** Some jurisdictions only permit self-sampling in a clinician's office while others allow people to perform self-collection at home. Self-collection kits can be mailed directly to the individual or picked-up at a clinician's office. Two challenges for mailed kits are reaching individuals when addresses change and knowing whether the kit was received by the intended recipient. While changing addresses is a challenge that is not unique to self-sampling, jurisdictions helped to mitigate the challenge with better IT systems to track addresses.[24] These challenges were also noted in *Australia* when encouraging participation of Aboriginal and Torres Strait Islander communities.[18]

   It was also noted that some individuals associate mail from national entities with negative events (e.g. fines or other such notices) and potentially avoid opening this mail. *Australia* will have HPV primary screening program laboratories send out the kits to avoid any national government letterheads on the envelope.

   There can be stigma around HPV as a sexually transmitted infection and there were concerns that an unsolicited HPV self-collection kit mailed to a person's home can exacerbate this stigma and deter participation. Appropriate labelling and anticipating the arrival of a kit in the mail through "opting-in" helps make it less stressful for people receiving this kit. In *Finland*, self-collection devices are sent in a plain envelope with no additional labels other than address and it is reported that this has generally not led to privacy concerns.

2. **Opting-In, Opting-Out, and Requesting Kits:** There two primary approaches to identifying when to mail a self-sampling kit when a person is due for screening. One is an "opt-in" approach where the person requests the kit and the other is an "opt-out" approach where a kit is sent unless the person requests that it is not sent. There are trade-offs with these approaches, as an "opt-in" approach is less expensive while and "opt-out" approach may reach more people that are under- or never-screened. Typically, either a letter is mailed to eligible individuals asking them whether they would like to receive a kit ("opt-in"), or a letter is mailed informing the individual that a kit will be sent and they can "opt-out" if they wish.[15,24] *Finland* and the *Netherlands* did consider automatically sending test kits to all individuals who did not go for screening after several reminder attempts. However, this approach would result in many wasted/unreturned kits, therefore, requiring people to opt-in to receiving a self-collection kit was seen as a more cost-effective approach. Different opt-in approaches should be explored and tested prior to implementation.[30,31]

3. **The Need for Links to Screening Registries:** When samples are not collected in the typical clinical setting, there is the risk that the necessary information and screening record from the individual may not make its way into the registry if health records are not linked.[32] Setting up a system that facilitates the inclusion of all screening results into the registry, whether they were collected from a self-sampling study or through an outreach initiative, ensures people are not over-screened, which can lead to over-treatment.

4. **Public Concerns About Sample Collection and Validity:** The two largest concerns individuals have regarding self-sampling are feeling uncertain that the test is reliable and not feeling confident that they collected the sample correctly.[27] However, in *Finland* a study showed that this uncertainty was not a barrier to self-sampling and 93% of women reported confidence in collecting the sample correctly.[15]

5. **Cost:** While there may be additional costs associated with mailing kits out, self-sampling is typically seen as a cost-effective approach to screening because the additional costs for mailing the kits are significantly less than the costs involved with clinician-collected samples. It was noted that in the *Netherlands* this could be as low as one-fourth of the price of clinician-collected samples.

6. **Regulatory Barriers:** Jurisdictions faced regulatory barriers to implementing self-sampling, as commercial HPV assays used in HPV testing are proven by the manufacturer to work with clinician-collected samples but not necessarily with patient-collected samples. Jurisdictions lacked "suitable clinically validated HPV assays with manufacturer validated claims for their use of self-collected samples (on label use)."[31] Some jurisdictions overcame the regulatory barriers by laboratories independently validating self-collection protocols against paired clinician-collected specimens.[31] Ultimately it is up to each jurisdiction to determine what is feasible and allowable.

   Australia, the *Netherlands* and *Finland* ensured high quality testing through laboratory level validation. In *Australia*, the Therapeutic Goods Administration (*Australia*'s regulatory authority for therapeutic goods) did not allow for full approval of the HPV collection device for self-sampling, but allowed for self-sampling by requiring each laboratory to validate the specific collection device used for self-collected HPV tests. This requirement, however, limited access to self-sampling as initially only one laboratory undertook this process. "It is unlikely

that full implementation of self-collection will occur until commercial HPV assays include self-collection as 'intended use'. This is of critical importance."[28]

Jurisdictions that implemented self-sampling noted that regulatory approval required lengthy processes and needed to start early in planning to avoid implementation delays. In *Australia*, unanticipated regulatory processes delayed implementation by 1 month and limited the scale of implementation because only one lab had the necessary test validation approvals.[28]

Another regulatory consideration is privacy. In *Australia*, the National Cancer Screening Register Act (2016) and Rules (2017) were created to guide the reporting of information in the registry that is mandatory for all pathologists and colposcopists involved.

7. **Pilot Programs:** Self-sampling pilots were often conducted and helped to demonstrate successful results and plan for broader implementation. Measures to collect during pilots can include positivity rate, positive predictive value of a positive test result, and cost-effectiveness, as well as resolve any organizational problems such as invitations and management protocols before being fully implemented.[16]

   Self-sampling is a promising and evolving approach to increase participation rates. While further research continues to be conducted, lessons from self-sampling implementation in other jurisdictions identifies several experiences and considerations to enable successful implementation elsewhere.

8. **Maintenance of Self-Sampling During COVID-19:** Given the physical distancing required during the COVID-19 pandemic, some cervical cancer screening programs were temporarily suspended, and self-sampling is being considered as a method to re-start programs and keep them functional during future waves of COVID-19. Laboratory capacity is a consideration and limiting factor as the same technology can be used for both HPV testing and COVID-19 testing.

9. **Public and Health Care Provider Education:** The public's concerns regarding the sample collection and validity can be directly addressed through communication approaches and educational resources for individuals and their health care providers. It is important that the health care providers are also equipped with adequate and pertinent information to help address the concerns as many individuals look to their health care provider for explanations and reassurance.[25]

10. **The Role of Primary Care Relationships in Supporting Participation:** To be effective at eliminating cervical cancer, self-sampling requires individuals who are HPV+ to have appropriate follow-up. In follow-up, a clinician-collected sample is required if cytology is needed for triaging an HPV+ result, however, self-sampling devices do not properly capture and preserve the cervical cells needed for cytology. Relationships between the patients and primary care providers are important in supporting participation in follow-up activities, including appointments for triage cytology and referrals to other tests and specialists.

    The role of primary care is also important for communicating information on conducting self-sampling and explaining the results. In *Australia*, enabling factors to increase self-sampling participation of under- and never-screened individuals included creating a trustworthy and empathetic relationship with health care providers, clear explanations on self-collection and understanding individuals' past experiences with sample collections.[26]

    Nurses working with Indigenous populations proactively call their patients to explain results and arrange sample collection for triage cytology testing to ensure that individuals are not lost to follow-up. In an *Australian* pilot study, additional support, resources, and flexibility in the approach to care delivery were used with under- and never-screened women to help make the care conducive to completing the screening and follow-up steps of the pathway. These included additional time offered by health service staff to engage participants, explain the results and track/follow-up with these individuals. Other efforts included offering transport/accompaniment to follow-up appointments and coordinating with case-workers and support plans for individuals' admission dates into emergency accommodation. These are factors to consider when designing the use of self-sampling in a program.[26]

11. **The Use of Community Campaigns:** Self-sampling participation is further increased with the use of community campaigns as an outreach approach. An analysis of self-collection participation trials showed that individuals who were in study groups exposed to community outreach, media support, and door-to-door campaigns had a higher participation rate than individuals who were invited for a clinician-collected sample (15.6% vs 6.0% for community campaigns and 94.2% vs. 53.0% for door-to-door campaigns).[31]

4.2.4 Test Types (Steps 2: HPV Primary Screening & 3: Triage)

There are several types of tests used in the primary screening and triage process. The four most common are:

- HPV partial genotyping
- Liquid-Based Cytology
- P16-Ki67 immunostaining
- Methylation

While some tests are common across jurisdictions, others are used less frequently but could become more widespread in the future if further research confirms usefulness in accurately detecting HPV. Many jurisdictions are moving towards HPV partial genotyping, with most being able to distinguish at least HPV+ 16/18, and some able to identify other high-risk strains.

Partial genotyping of HPV+ 16/18 allows for identification of the highest risk strains, however, further research may show that it is valuable to identify other types of HPV as other strains can contribute to the development of cancer.[5] The efficacy of using partial genotyping, however, is dependent on age. One study found that partial genotyping of only HPV+ 16/18 during triage can result in suboptimal predictive value of cases that may result in high-grade lesions in a population of unvaccinated women. HPV+ 16/18 attributed disease is more prevalent in younger women and "in women over age 45, only a third of HSIL+ findings were attributable to HPV+ 16/18, while other hrHPV types and hrHPV negativity were more prevalent." [33] This has led to the suggestion that co-testing with cytology may be warranted in women over age 45.[33] Some suggest that no genotyping be used as a routine triage method. Which HPV types to include in the assay should consider the prevalence of disease and absolute risk of disease related to HPV genotype.[34]

Benefits of genotyping at least HPV types 16/18 includes allowing for triage pathways to be ready for people who have been vaccinated against HPV. In *Australia*, vaccines inoculate against HPV 16/18 (some also protect against other strains of HPV) and the prevalence of HPV+ 16/18 in people who have been vaccinated at a young age is less. As a result, people who are HPV+ 16/18 are managed differently from individuals who have other types of hrHPV (i.e. non-HPV+ 16/18). This helps to avoid over-referral of the younger age groups.[28] *Australia* also found that genotyping improved cost-effectiveness.

One possible future for testing is the use of HPV+ 16/18 primary screen with methylation, as it provides logistical advantages (i.e. works with self-screening). However, this test is still being researched and is not widely implemented.

The table below provides additional information about the test types.

Table 5: Test Types Used in Primary Screening and Triage Process

TEST TYPE	DESCRIPTION	GENERAL COMMENTS
HPV partial genotyping	· Identifies if HPV present and type · Used for primary screening; can also be used for triage	· Type of HPV included in the assay often includes HPV+ 16/18 (the highest risk types), however, also influenced by type prevalence in disease in the population. Jurisdictions may identify other hrHPV types beyond 16 and 18
Cytology	· Mainly used for triage (in HPV primary screening pathways)	· Has the largest volume of historic follow-up data · Cytology cannot be used for triage with self-sampling
p16-Ki67 immunostaining	· Measures a cellular protein related to the activity of HPV oncogene E7 · Primarily used for triage; improves risk stratification	· Provides high specificity when combined with HPV+ 16/18 genotyping · One trial saw high percentage of CIN3+ at follow-up who had p16 presence at baseline; may more accurately distinguish between transient HPV infections and those that are likely to progress to cancer[5,34] · May not yet be cost effective
Methylation	· Molecular test (intact cervical cells not required) related to development of malignancies and can be measured accurately	· The test is still in early research stages but expected to improve and shows promise in relation to specificity and sensitivity[5] · Can be used with HPV+ 16/18 genotyping as an alternative option to HPV+ 16/18 with cytology · Methylation, as a triage option, can be done with self-sampling as it does not require preservation of intact cells

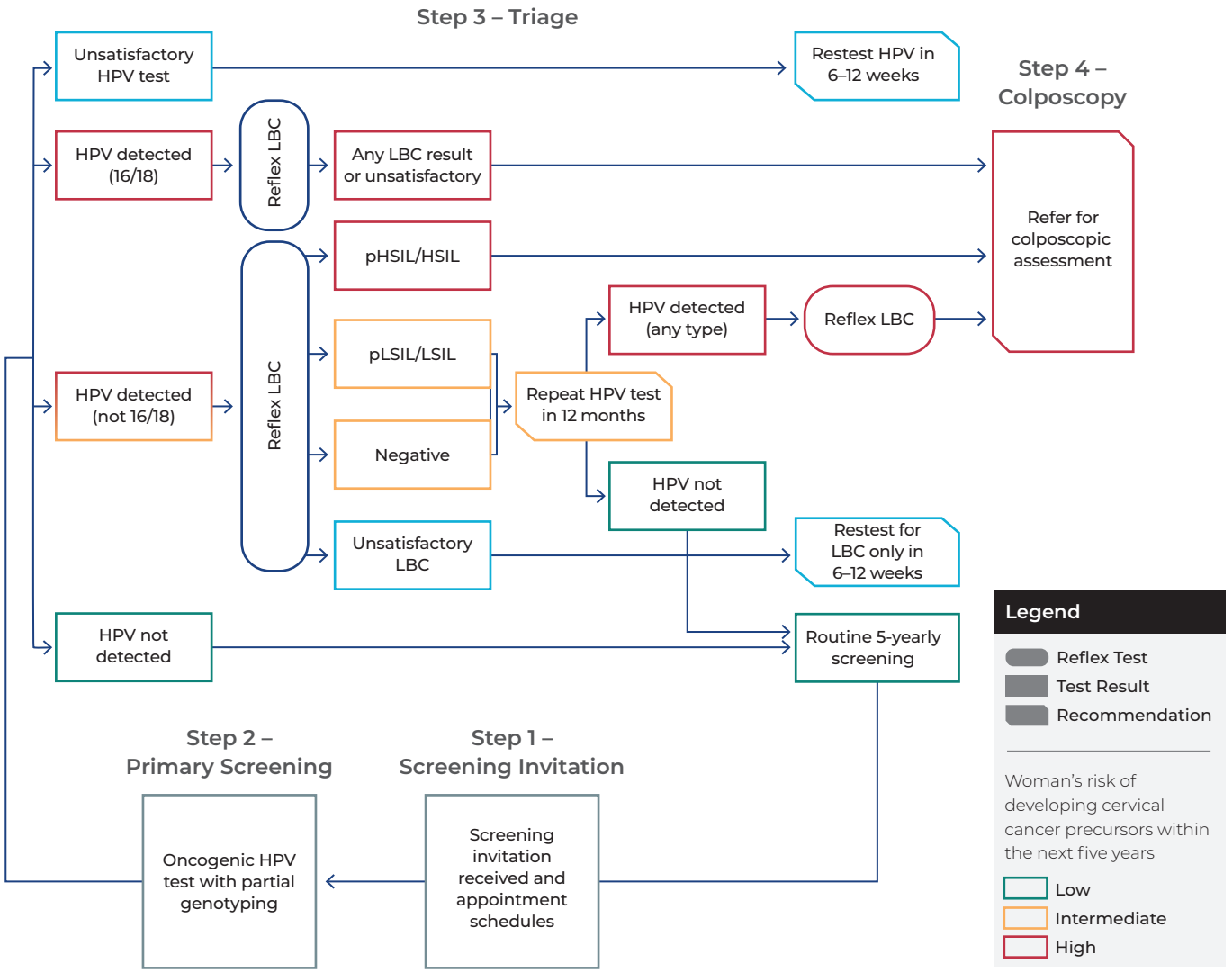
4.2.4.1 Triage Pathways (Step 3: Triage)

To show an example of how the screening and triage steps of two pathways can differ, Steps 1 and 2 of the pathways for *Australia* and the *UK* are shown below in some detail. Differences in the number of retest cycles and the treatment of HPV+ 16/18 can be seen.

Australia

In *Australia*, HPV+ 16/18 or HPV+ not 16/18 with HSIL is deemed higher risk and is referred to colposcopy. HPV+ not 16/18 with LSIL is deemed moderate risk and there is 1 cycle of retesting at 12 months in order to determine if referral to colposcopy is needed (See Appendix 6.3 for terminology reference). A partial pathway is shown below.

Figure 8: Australia's HPV Primary Screening Pathway (Steps 1-3 shown)

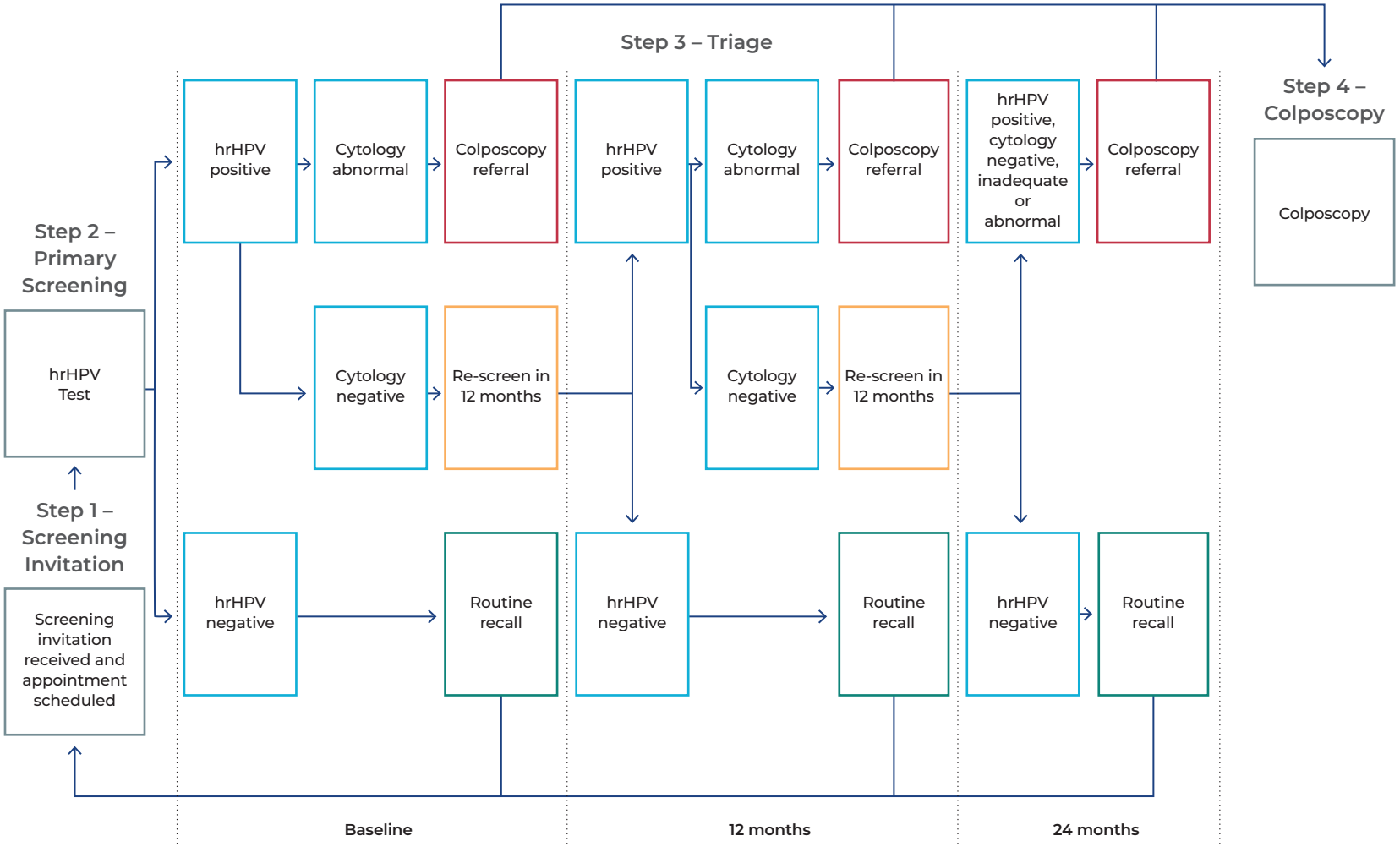


Acronyms: LBC – Liquid-based cytology; pLSIL- possible Low grade squamous intraepithelial lesion; LSIL- Low grade squamous intraepithelial lesion; HSIL- High grade squamous intraepithelial lesion. Source: Cancer Council Australia, Clinical Guidelines Network website

The United Kingdom

In the *UK*, there is no differentiation between the types of HPV in the pathway. All hrHPV+ results go to cytology and 2 cycles of HPV retesting are used to ensure the appropriate cases are referred to colposcopy. A partial pathway is shown below.

Figure 9: The United Kingdom's HPV Primary Screening Pathway (Steps 1-3 shown)



Source: UK's government website for Cervical Screening: primary HPV screening implementation guidance website.

4.2.5 Triage – Risk-Based versus Static Pathways (Step 3: Triage)

Another way triage can vary is in the overall approach and whether a pathway is used at all. Most notably, guidelines from the American Society of Colposcopy and Cervical Pathology's (ASCCP) 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors suggest follow-up be decided upon using risk tables rather than a static triage step (terminology note: these guidelines outline the suggested pathway to be followed in the United States).

This risk-based approach uses not only HPV and cytology results but also past HPV and cytology results and past medical history to determine risk of CIN3+ and plan next steps based on this risk. Below is a sample risk table for results obtained in follow-up of HPV-negative ASC-US in this case.[35]

Table 6: Sample Risk Table for HPV-negative ASC-US Results Obtained in Follow-Up[35]

HISTORY	CURRENT HPV RESULT	CURRENT CYTOLOGY RESULT	*n*	%	CIN 3+ CASES	CIN 3+ IMMEDIATE RISK, %	CIN 3+ 5-YEAR RISK (%)	RECOMMENDED MANAGEMENT	RECOMMENDATION CONFERENCE SCORE, %
HPV-negative ASC-US	HPV-negative	NILM	13,918	82	14	0.00	**0.14**	5-y follow-up	58
HPV-negative A SC-US	HPV-negative	ASC-US	1,701	10	w11	0.06	**0.78**	1-y follow-up	82
HPV-negative ASC-US	HPV-negative	LSIL	193	1.1	5	2.4	**3.1**	1-y follow-up	80
HPV-negative ASC-US	HPV-negative	ASC-H	57	0.34	3	5.7	5.7	Colposcopy	65
HPV-negative ASC-US	HPV-negative	AGC	59	0.35	0	0.00	0.00	Colposcopy	S/S*
PV-negative ASC-US	HPV-negative	HSIL+	11	0.07	1	**11**	11	Colposcopy	36
HPV-negative ASC-US	HPV-negative	ALL	15,939	94	34	0.06	0.27		Special Situation
HPV-negative ASC-US	HPV-positive	NILM	392	2.3	6	0.96	**2.4**	1-y follow-up	97
HPV-negative ASC-US	HPV-positive	ASC-US	288	1.7	13	**2.1**	**6.6**	1-y follow-up	97
HPV-negative ASC-US	HPV-positive	LSIL	228	1.4	5	2.6	**2.6**	1-y follow-up	85
HPV-negative ASC-US	HPV-positive	ASC-H	25	0.15	5	**24**	24	Colposcopy	53
HPV-negative ASC-US	HPV-positive	AGC	5	0.03	0	0.00	0.00	Colposcopy	Special Situation
HPV-negative ASC-US	HPV-positive	HSIL+	26	0.15	8	**36**	36	Colposcopy/ treatment	86
		TOTAL	**16,903**	**100**	**71**				

As these risk-based guidelines consider more variables to determine risk, an app was developed to allow physicians to type in the available clinical information and receive a recommended next step for the specific patient, which makes the complexity of the guidelines more manageable.

Next step options are also similar to other pathways which may proceed to waiting and retesting, colposcopy, and/or eventual treatment (see Basic Overview of Pathway Steps, section 4.1.1). Next step options in the United States include:

- 1-year surveillance;
- 3- year surveillance;
- 5-year surveillance;
- Colposcopy/biopsy;
- Optional treatment or colposcopy/biopsy; and
- Treatment.[35]

The guidelines on the Pathways are purposely not provided for the *US* as a risk-based approach is used. Additional guidelines can be found in the American Society for Colposcopy and Clinical Pathology (ASCCP) website.

4.2.6 Abnormal Screen Follow-up (Steps 4: Colposcopy, 5: Treatment & 6: Post-Treatment Follow-up)

Similar to the screening steps of the pathway, there is a lot of variation across jurisdictions in the abnormal screen follow-up steps of the pathway, which typically include:

- Colposcopy;
- Treatment; and
- Post-Treatment Follow-up.

Colposcopy (Step 4)

Pathways at the colposcopy step (Step 4) vary in length and complexity across jurisdictions. Parts of the pathway in Step 4 are generally concerned with deciding on next steps after the colposcopy has been completed and several factors are considered. Depending on the jurisdiction, factors include:

- Adequacy of colposcopy examination;
- hrHPV status;
- Grade of cytology;
- Biopsy results and impression of CIN;
- Colposcopic impression of CIN; and
- Other variables such as patient preference.

For example, factors considered in the *UK* include adequacy of colposcopy examination (i.e. whether the colposcopy could be properly completed), biopsy, impression of CIN, and repeat HPV testing. Factors considered in *Australia* include LBC results, colposcopy examination, biopsy, and repeat co-testing. As a proxy to demonstrate the differing levels of complexity across jurisdictions on referral to colposcopy, it is notable that the *UK* has 2 pages of pathway diagrams for next steps while *Australia* uses over 12 pages. These choices are made by the clinician and patient.

Next steps after Step 4 (Colposcopy) may include:

- A period of waiting and then repeat HPV testing and cytology (which may return the individual to routine screening [Step 1]);
- Repeat colposcopy based on HPV and cytology results; or
- Treatment (Step 5).

Treatment (Step 5)

Treatment (Step 5) is typically left primarily to a clinician's discretion. While some pathways (or guidelines) do make some recommendations, the full spectrum of treatment decisions are not described in the HPV primary screening and abnormal result follow-up pathways. For example, in the *UK* the guidelines say that a range of treatment options are acceptable yet identifies certain situations when a certain treatment option be excluded. *Australia*'s Optimal Care Guidelines indicate that surgical, radiation, and chemotherapy options may be considered.[17] Special considerations are made for people wishing to preserve their fertility and palliative care may also need to be considered depending on the patient's case.

Post-Treatment Follow-up (Step 6)

HPV primary screening and abnormal result follow-up pathways generally provide direction for Post-Treatment Follow-up. Post-treatment follow-up is increasingly relying on HPV testing to determine whether the individual requires additional treatment or can return to screening,

which may or may not be routine screening. In some jurisdictions this is called "test of cure." Variations in Step 6 include:

- Steps after the HPV test results;
- Whether cytology is used as a follow-up test if HPV test results are positive or a co-test; and
- How many sequential negative HPV test results are needed and how frequently before releasing the individual from post-treatment follow-up.

4.2.7 Equity and Access (All Steps)

Increased participation in screening programs is one of the most impactful ways to prevent cancer. Most cervical cancer is found in people who are not screened (in *Australia* 90% of cancers occur in under-screened individuals).[12] In other jurisdictions, a special focus on working towards equity was present for the following groups:

- Indigenous peoples
- Recent immigrants and people not familiar with the jurisdiction's official languages
- Victims of rape and survivors of sexual abuse
- Marginalized individuals
- Gender diverse individuals
- Individuals with special needs (physical, intellectual, psychosocial)
- Long-term unemployed individuals
- Elderly individuals
- Individuals who were born to mothers who took Diethylstilbestrol (DES) during pregnancy, as a link was found between prenatal DES exposure and higher risk of cervical cancer

Importantly, the screening clinical pathway should not change for these groups as it is the best care based on the evidence. The program delivery and language, however, may need to be modified to make it more appropriate for these groups.

There were several approaches used to improve equity and participation in screening. In *Australia*, an optimal care pathway for women with cervical cancer was developed to improve the experience of cervical screening for individuals and efforts are being made to provide support for those with disabilities, rape victims and survivors of sexual abuse.[17] Australia also developed the document "Optimal Care Pathway For Aboriginal and Torres Strait Islander People with Cancer." For individuals with physical disabilities, the use of the Australian Institute of Health and Welfare disability flag upon admission and noting disabilities in the referral forms to diagnostic assessment is encouraged. Additional support, including issues with disclosure of past history of sexual abuse/trauma, considering potential barriers associated with informed consents, encouragement to bring a support person to the appointment, and reasonable adjustments such as self-sampling are also recommended for rape victims and survivors of sexual abuse.[17]

Additional efforts include:

1. **Engaging with the Community**
2. **Conducting Research/creation of Outreach Approaches**
3. **Developing Community-Specific Materials and Approaches**
4. **Using Self-sampling**

These approaches are discussed below.

1. **Engaging with the Community:** Screening programs engage with communities of focus to understand community-specific needs and approaches to enable equity. These approaches are typically related to program delivery aspects such as the best ways for people to access screening, how to communicate with the community (channels and appropriate language) and overcoming any barriers to participation. Engagement happens during planning as well as on an ongoing basis and is most effective if consistent relationships between the program and community can be developed. Feedback from the community can be used to monitor participation rates and modify outreach accordingly.

   In *Australia*, the screening pathway does not vary, however, outreach efforts are tailored for the Aboriginal and Torres Strait Islander women (who have a higher prevalence of HPV+ 16/18 than non-Aboriginal women)[36]. There are

state- and territory-level health programs, with nurses and community liaisons dedicated to these communities delivering screening program-related information and services. Optimal care pathways have been developed for these communities to help guide the health care team navigate through the cancer pathways.[37] The document calls out specific beliefs, behaviors and needs of the Aboriginal and Torres Strait Islander people. It explains the holistic health and wellbeing and the role of knowledge, values beliefs cultural needs and health history in decision making processes for treatment and care. The supportive care needs of the patient and families are routinely identified, and a patient is asked whether they wish a support person needs to be present during discussions. Local support services are available and in between specialist appointments, local health professionals and/or Cancer Council nurses provide information and reassurance via a national information and support telephone service (this service is also available for health care providers).[37]

The importance of engaging with the community is also being seen in Canadian pilot and research studies. In *British Columbia*, the HPV FOCAL trial focused on comparing primary HPV testing with liquid-based cytology for cervical cancer screening.[6] For this trial, the investigators spent some time and engaged with the First Nations, Inuit and Métis groups to determine what would work for them to participate in self-sampling. The team met with primary care physicians who were familiar with the community and held focus groups with elders and people of the community. The online capabilities of these groups were also explored as self-sampling would involve online information. The good working relationship with the Métis Nation family practice locations helped to identify whether individuals were already screened and allowed the study address community concerns and provide information about the differences in the screening program, including the older starting age (e.g. it is due to medical technological advances in HPV testing that allows for an older start age and not due to the government's desire to save money).

2. **Conducting Research:** Prior to and throughout implementation, research on outreach approaches helps to identify the true needs of individuals sought for participation. Broader research also helped to identify what inequalities existed. This knowledge can help tailor program delivery more appropriately and increase participation rates.

   In *Australia* it was recommended that the screening pathway continue as it would for the general population, but that specific efforts should be made for providing invitations to screening, diagnostic, and treatment services in an accessible and culturally appropriate manner.

   In *Australia*, research was consolidated into a short paper, *Inequalities in cancer outcomes by Indigenous status and socioeconomic quintile*, to identify "where and why disparities occur across the cancer control continuum."[38] The paper identified poorer health outcomes and suggested why this is happening, including poorer screening and poorer access to services.

   In the *UK*, representatives of not-for-profit groups such as Jo's Trust conduct research on community communication and health care service needs that help identify more effective outreach efforts as well as identify sub-groups of the population that are under-screened and have may have not been detected by larger studies involving the general population. These efforts led to a "train-the-trainer" type program that trains the health care professionals to train others in their own community about the HPV Primary Screening program. It also led to a focus on studying "barriers to cervical screening among women aged 50–64 years from hard-to-reach groups whose perspectives are often absent from research on cervical screening but are critical to developing appropriate interventions to increase engagement with the screening offer."[39] By 2036-2040 it is projected that the peak age of cervical cancer diagnosis will shift from the late 20s to the 50s age ranges in England.[39]

3. **Developing Community-Specific Material and Approaches:** All jurisdictions noted that tailored communication methods and language have been pivotal in successful outreach. HPV can be a sensitive subject that is often hard to explain and understand. Considerations need to be taken related to language that may be sensitive, viewpoints and perceptions of HPV, and clarity of messaging. They found that pictures worked better than words and the use of videos with written material was a good combination when communicating information about HPV and screening. Providing information in the appropriate language is also recommended.

   In *Australia*, a professionally trained interpreter is recommended when communicating with people who have a limited proficiency in English. To support Aboriginal and Torres Strait Islander people, *Australia* created several types of resources. These include:

   - **Liaisons and Community Specific Health Workers:** health care professionals and community liaisons promote health programs and provide care in a culturally and language-appropriate manner.
   - **Optimal Care Pathway Consideration:** A quick reference guide for clinicians was created and contains considerations to support the delivery of optimal care for these communities in community appropriate ways (related to multiple types of cancer).
   - **Patient and Health Worker Information:** provide patient or community member focused material, including material adapted for the community from general information and picture card education.[40] Cancer Council NSW also created a website with information for health workers on supporting people with cancer from Aboriginal communities.

   Similarly, in the *UK*, they created easy-to-read guides in various languages, and positioned their message around the notion that screening and receiving positive test results can be challenging to receive and why it's still important to screen.

   The *Netherlands* also created a simplified and translated version of the information pamphlet with additional videos to ensure the information is appropriate for minority groups.

4. **Using Self-Sampling:** Jurisdictions have highlighted self-sampling as a valuable outreach effort for groups that may not have easy access to health services or for individuals who do not feel comfortable with a clinician collecting the sample. In *Australia*, there is a positive adoption of self-sampling amongst eligible individuals, including those from Indigenous and migrant communities who may not be comfortable with a clinician-collected sample. See section 4.2.3.2 Self-Sampling Implementation Considerations for more information on self-sampling.

4.2.8 Risk and Health System Resource Use (All Steps)

It is important to have a well-designed triage component of the pathway to mitigate risks that would otherwise be present with HPV primary screening. A well-designed triage process reduces these risks. The HPV primary screen alone has higher sensitivity but lower specificity compared with the Pap test. It therefore has a higher probability of detecting disease but also has a higher false-positive rate that can lead to over-referral to colposcopy. Conceptually, over-referral to colposcopy is not desirable from at least two perspectives:

- **Patient Perspective:** Over-referral can lead to over-treatment, which can harm patients, including through negative consequences for childbearing. Not all people who test positive for HPV go on to develop pre-cancer or cancer and HPV can resolve on its own without treatment. The challenge, therefore, is how best to identify and treat HPV cases that may develop into cancer.

- **Health System Resources Perspective:** Over-referral also uses more health system resources than is optimal. Colposcopy often becomes the bottleneck in the care pathway when HPV primary screening is first implemented and may continue to be the bottleneck unless a triage process is designed into the pathway to ensure only the right cases get to colposcopy. This bottleneck is caused by a spike in referrals to colposcopy and a relatively constant colposcopy capacity. A temporary bottleneck was experienced in all the jurisdictions examined that implemented HPV primary screening.

To avoid potential over-referral, triage processes are used to identify which patient cases are anticipated to develop into cancer from those that will not. A robust triage process:

- Decreases the risk of over-referral appropriately;
- Focuses referrals on cases that will result in CIN 2+ cervical cancer and improves their outcomes; and
- Stewards health system resources.

Jurisdictions design the triage component of the pathway to balance risk and resources by using various approaches such as retesting cycles, balancing test information sources, multiple health professional roles or monitoring outcomes.

Retesting cycles are periods of waiting and retesting, typically after 6-12 months, for HPV and/or cytology when the first test result was positive. The reason for the waiting period is that some HPV infections resolve without treatment, so retesting appropriately sends these cases back to routine screening without treatment. Other jurisdictions place different levels of reliance on the types of test information. In balancing test information sources, some jurisdictions place greater emphasis on cytology, while others are starting to rely more on the presence of HPV+ 16/18.

For example, the *Netherlands* refers to colposcopy based on cytology and appears to be risk averse in its approach, since any non-NILM and ASC-US+ result gets a referral to colposcopy (see Appendix: Glossary of Selected Terms for a description of terms). *Australia* reduces risk of false-positives by requiring some abnormal cytology results to go through retesting instead of being directly referred to colposcopy. To help balance risk, however, it does refer HPV+ 16/18 from self-collected samples directly to colposcopy without cytology and then a sample for liquid-based cytology is collected at the colposcopy appointment.

To curb the high cost of physicians, some program models use multiple health professionals, including both nurses and physicians to collect the clinician HPV test samples versus physicians only. Other jurisdictions monitor local data to determine which aspects of the pathway are effective in creating the desired outcomes.

4.2.9 Pathway Complexity (All Steps)

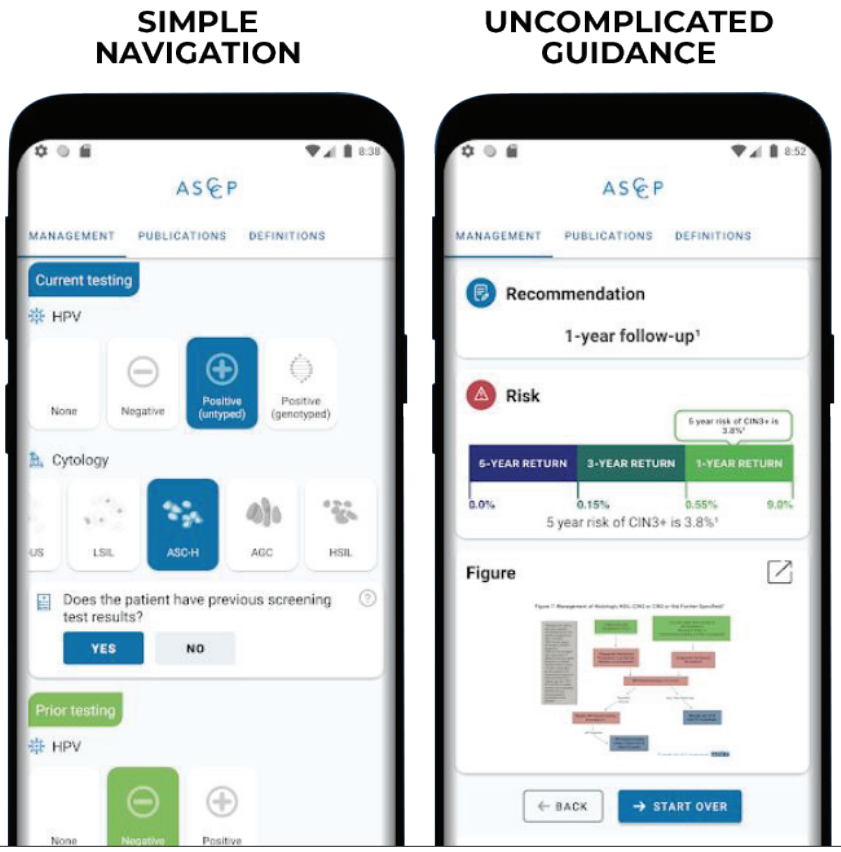
HPV primary screening and abnormal result follow-up pathways can become very long and complex; documenting them can take many pages of text and diagrams. Clinicians and patients are understandably challenged to follow lengthy and complex pathways. While pathways need to be appropriately designed based on scientific evidence, they also need to be simple enough to implement and follow once established.

Jurisdictions have addressed this challenge by using either:

- **Simple Pathways:** Intentionally creating a pathway that is shorter and has fewer decision points and paths. For example, the *UK*'s pathway is only a few pages.

- **Technology:** Technology can help to create a simple experience for clinicians. For example, while the pathway (the term guidelines is used) in the *US* is very complex, the American Society for Colposcopy and Cervical Pathology (ASCCP), which develops and provides guidelines, has developed an app that allows the clinician to type in the patient information and obtain a recommendation for that patient's situation. A snapshot of the app is provided below from the ASCCP website.

Figure 10: A Snapshot of ASCCP's Management Guidelines App



Source : ASCCP website

4.3 PRACTICAL CONSIDERATIONS FOR IMPLEMENTATION

Key findings:

- Elements for successful implementation include creating an initial steering committee, registry and supportive IT systems, guidelines and pathways, and predictive models.
- The development of a clear implementation plan can facilitate the preparedness for the laboratory and colposcopy needs, the two health services that are impacted the most with an HPV primary screening program.
- Successful program implementation depends greatly on extensive communication and support material provided to the users of the program (health care professionals and public), and ongoing monitoring of the program's performance.

4.3.1 Phases of Implementation

Jurisdictions that implemented HPV primary screening programs had some common planning elements and lessons learned. Implementation is a long process and considerations for implementation can be categorized into three phases shown in the diagram below.

Details on the implementation phases are provided below.

4.3.1.1 Building a Foundation

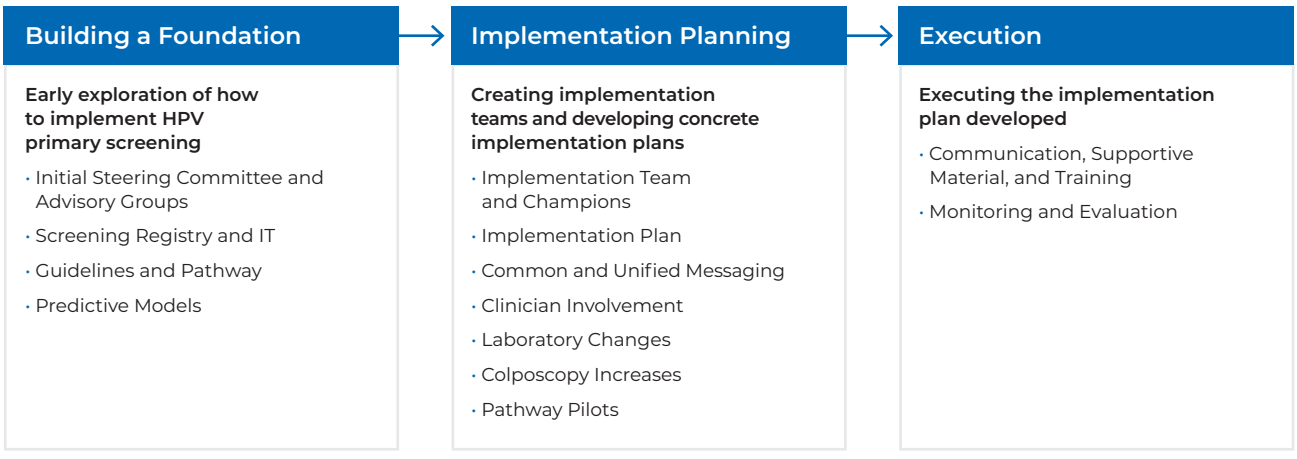
The following implementation considerations were considered when the jurisdictions were in the early stages of planning implementation. A few initial considerations include an Initial Steering Committee and Advisory Groups, Screening Registries and IT, Guidelines and Pathway and Predictive Models. These are described in more detail below.

Initial Steering Committee and Advisory Groups: Dedicated individuals involved early in planning include leaders, champions, and program managers.

In *Australia*, the federal- and state-based governments created the "Renewal Steering Committee" to determine the screening pathway and the implementation plan. It was comprised of gynecologic oncologists, colposcopists, cytopathologists, general practitioners, program managers, consumers and epidemiologists. The committee was responsible to submit the pathway to the Medical Advisory Group.[41]

- **Medical Advisory Group:** comprised of health care professionals who review and recommend the new pathway and the pathology tests for public funding under Medicare to the health minister.

Figure 11: Implementation Phases



- **Government Advisory Group:** health officials who endorse the recommendations from the Medical advisory group.

In the *Netherlands*, patient representatives are present on several groups including overall communications, pre-testing communications materials (includes more detailed work and includes individuals from specific populations when testing targeted material), and the overall board/governance.

Screening Registry and IT: Registry and IT support systems require early, detailed planning and testing, as a program cannot be implemented without these foundational elements.

In *Australia*, the screening registry was a particular challenge as they transformed the regional registries into a national one. This was a large IT system change and implementation took approximately 4.5 years as complications caused a delay in the screening program implementation, created confusion amongst the health care providers and users, and cost the government additional funds to maintain the old system. A lesson was that health registries are complex and require functions beyond solely being a database and "providers of such IT systems need to include multidisciplinary teams, including public health and laboratory professionals, in addition to health information managers with relevant experience."[28]

The *Netherlands* illustrated that a longstanding, functional registry system supported a smooth implementation, identifying and inviting eligible program participants without issues.

In the *UK*, information systems were informative to health system planners in tracking progress of the implementation. For example, tracking backlogs helped to identify where additional resources were needed.

Guidelines and Pathways: Clear guidelines and pathways that are easy to understand and use are essential in a successful HPV primary screening program. They can take some time to create (one jurisdiction mentioned that it took about 18 months) and it is important to start early because approvals are needed before implementation can start. More information on pathways is provided in previous sections.

The *US* and the *Netherlands* are making it easier for clinicians to use their pathways by creating electronic apps accessible online or using a smartphone. Online apps are dynamic tools that replace static pathways online or in paper print. They are termed "dynamic" because updates can be made in the back end without affecting the user's view.[42]

Predictive Models: Models on incidence, death rates, and costs helped jurisdictions explore the impacts of implementing HPV primary screening. From a health system planning perspective, models in other jurisdictions typically predicted an increase of colposcopies (see additional information in Implementation Planning section 4.3.1.2 below) and a decrease in cytology tests.[28,43,44]

All the jurisdictions predicted a decrease in incidence, deaths and costs. In *Australia*, the annual predictions were 24% fewer cervical cases, 30% fewer deaths and a 26% decrease in costs.[36]

4.3.1.2 Implementation Planning

A change to a screening program is a large undertaking for any health care system. Concrete and detailed planning with the right people is critical for a successful implementation. Detailed plans need to address tasks and decisions on the pathway, regulatory and health approvals, resource planning and pilots of the pathway, and a few of these are detailed below.

Implementation Team and Champions: these individuals are responsible to manage and endorse the program from beginning to end. The Implementation Team manages the implementation from start to end and is comprised of people with various expertise to carry out the implementation tasks. **Champions** are well respected people who advocate for change in their respective professional groups (e.g. gynecology/oncology, cytology, colposcopy, general practitioners, nurses, equity community leaders).

Implementation and Related Plans:
A comprehensive implementation plan is needed to communicate what the program will involve, set expectations, and enable a smoother transition. It helps identify policy decisions, steps and tasks to be done, and process interdependencies to include in planning. Implementation and related plans cover a broad range of topics including:

- Clinical pathways
- The roles and responsibilities of health care workers
- What patients will experience as they move through the pathways
- Funding models and reimbursements to primary care providers
- Changes to the pathology business models
- Workforce planning, including the re-training of cytologists
- Safety and quality
- Registry requirements
- Evaluation
- The sequencing of implementation activities
- Communications

These topics can take a longer time to address retrospectively and cause unintended delays in implementation if not planned well in advance.

These plans can take multiple forms and are typically divided into multiple documents depending on the target audience. For example, a detailed implementation plan and tools may be developed for the team involved in implementation, clinically-focused descriptions of the clinical pathway and guidelines or standards could be outlined for clinicians, public facing-communications documents with plans explained in language that doesn't required understanding of technical language, and an evaluation plan could all be created. Several different examples of implementation and related plans exist, including:

Australia's implementation plan was developed by the Initial Steering Committee around five workstreams with clear tasks and owners for each task. The Committee structured its work around five workstreams, composed of Medical Benefits Schedule, Registry, Workforce and Practice Change, Safety and Quality, and Communication and Information.[41]

The *UK* developed a clear implementation plan that identified the lengthy procurement process for the laboratories.

The *Netherlands*' plan is called the "Framework for the Execution of Cervical Cancer Population Screening" and it describes the regulatory legislative framework, relations between implicated organizations, and the evaluation plan that ensured a high quality, attainable and affordable screening process.[10]

In *Finland* the Taskforce for the implementation created a document with their mandate, timetables and various analyses and models (including information on HPV, vaccination, screening, clinical trials, organized screening, mathematical model of HPV, transition model, and progression model).

Common and Unified Messaging: There are many stakeholders involved in implementing a screening program, especially if it involves a change from one program to another. In general, jurisdictions had a common message and a document with information on how the screening process would work and supporting evidence/data for the process.

The UK had implementation and communication challenges that highlight the importance of early and clear communication. Lack of communication had an unintended negative impact on cytology capacity as the cytology workforce started to decrease when staff, anticipating a lack of jobs after HPV primary implementation, looked to find work elsewhere. As a result, the time from screening to receipt of results for cytology went from 89% completed in 2 weeks to 48% during implementation.[45]

Australia's champions rooted communications in the evidence and data, focusing on outcomes from local pilot studies. In doing so, the champions were able to address anxiety or doubts from stakeholders and keep them focused on increasing screening outreach throughout the implementation process. Documents were developed to outline common and unified messaging.

Clinician Involvement: Clinicians, particularly primary care clinicians, are critical to a successful screening implementation given their central role in the system – they are the link between the population and the health care system. Involving clinicians early in planning, during the decision-making process, and throughout planning can address concerns with adherence to a program once launched.

- In some jurisdictions it was noted that a clinician's encouragement to participate can increase screening participation rates.
- In *Finland*, the Steering Committee involved clinicians in all hospital districts in the decision to move forward with HPV primary screening.

Laboratory Changes: Jurisdictions found that early planning for the decreased volume of cytology tests was not only beneficial to the health system but also to the people working in the laboratory, who would experience the most change with the new screening program. The decrease in cytology tests is quite significant when a jurisdiction switches from cytology-based testing to HPV-based testing. The impact of these changes results in fewer laboratories required. *Finland* required 3 laboratories to support a population of approximately 5.5 million people. The *Netherlands* has 5 laboratories (with 3 machines in each laboratory), to support a population of approximately 17 million people.

- In the *Netherlands*, only 9% of the cervical tests are cytology-based (reflex testing) and in *Finland* it is about 25% (reflex testing and tests of younger individuals (25-30 years)).
- All jurisdictions noted that the decreased need for cytology health human resources was managed through a combination of the following avenues:
  - decreasing the number of cytology graduates,
  - retraining of current cytologists into other areas, and
  - coincidental retirement of colposcopy technicians
- **Retraining areas** included histology, molecular pathology, immunology and rapid on-site evaluation (ROSE).[46,47] In the *UK*, there was redeployment in other pathology disciplines and a small scale program and apprenticeship for cytoscreeners to retrain in mammography for breast screening.[48]
- **Cytology workforce sustainability** is a concern in *Australia* even though there is decreased demand for cytology as the cytology workforce has been declining since implementation of HPV primary screening.[28]

Colposcopy Referral Increases: Referrals to colposcopy increased during the first round of implementation. This was the first five years for the *Netherlands* and *Finland*.[44] Increases varied and ranged from about 30% to as high as 200% of the volumes of cytology-based testing among the jurisdictions.[43] In addition to engaging with the respective Colposcopy Associations/Societies to identify the impacts and volume projections for colposcopy referrals, some other approaches to minimizing impacts on colposcopy wait times includes proper pathway design and increasing colposcopy capacity.[49] A few examples are provided below:

- **Pathway Design:**
  - Periodic wait and retest cycles to allow for some HPV infections to naturally resolve without treatment
  - Using other tests with greater specificity to more accurately predict which people will get cancer (e.g. cytology triage)
  - Understanding the link between histology and risk of cancer (e.g. some jurisdictions refer any NILM while others refer based on cytological abnormalities associated with CIN2+)

- **Increasing Clinician and Lab Capacity:**
  - Communicating with existing colposcopists and requesting that more capacity be made available if possible
  - Allowing other clinician roles to lead colposcopies, such as nurses[13]
  - When some regions and their labs pilot and shift to focusing on HPV primary screening in advance of the broader jurisdiction, these labs may have additional capacity to support backlogs when other regions and labs are shifting focus to HPV primary screening

Pathway Pilots: All jurisdictions noted that pilot testing of the new pathway generated local data. Pilots also helped to ensure operational challenges were identified early and addressed before implementing broadly.

- The *Netherlands* carried out pilots prior to implementation. The screening outreach of the pilots helped sensitize the population to HPV testing and reduced the potential for HPV stigmatization in the population upon implementation of the program.
- *Finland* did not experience many issues with stigma. The way that HPV was positioned in public-facing communication worked well to minimize stigma as it indicated that HPV is quite common and about 80% of women will get HPV.
- In the *UK*, implementation was staggered by country subsequent to the completion of the pilots of each country.

4.3.1.3 Execution

Considerations for the execution phase include preparing and enabling health care professionals and individuals to navigate the program through communication, supportive material and training helps in navigating the program effectively. Setting up an ongoing monitoring and evaluation framework also ensures the program is running as it was set out in the guidelines, pathways and predictive models. A few examples are provided below.

Communication, Supportive Material, and Training: Program implementations that have carried out extensive communication, supportive material and training have a higher chance of success. These include concise, simple information in pertinent languages of the population, in an electronic (text, video, social media) or paper-based format. These approaches ensure that the users of the program (health care professionals and the public) have appropriate educational material, training, and access to someone who can provide information if they have questions. Clinicians and the public require information regarding evidence that HPV primary screening works and is safe and what to expect with the screening process, results and abnormal result follow-up process. The public can also have psychological barriers to participation and increased anxiety and distress from an HPV+ result regardless of whether cytology is abnormal, and additional information can be supportive.[50]

In the *UK*, pre-implementation research identified that whether individuals find screening acceptable could be a limiting factor to participation due to fear of judgement from the community or partners that primarily associate HPV with the idea of sexually transmitted disease.[51] Communications planning and work done to address potential concerns were successful in helping to ensure these concerns were addressed and negative impacts to participation were limited. For clinicians, e-learning courses were developed for sample takers, colposcopists, and laboratory staff. The e-learning courses helped to ensure clinicians understood the changes to screening protocol, could answer common questions from patients, and had the required skills.

In *Finland*, lack of participation due to stigma was not experienced. Adequate support structures can help users feel comfortable with the change and accept it more readily.

Community outreach through campaigns have also been shown to be effective in increasing awareness and participation. As mentioned in section 4.2.3.2 Self-Sampling Implementation Considerations, a study that analyzed self-collection participation trials found that individuals who were in study groups exposed to community outreach, media support, and door-to-door campaigns had a

higher participation rate than individuals who were invited for a clinician-collected sample (15.6% vs 6.0% for community campaigns and 94.2% vs. 53.0% for door-to-door campaigns).[31] Other examples of outreach in *Australia* include social media campaigns for people under 25 years old, LGBTQI individuals and an informational website. In the *UK*, there was a national campaign to encourage people who were due or overdue for screening to participate.[52]

Examples of the type of information and channels used to convey the information to different groups are included below.

Table 7: Examples of the Information and Channels Used to Convey Information

	TYPE OF INFORMATION	SUPPORTIVE CHANNEL
Public	· Questions on stigma from the public can arise, such as "Has my partner been unfaithful?", "Do I have cancer?" along with worries that "People won't date me because I have HPV." · Key messages/answers that have worked include, "80% of people will get HPV", "The immune system naturally gets rid of most HPV infections", "It doesn't mean you have cancer", "Most people won't know they have it", and "It's a virus", "It's not necessarily easy and explain why its important." · Specific messaging groups of individuals that can have a harder time with screening (such as victims of sexual violence, people with physical disabilities)	· The public have access to telephone helplines to ask and obtain answers to their questions · The key messages and additional information about HPV and screening are provided on websites and blogs · Jurisdictions such as the UK are providing information on HPV on the back of positive test results to manage the initial anxiety · Telephone helplines (contact a cancer care nurse)
Clinicians	· In-person and online training courses · Content tailored for different purposes (e.g. for health care providers working in under-served communities) · Training offered well in advance of implementation (in *Australia*, however, the delay in the implementation also delayed training, leading to confusion and not enough time to prepare and ask questions before the implementation) · Training of health administrators, such as primary care receptionists and nurses to help them feel comfortable speaking about screening · Information on areas of inequity	· Telephone helplines (contact a cancer care nurse) · Blogs · Website with guidelines and pathways · Research papers

Jurisdictions also created publicly available material to communicate information to the public and health care providers. Below are a few examples of such material.

Table 8: Examples of Communication Material

	TYPE OF INFORMATION SUPPORTIVE CHANNEL
Public	**Australia** Who is cervical screening for? This webpage has comprehensive information on cervical screening and has information in various languages. It covers topics about the screening test and how it has changed, along with information on HPV and cervical cancer. It also has links to other resources about the National Screening Program, the screening appointment, and results. **The Netherlands** Screening for cervical cancer: invitation.[53] This brochure is available in Dutch, English, Arabic and Turkish and it provides information on screening to allow the individual to decide if they would like to participate. Screening for cervical cancer: Result.[54] This brochure is also available in Dutch, English, Arabic and Turkish and it explains the different results of the screening and HPV.
Health care professionals	**Australia** Information for health professionals. This website provides information on the National Cervical Screening Program, the guidelines, and health professionals' roles in the screening. Optimal care pathway for women with cervical cancer.[17] This document serves as a good example for describing optimal cancer care by mapping the patient journey from prevention and early detection to management and treatment. It is intended to improve patient outcomes by providing care information based on a standardize pathway of care. Optimal care pathway for Aboriginal and Torres Strait Islander people with cancer.[37] Similar to the guide above, this document is about facilitating care along a standardized path, with the additional aim of improving outcomes and experiences for the specific community.

Monitoring and Evaluation: The Monitoring and Quality Assurance Teams created quality and benchmarking frameworks to monitor the progress of their screening programs. These documents were reviewed and updated periodically, adjusting benchmarks with the additional data collected. They included descriptive indicators based on points throughout the pathway and who is responsible for collecting data (almost all professionals involved in the screening pathway are expected to collect data in one form or another that contributes to overall reporting).[36,10,55,56]

In *Australia*, the National Cervical Screening Program Quality Framework defines how "the Program will be measured, monitored and evaluated, and how the high standards of program management and service delivery will be achieved and maintained."[57] It defines the standards and benchmarks that will be used to monitor performance and outcomes of the program and it includes the governance framework, quality standards and targets.

The Monitoring and Quality Assurance team is responsible for developing the content and tools in the quality and benchmarking framework. The team is comprised of health care professionals including general practitioner, pathologists, gynecologists, gynecologic oncologists, colposcopists, cytopathologists, epidemiologists, technicians, consumers, and program managers that advise the organizations responsible for Monitoring and Quality Assurance of these programs.

The following table summarizes the pathway steps and a few examples of corresponding indicators.

Table 9: Examples of Indicators by Pathway Step

PATHWAY STEP	EXAMPLE OF AN INDICATOR	EXAMPLES OF GROUPS RESPONSIBLE FOR COLLECTING DATA
1. Screening Invitation	· Number of invitations sent · Participation rates · Self-collection invitations (screening invitation, reminder for self collection eligible)	· Registry/Government
2. HPV Primary Screening **3. Triage**	· HPV results · Cytology results · Self-collection results (participants positive for oncogenic HPV (not 16/18) who have an LBC test within 6 months, participants positive for oncogenic HPV+ 16/18 who have a colposcopy within 6 months) · HPV test collection method · Follow-up rates	· Laboratories · Screening clinicians (e.g. general practitioners, screening nurses)
4. Colposcopy	· Colposcopy referral · Colposcopy wait-times · Colposcopy rates · Biopsy rates	· Colposcopists · Laboratories
5. Treatment **6. Post-treatment Follow-up**	· Diagnosis rates · Procedures and outcomes · Retest results	· Clinicians · Government
Outcomes (pathway step agnostic)	· Wait-times and attendance at different points in the pathway · Outcomes on incidence and mortality	· Clinicians · Government

4.3.2 Summary of Teams and Stakeholders Involved in Implementation

As mentioned in section 4.3.1 Phases of Implementation section above, various stakeholders and are involved with initial planning. Other groups/sub-groups of stakeholders are implicated at different stages in the process.[10,41] The table below describes when and why these groups are involved:

Table 10: Other Stakeholders Involved in Implementation

STAKEHOLDER	BUILDING AN INFRASTRUCTURE	PRE-IMPLEMENTATION PLANNING	IMPLEMENTATION
Government: Health officials, ministry representatives	Approve the program and endorse it	Work on the payment schemes and other governmental /regulatory approvals	Monitor and evaluate the program once implemented
Clinicians: Physicians, nurses, other inter-disciplinary teams	Develop the pathway, and identify areas and people for further planning and involvement	Inform the implementation plan, guidelines, protocols and governmental affairs	Engage to clarify questions from their peers and patients on the pathway/program and challenging situations, gather feedback and participate in data collection
Labs: Lab leadership, cytopathologists	Develop the laboratory testing protocols	Inform the implementation plan, guidelines, protocols, and governmental affairs	Engage to clarify questions from their peers and patients on the pathway/program and challenging situations, gather feedback and participate in data collection
Public: **a) Community partners/ organizations** **b) Eligible individuals, specific communities**	Inform the pathway development	Inform the implementation plan by: a) voicing the needs of their members b) contributing their needs and socioeconomic challenges	a) Provide educational material to their members, and conduct research on outreach approaches b) Access the educational material, participate in the program, and provide feedback

5 Summary of Lessons Learned

There is much to learn from other jurisdictions and several themes emerged through the research and key informant interviews. The following list provides a synthesized summary of key lessons learned from the findings:

Lessons learned:

1. Tailor programs to communities experiencing inequity in screening to increase participation
2. Develop a Care Pathway Early
3. Balance Risk with Resources
4. Focus on Participation Rates as a Key Mechanism to Decrease Cervical Cancer
5. Consider How Self-Sampling Can Be Used to Increase Participation in Cervical Screening Programs
6. Consider the Extent to Which the Screening Program is Involved in Follow-Up of Abnormal Results
7. Create A Plan to Limit and Manage the Temporary Increase in Demand for Colposcopy
8. Engage with Clinicians and the Public to Communicate the Superiority of HPV Primary Screening
9. Monitor Advancements in Cervical Screening Technologies and Approaches

These are described in more detail below.

1. **Tailor Programs to Communities Experiencing Inequity in Screening to Increase Participation:** Inequity is faced by some communities leading to decreased participation in screening (i.e. under- or never-screened) and poorer outcomes. Several tactics can be used to increase equity and participation of these communities. Tactics include engaging with these communities to understand their unique needs and barriers to participation, conducting research to further understand needs and barriers, co-designing ways that programs can be modified to overcome barriers, and building ongoing relationships of feedback and engagement with these communities. Communication approaches and materials that are tailored to the needs of the community allow for clear communication and help to avoid misconceptions about screening. Self-sampling is also promising as it increases participation for many communities that experience screening inequity.

2. **Develop a Care Pathway Early:** There are many variations in the pathways across jurisdictions, but common elements exist. A foundational element is forging agreement on what the pathway will be.

   It is important to start development of these pathways early because it typically takes a long time to review the evidence and agree on

pathway options. This challenge is exacerbated by the limited time available from the clinicians and researchers with expertise in HPV primary screening and abnormal result follow-up who need to be involved. Timelines for this process ranged from a "quick" 18 months to 5 years.

3. **Balance Risk with Resources:** Pathway design has impacts on health system resources use, clinician practice, and patient experience. Jurisdictions also recognized that an increased use of resources does not necessarily lead to a significant improvement in patient outcomes. While the development of pathways must be firmly rooted in the evidence, system leaders and the people designing the pathway also need to make value and risk judgements. Value judgements include such questions as:
   - What amount of health system resources should be used to achieve a marginal increase in cervical screening outcomes?
   - Are our communities willing to accept some additional risk of missing preventable cervical cancer cases in order to allocate resources to another area of the health system that may have a greater impact on overall health?

   Some jurisdictions choose a more risk averse approach where cases with less risk of cancer are referred for further testing and possibly treatment. Other jurisdictions take a less risk averse approach and return those that are HPV+ but with low risk of cancer to routine screening. Some jurisdictions felt they were too risk averse when starting their HPV primary screening programs and did not see a correlation with better outcomes.

4. **Focus on Participation Rates as a Key Mechanism to Decrease Cervical Cancer:** When allocating resources for screening programs it is important to maintain a focus on the ultimate goal of cervical screening – mortality and morbidity outcomes – and appreciate the possible magnitude of impact on these outcomes.

   While pathway design is important, it was reported that the minutiae of pathway design is less important for cervical cancer outcomes than simply increasing participation rates. While this judgement should be informed by the data, however, it appears to be generally accepted that increasing participation rates has a greater positive impact on outcomes than the finer aspects of pathway design.

   Ways to improve participation identified in the environmental scan include:
   - Self-sampling, especially for populations with barriers to screening access
   - Good relationships between the patient and a clinician, typically in primary care, that is supportive of HPV primary screening
   - Communications materials, especially when tailored to the target audience

5. **Consider How Self-Sampling Can Be Used to Increase Participation in Cervical Screening Programs:** Self-sampling is seen as a promising method to enable participation in screening for under-screened populations, during the COVID-19 pandemic, and, in some jurisdictions, for the general population. While self-sampling shows promise and has been successfully implemented in some jurisdictions, it has only been in place for a few years. Regulatory and logistical challenges remain and may be largely overcome but may limit successful implementation of self-sampling.

   Canadian and local regulatory requirements need to be understood early in the process. Approval may or may not be granted in Canadian jurisdictions for using collection devices in self-sampling if the collection device does not indicate self-sampling as an intended use. If approval is not granted, there could still

be opportunity for implementing self-sampling if laboratories are allowed and able to validate the specific collection device for self-sampling sampling use in the specific laboratory processing the sample. If laboratories lack incentives to complete this validation the capacity to process self-samples may not be sufficient. This highlights the importance of early understanding of how self-sampling would occur within the regulatory requirements.

There are also varying perspectives about whether self-sampling has a significant impact on increasing abnormal screen follow-up and reducing cervical cancer. While self-sampling is anticipated to increase screening participation, participants must be willing to complete follow-up and have accessible options to do so. As a result, some jurisdictions are further ahead in implementing self-sampling than others and self-sampling is generally seen as a screening method to complement clinician collected samples.

6. **Consider the Extent to Which the Screening Program is Involved in Follow-Up of Abnormal Results:** The transition between an abnormal result and follow-up care can be a step where people get "lost" in the care pathway and don't end up receiving the follow-up care they need. This can also be the step where the screening program's role ends and there is a "hand-off" to other clinician roles and so a common understanding of roles and responsibilities and communication is important. The screening program's role varies across jurisdictions and different mechanisms can be put in place to minimize loss to follow-up. In *Finland*, there are organized colposcopy clinics that schedule follow-up directly with the people whose screening results indicate need for colposcopy, creating a mechanism within the screening program for follow-up. In the *Netherlands*, it is the responsibility of the woman to arrange an appointment with a gynecologist when advised by the screening program, however, the screening program does track whether the lab receives additional test samples for the patient, an indication of whether follow-up care is being provided. If follow-up test samples are not received at the lab, the lab notifies the primary care provider which is then responsible to attempt follow-up with the person. The extent of the involvement of an organized screening program and mechanisms used to maximize the likelihood that patients participate in abnormal screen follow-up should be considered.

7. **Create A Plan to Limit and Manage the Temporary Increase in Demand for Colposcopy:** There is often a 2-3 times increase in referral to colposcopy when HPV primary screening is introduced. Ways to smooth demand include pathway design, screening age and interval, and test types used.

   There may be greater ability to decrease the number of referrals to colposcopy in the future as new techniques and technologies are proven. For example, the p16 test is showing potential as a way to more accurately predict what cases will progress to cancer and therefore decrease the impact on colposcopy.

   It is important to note that the increase in referral to colposcopy is temporary. After people move through their first round of HPV primary screening and follow-up of abnormal results, the demand for colposcopy decreases. This, along with the impact of HPV immunization, can decrease colposcopy demand to below pre-implementation levels.

8. **Engage with Clinicians and the Public to Communicate the Superiority of HPV Primary Screening:** Both developing the pathway/guidelines and change management requires significant amounts of effort. As one interviewee said, "90% of the work is the guidelines – the other 90% is convincing clinicians to change practice." Jurisdictions that implemented HPV primary screening needed to continually educate and reinforce for clinical and patients why HPV primary screening was superior to the prior screening approach.

   A robust understanding and clear presentation of the evidence is required. Convincing takes multiple forms:

   - **For clinicians**, face-to-face meetings with people they know and respect (e.g. through a clinician conference) works well. They need to be able to see the evidence, dialogue with their peers, and ask questions. They also need to be able to call a person knowledgeable in the process when needed to clarify what to do.
   - **For patients**, clear messaging in patient-friendly language is seen as most successful. There is some evidence that it is the doctor or the nurse the person has a relationship with that has the greatest impact on whether that person will participate, which is why convincing clinicians about the benefit of HPV primary screening is so essential.

   Some stakeholder groups resist these changes for reasons other than an understanding of the evidence. In other jurisdictions, these included:

   - **Cytologists:** Technicians in the laboratories that face job losses with decreased work in cytology when HPV is implemented. Providing training to decrease the negative impact on career related incentives is seen to help.
   - **Pathologists:** Physicians that report on the cytology samples and may be paid per sample reported on.
   - **Primary Care Clinicians:** Physicians that have been provided with good evidence about the past approach to cervical screening but now with advances in technology and research need to be convinced that HPV primary screening is superior before changing practice.

9. **Monitor Advancements in Cervical Screening Technologies and Approaches**: HPV primary screening science and technology is advancing quickly. Only a few years ago, HPV primary screening had yet to be implemented and the effectiveness of self-sampling was questioned, whereas now, both are being embraced and explored.

   New test technologies appear to show promise for even better triage pathways that more accurately predict who will get cancer and need treatment, allowing for better use of health system resources and patient outcomes. New studies and technology can be routinely scanned to ensure cervical screening practices are using the best evidence.

6 Appendix

6.1 APPENDIX: ENVIRONMENTAL SCAN RESEARCH QUESTIONS

The research questions that directed the Environmental Scan are included below for the pathway design and implementation.

Screening and abnormal screen follow-up pathways:

1. What **health system structures support** HPV primary screening and **abnormal result follow-up**?
2. What are the HPV primary screening and abnormal result follow-up **pathways**?
3. What **factors** were considered in the **design** of the pathway? What were the trade-offs?

Implementation Design & Outcomes:

4. What were the **barriers and enablers** to implementing HPV primary screening and follow-up? How were the barriers overcome?
5. Were there focused approaches to **promote equitable access** for Indigenous and/or under-serviced populations? If so, what were/are they?
6. What were the **impact and outcomes**? Was anything surprising?

6.1.1 Appendix: Pathway Design Jurisdictional Comparison

The following table provides a jurisdictional comparison of the HPV primary screening and abnormal screen follow-up practices discussed in this report.

Table 11: Jurisdictional Comparison of HPV Primary Screening and Abnormal Screen Follow-Up

	UNITED KINGDOM	NETHERLANDS	AUSTRALIA	UNITED STATES
Invitation, reminder, and results channel	• Mailed letters to individuals • Electronic prompts for general practitioners	• Mailed letters to individuals, who make appointment with primary care provider for screening • If no response within 4-6 months of the invitation letter, reminder letter is sent that includes a request form for a self-sampling device, if desired[10] • Individual screened and primary care provider receives screening results; primary care provider sends referrals when necessary	• Mailed letters[11] • Text message appointment reminder and recall system[36] • Reminders sent between 6-24 months after initial letter depending on screening history and results	Invitations, reminders, and provision of results done by primary care provider, as no organized screening program
Screening Test Used	hrHPV	hrHPV (does not include partial genotyping or indicate which HPV type)	Oncogenic HPV test with partial genotyping for HPV+ 16/18. Some tests may also distinguish HPV 31, 45, or other oncogenic HPV types	The 2012 American Cancer Society guidelines recommend co-testing with pap and HPV with a reflex triage of HPV+ 16/18 genotyping

	UNITED KINGDOM	NETHERLANDS	AUSTRALIA	UNITED STATES
High level screening pathway description	• hrHPV- to routine screening • hrHPV+ to cytology; abnormal cytology to colposcopy • 2 rounds of hrHPV retesting at 12 months if hrHPV+ and cytology normal • After 2 rounds of retesting with hrHPV+ result, to colposcopy	• hrHPV- to routine screening • hrHPV+ to reflex cytology; abnormal (ASC-US+) to gynecologist for colposcopy • 1 round of triage cytology retesting 1 year if hrHPV+ and reflex cytology normal • Return to routine screening if triage cytology NILM and to colposcopy if ASC-US+58	• hrHPV- to routine screening • hrHPV+ not 16/18 to cytology; HPV+ 16/18 to colposcopy if self-collection; HPV+ 16/18 with any LBC result to colposcopy • LSIL to repeat HPV in 12 months; to routine screening if HPV-; to colposcopy if any HPV+ • HSIL to colposcopy	• No static pathway; rather risk tables are used based on "based on the risk... for the many different combinations of current and recent past screening results." 1 of 6 clinical actions is recommended: treatment, optional treatment or colposcopy/ biopsy, colposcopy/ biopsy, 1-year surveillance, 3- year surveillance, or 5-year surveillance.[35]
Cycles of retesting if initial HPV+ with normal cytology	2 HPV @ 12 months each; any HPV type	1 triage cytology @ 6 months; any HPV type	1 @ 12 months (HPV+ not 16/18 only)	Based on risk as per risk tables and 2019 ASCCP Guidelines

	UNITED KINGDOM	NETHERLANDS	AUSTRALIA	UNITED STATES
Colposcopy pathway	Next steps dependent on • adequacy of colposcopy examination, • hrHPV status, • grade of cytology, • biopsy results and impression of CIN, and/or • colposcopic impression of CIN. Next steps may include: • repeat colposcopy, • discussion with the multidisciplinary team, and/or • recall hrHPV testing (e.g. 6, 12 or 36 months) See Appendix: Additional Pathways for specific pathways	Pathways after colposcopy depend on the level of CIN identified and whether the patient wants treatment. No CIN or CIN 1 is usually not treated and returns to screening/ monitoring[59,60]	Pathways start based on the LBC prediction before colposcopy. Colposcopy and follow-up pathways depend on factors including: • cytology results/ histology • what is visualized during colposcopy and on the transformation zone • biopsy results, and • results from subsequent cycles of HPV and cytology retesting and colposcopy. Pathways generally result in return to normal screening, further testing, or treatment. See Appendix: Additional Pathways for specific pathways	Based on risk as per risk tables and 2019 ASCCP Guidelines

	UNITED KINGDOM	NETHERLANDS	AUSTRALIA	UNITED STATES
Treatment	No superior conservative surgical technique[55]	The advice for the treatment of the preliminary stage is usually:[61] • CIN I: do not treat. Usually this deviation disappears automatically within 2 years. The chance of complications from the treatment is greater than the chance that cancer will develop from these cells. • CIN II: together with your doctor, you will weigh up treatment based on the following factors. Or to monitor the deviation with smears every 6 months. This deviation also often disappears after a while in young individuals. • CIN III: treatment	Modalities include carbon dioxide laser ablation, cold-knife cone biopsy, LEEP, LLETZ, profiled electrosurgical excision, SWETZ, NETZ, and laser cone biopsy[62]	Common treatments include: surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy[63]

	UNITED KINGDOM	NETHERLANDS	AUSTRALIA	UNITED STATES
Post Treatment Follow-up; "Test of Cure"	Recall hrHPV @ 6 and 36 months for CIN2+. Recall hrHPV @ 6, 12 and 36 months for CGIN. If hrHPV+, then cytology and possible referral to colposcopy.	Determined with Gynecologist and monitored for at least 1 year.	Post-treatment for HSIL (CIN2/3), co-test of HPV and LBC @ 12 months and another 12 months if HPV- or HPV not 16/18 and/or LSIL. If HPV + not 16/18 or abnormal cytology not HSIL, then annual co-testing until negative co-tests on 2 consecutive occasions. To colposcopy if HPV+ 16/18 and/or HSIL.[64] For AIS, annual co-testing indefinitely.	After treatment for HSIL, HPV-based testing at 6 months; if 3 annual negative HPV tests then HPV-based testing for at least 25 years.[65] Other situations exist in the 2019 ASCCP Guidelines.

6.2 APPENDIX: ADDITIONAL PATHWAYS

This appendix provides the HPV primary screening and abnormal pathways from the jurisdictions examined.

6.2.1 United Kingdom

Figure 12: The United Kingdom's HPV Primary Screening Pathway

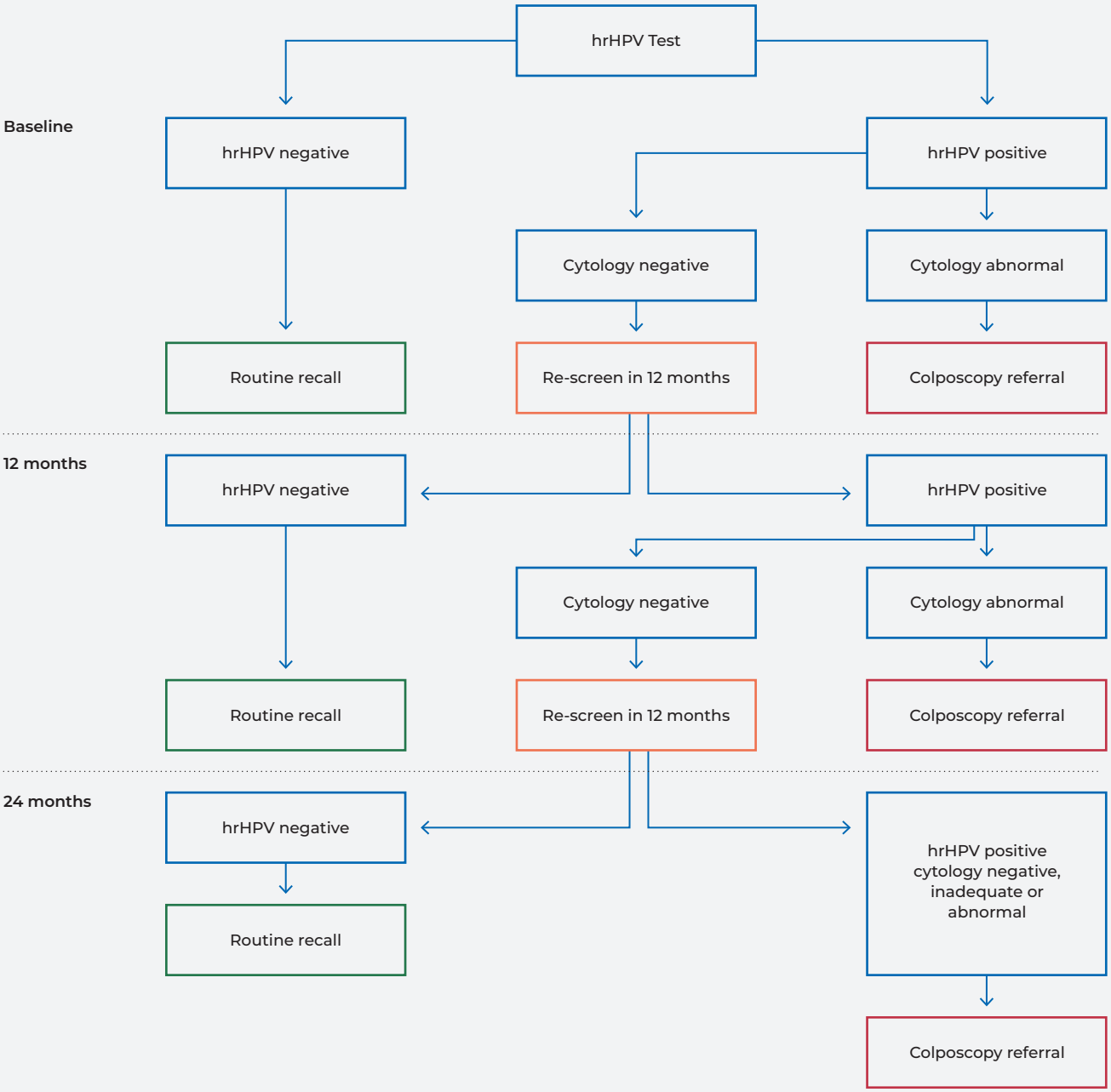
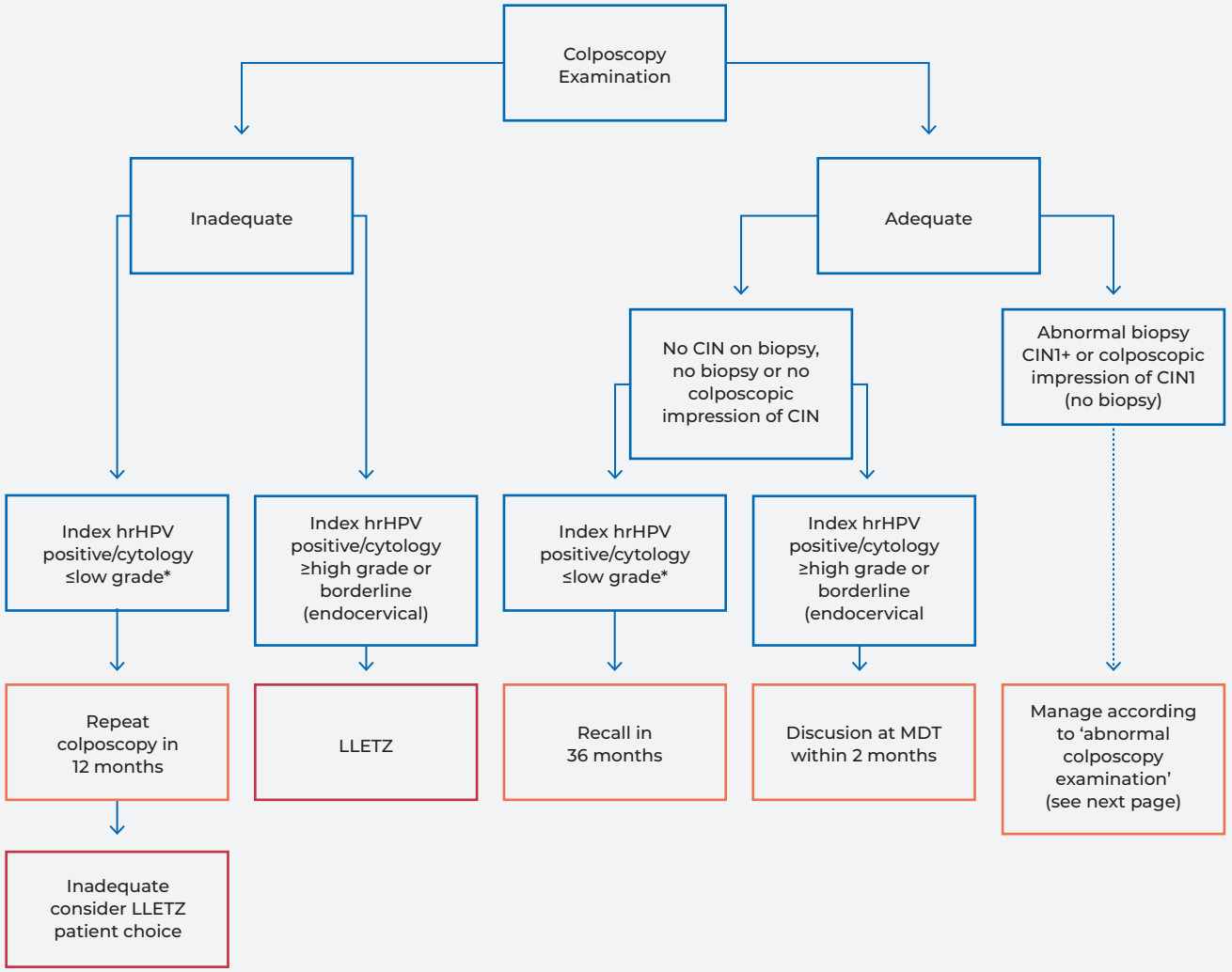
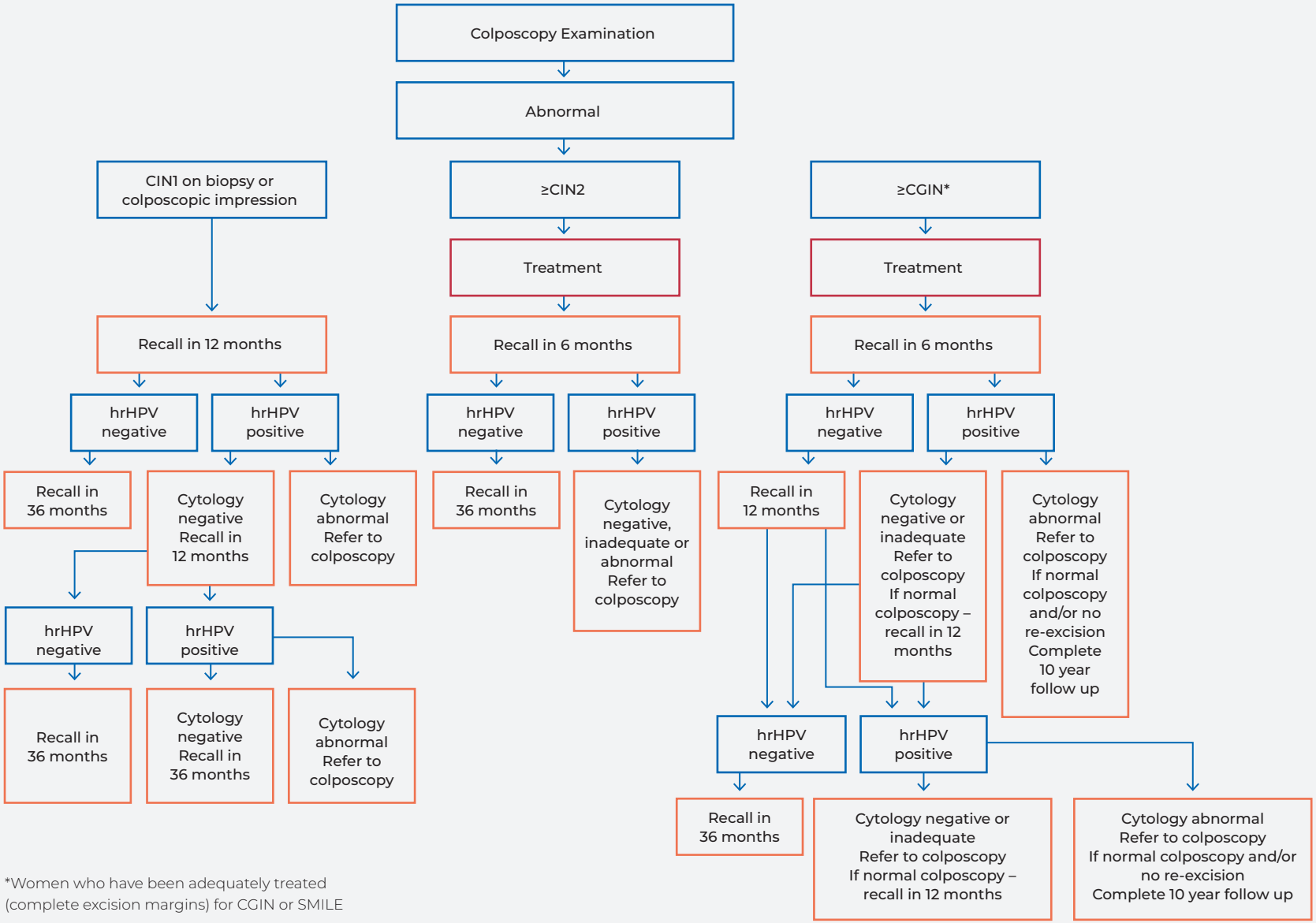


Figure 13: The United Kingdom's Cervical Screening Colposcopy Management Recommendations for Inadequate/Adequate Examinations[66]



*excludes borderline change in endocervical cells

Figure 14: The United Kingdom's Cervical Screening Colposcopy Management Recommendations for Abnormal Examinations



*Women who have been adequately treated (complete excision margins) for CGIN or SMILE

More information can be found in the *UK*'s government website for Cervical Screening: primary HPV screening implementation guidance webpage at: https://www.gov.uk/government/publications/cervical-screening-primary-hpv-screening-implementation.

6.2.2 Australia

Figure 15: Australia's HPV Primary Screening Pathway

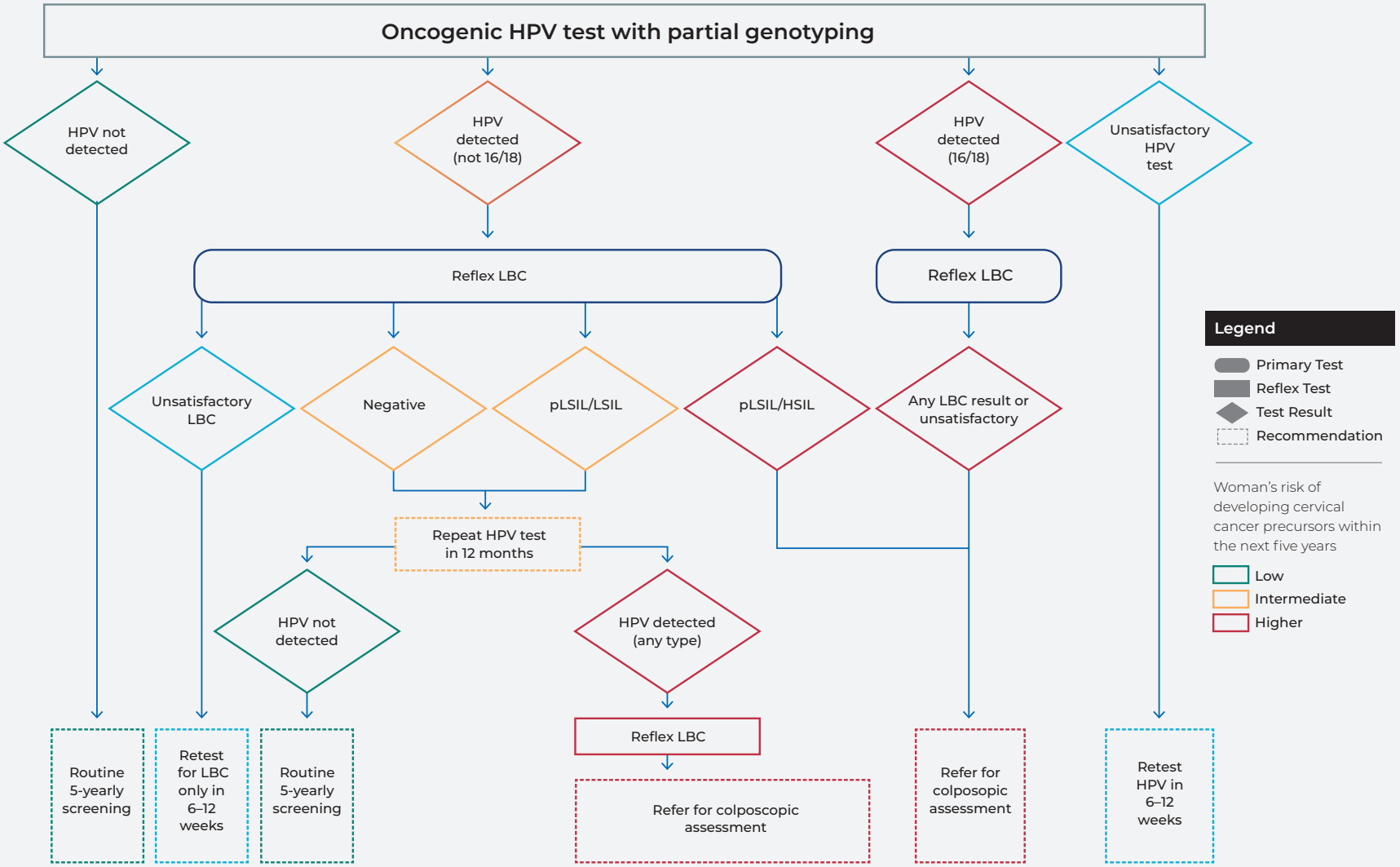
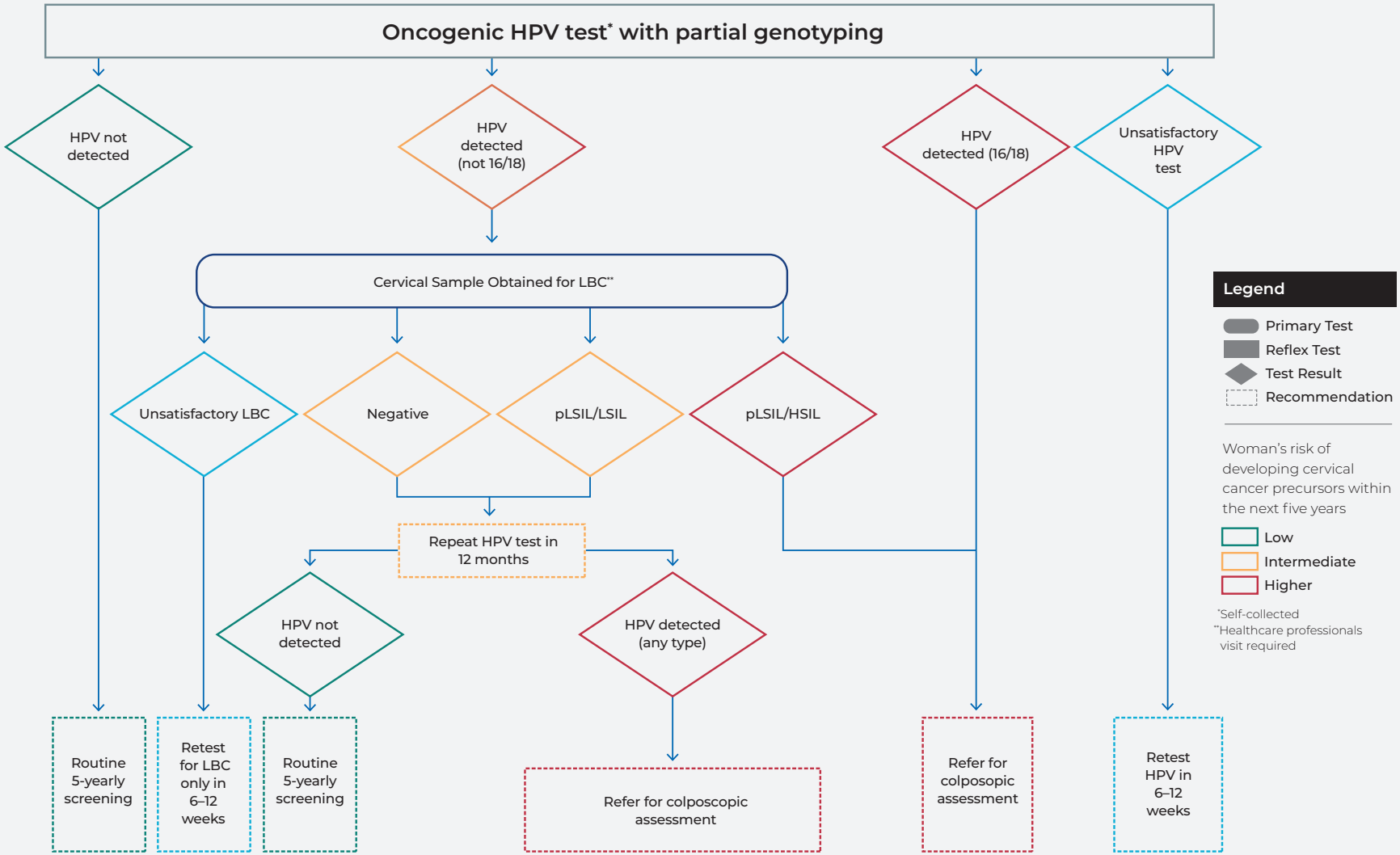


Figure 16: Australia's HPV Primary Screening Pathway for Self-Sampling



Australia has numerous pages of abnormal result follow-up pathways. Below are two examples, and the rest can be found in the Cancer Council Australia, Clinical Guidelines Network website at: https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening.

Figure 17: Australia's Normal Colposcopy Pathway after LBC prediction of pLSIL/LSIL
(Note: area of figure in less prominent colour is as per Australia's figure)

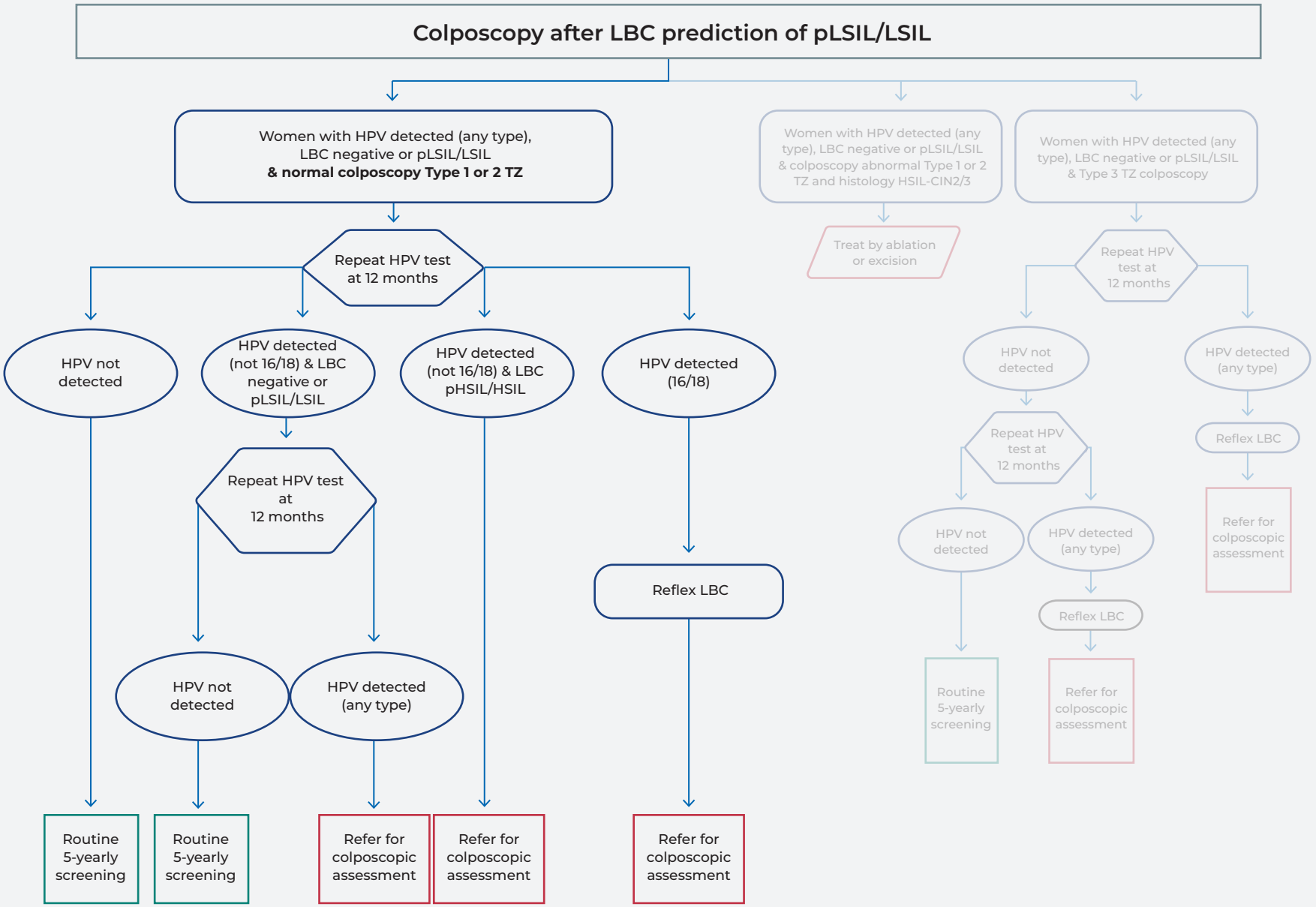
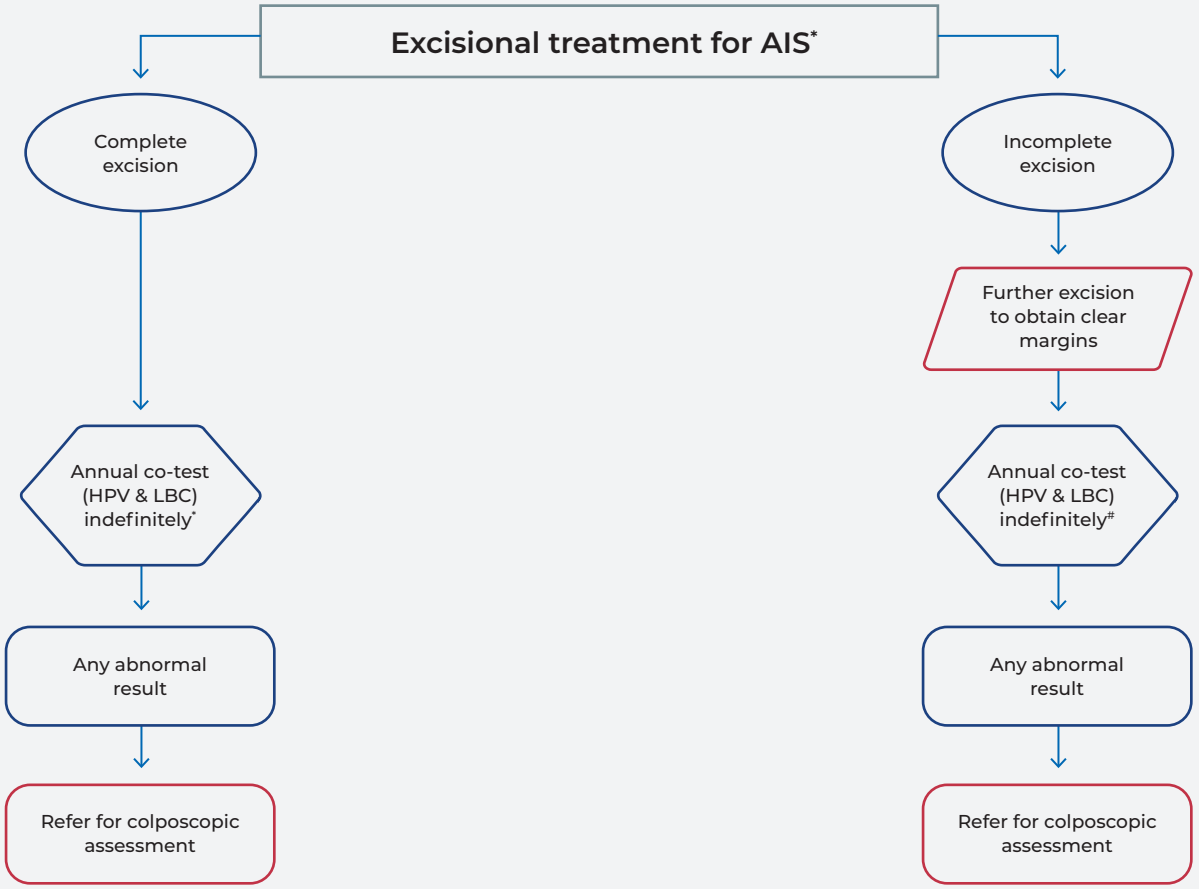


Figure 18: Australia's Follow-Up Pathway After Excisional Treatment for AIS

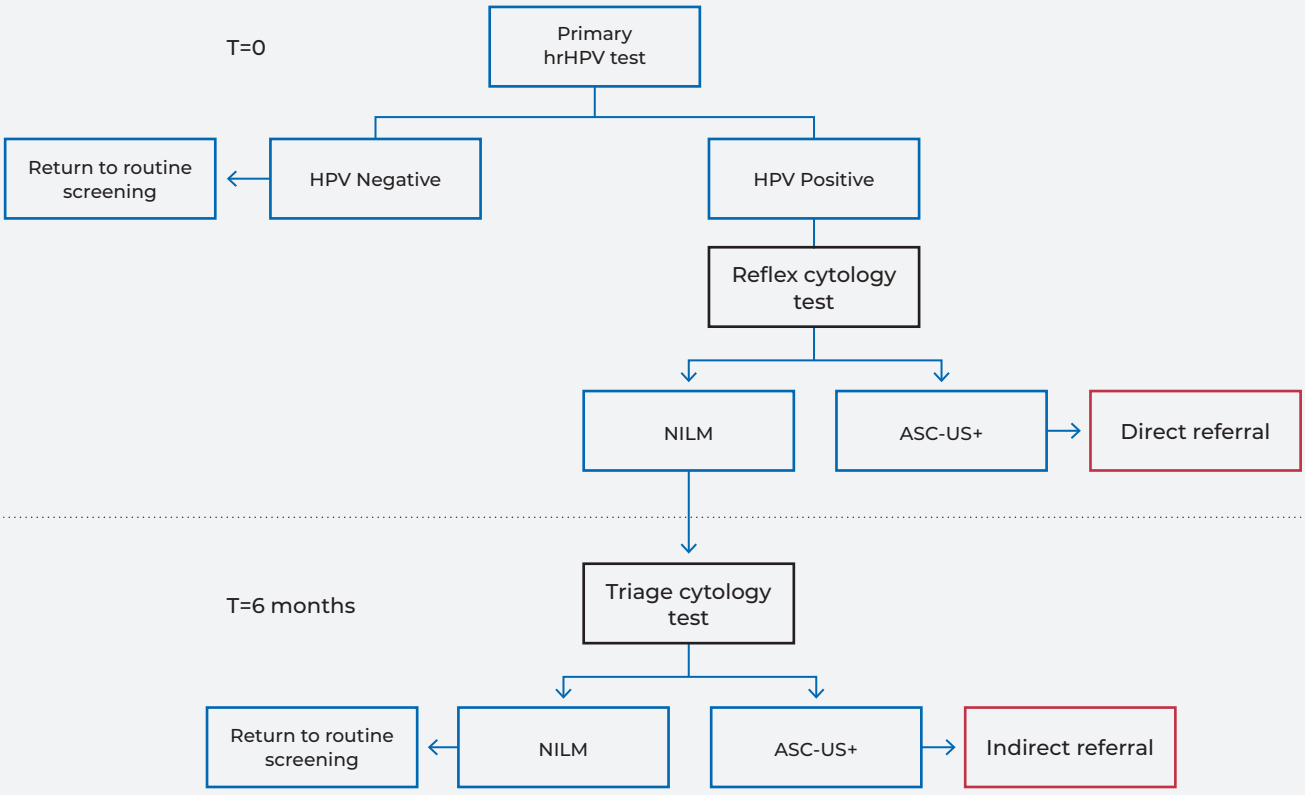


*AIS = Adenocarcinoma in situ

#Until sufficient data become available that may support a policy decision that cessation of testing is appropriate

6.2.3 The Netherlands

Figure 19: The Netherlands' HPV Primary Screening Pathway[67]



Additional information can be found in The Netherland's National Institute for Public Health and the Environment's website at:
https://www.rivm.nl/documenten/framework-for-execution-of-cervical-cancer-population-screening.

6.2.4 United States

Pathways are purposely not provided for the US as a risk-based approach is used. Additional guidelines can be found in the American Society for Colposcopy and Clinical Pathology (ASCCP) website at https://www.asccp.org/guidelines.

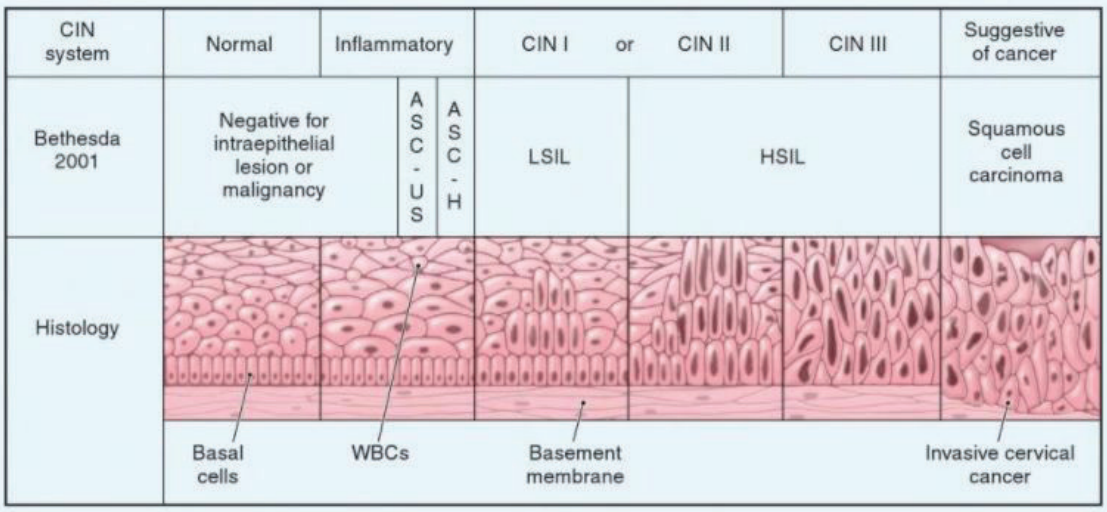
6.3 APPENDIX: GLOSSARY OF SELECTED TERMS

The following table provides the full term for acronyms or definitions as related to this document and topic.

TERM	FULL TERM AND/OR DEFINITION
AIS	Adenocarcinoma in situ
ASC-H	Atypical squamous cells, cannot exclude high grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
CGIN	Cervical glandular intraepithelial neoplasia
CIN	Cervical Intraepithelial Neoplasia
HSIL	High grade squamous intraepithelial lesion (CIN2+)
LBC	Liquid-based cytology
LSIL	Low grade squamous intraepithelial lesion
NILM	Negative for intraepithelial lesion or malignancy
Oncogenic HPV	Oncogenic HPV types are defined as those associated with the development of invasive cervical cancer, and include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68
pLSIL	Possible low grade squamous intraepithelial lesion
Reflex Cytology	Cytology performed on the same sample as the HPV primary screen was performed on
SMILE	Stratified mucin-producing intraepithelial lesion

The terminology used to describe cellular changes that may lead to cancer varies across jurisdictions. For reference, the following diagram illustrates the CIN and Bethesda systems in relation to histology terminology.

Figure 20: Cervical Cytology Classification Systems: Bethesda and Cervical intraepithelial neoplasia (CIN)



Source: Beckmann, Charles R. B., William Herbert, and Douglas Laube. Obstetrics and Gynecology. 7th ed. Lippincott Williams & Wilkins, 2013

6.4 APPENDIX: SOURCES

This appendix provides:

- weblinks for jurisdictional pathways and guidelines, and
- citations used in this environmental scan.

6.4.1 Key Weblinks

The following list includes weblinks to the key pathways and guidelines of the jurisdictions examined.

Canada

- The Canadian Partnership Against Cancer (the Partnership) is the steward for the **Canadian Strategy for Cancer Control 2019-2029** found at: https://www.partnershipagainstcancer.ca/wp-content/uploads/2019/06/Canadian-Strategy-Cancer-Control-2019-2029-EN.pdf
- The Partnership collects information on national, provincial, and territorial cervical screening guidelines, strategies and activities in the Cervical cancer screening in Canada: Environmental scan (2019-2020) found at: https://www.partnershipagainstcancer.ca/topics/cervical-cancer-screening-scan-2019-2020/

United States

- **Use of Primary High-Risk Human Papillomavirus Testing for Cervical Cancer Screening: Interim Clinical Guidance**[68]: 2015 updated and interim screening guidelines that provide recommendations on the use of HPV primary screening beyond the guidelines provided in 2012. Downloadable at the American Society of Colposcopy and Cervical Pathology (ASCCP) website: https://www.asccp.org/screening-guidelines
- **2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors**[65]: Guidelines for abnormal screening results published in 2020. Downloadable at the American Society of Colposcopy and Cervical Pathology (ASCCP) website https://www.asccp.org/management-guidelines
- **ASCCP mobile application** can be found on the ASCCP website found at: https://www.asccp.org/mobile-app
- **Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines**[35]: Accompanying document to the 2019 ASCCP Risk-Based Management Consensus Guidelines that includes published risk tables to guide management. Downloadable at: https://journals.lww.com/jlgtd/Fulltext/2020/04000/Risk_Estimates_Supporting_the_2019_ASCCP.4.aspx

Australia

- **National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding**[36]: Downloadable at: https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening and National Cervical Screening Program website can be found at: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-screening-1
- **Cancer Council Australia, Clinical Guidelines Network:** The clinical pathways are listed in *Australia's* wiki pages found at: https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening
- **National Cervical Screening Program Quality Framework:** This is the framework that defines how the program will be delivered and be measured, monitored and evaluated. The comprehensive document is found at: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/A96FA4D3791BDC88CA2582D50007559C/$File/NPS_NCSP_Quality_Framework_ACC.pdf
- **Optimal care pathway for women with cervical cancer:** A document that serves as a good example for describing optimal cancer care by mapping the patient journey, beginning with prevention and early detection. The full document and a quick reference can be found at: https://www.cancervic.org.au/for-health-professionals/optimal-care-pathways

- **Optimal care pathway for Aboriginal and Torres Strait Islander people:** Similar to the guide above, this document is about facilitating care along a standardized path, with the additional aim of improving outcomes and experiences for the specific community. The full document and a quick reference can be found at: https://www.cancer.org.au/health-professionals/optimal-cancer-care-pathways
- **Information for health professionals:** This website provides information on the National Cervical Screening Program, the guidelines and health professionals' roles in the screening and found at: https://www.cancer.nsw.gov.au/prevention-and-screening/screening-and-early-detection/cervical-screening/information-for-health-professionals
- **Who is cervical screening for?** This webpage has comprehensive information on cervical screening and has information in various languages. It covers topics about the screening test and how it has changed, along with information on HPV and cervical cancer. It also has links to other resources about the National Screening Program, the screening appointment and results. It is available at: https://www.cancer.nsw.gov.au/prevention-and-screening/screening-and-early-detection/cervical-screening/about-cervical-screening/who-is-cervical-screening-for

Netherlands

- **Framework for the Execution of Cervical Cancer Population Screening**[10]**:** "describes who is responsible for the execution of cervical cancer population screening together with the applicable rules and procedures." Can be downloaded at: https://www.rivm.nl/documenten/framework-for-execution-of-cervical-cancer-population-screening (components of the document are not in English), however, the cervical screening program website can be found in English at: https://www.rivm.nl/en/cervical-cancer-screening-programme
- **Screening for cervical cancer: invitation**[53]**:** This is a brochure for patients and available in Dutch, English, Arabic and Turkish and it provides information on screening to allow the individual to decide if they would like to participate. It is available at: https://www.rivm.nl/documenten/screening-for-cervical-cancer-invitation
- **Screening for cervical cancer: Result**[54]**:** This brochure is also available in Dutch, English, Arabic and Turkish and it explains the different results of the screening and HPV. It is available at: https://www.rivm.nl/documenten/screening-for-cervical-cancer-result

United Kingdom

- **Cervical screening: programme and colposcopy management**[49]**:** "Guidelines for commissioners, screening providers and programme managers for NHS cervical screening." Can be found at https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management
- **UK's government website for Cervical Screening:** primary HPV screening implementation guidance website lists the clinical pathways and can be found at: https://www.gov.uk/government/publications/cervical-screening-primary-hpv-screening-implementation
- **Jo's cervical cancer trust** is the UK's leading cervical cancer charity that provides quality information and support, and campaigns for excellence in cervical cancer treatment and prevention. The trust conducts policy work on treatment, care and prevention across the *UK* and conduct research to inform the work. The latest research includes the patient experience of having cell changes or cervical cancer. They are a great resource for questions and have helplines for people to call in with their queries. Their website is found at: https://www.jostrust.org.uk/

- **Clinician Training Resources:** Website provides an overview of what clinician e-learning resources are available. Some outlines to courses available through on-page links, however, the e-learning courses themselves require NHS login credentials. Overview can be found at the *UK* government's webpage titled "Primary HPV screening training resources launched": https://phescreening.blog.gov.uk/2019/02/11/primary-hpv-screening-training-resources-launched/

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