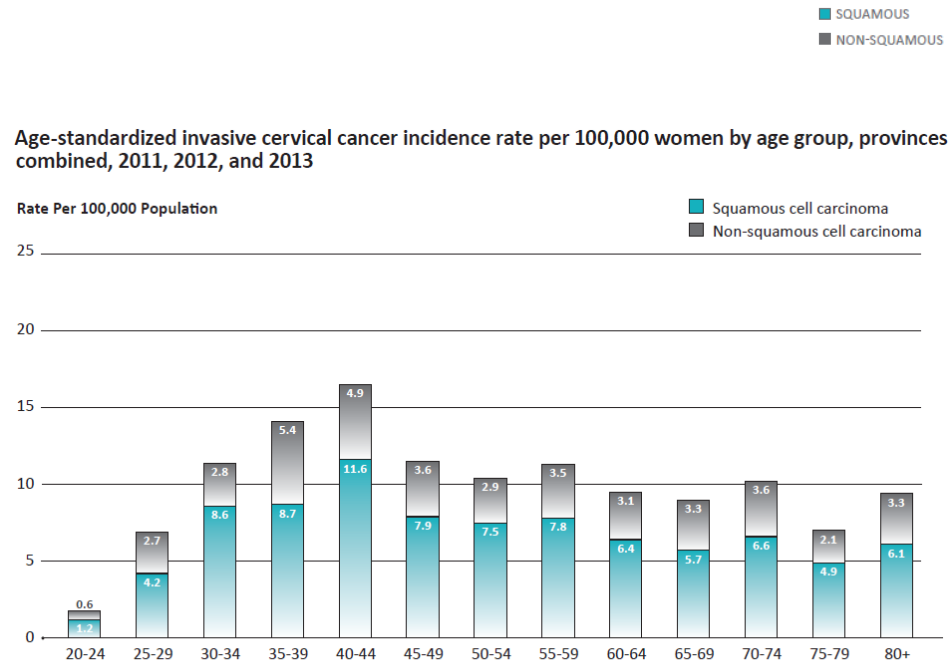
Chapter 2: Disease Burden and Cervical Cancer Screening in Manitoba

Learning Objectives	On completion of this section, the learner will be able to: 1. Understand human papillomavirus, disease burden, cervical cancer incidence, precursors, natural history, and risk factors. 2. Describe the CervixCheck, CancerCare Manitoba Program. 3. Identify the rationale for the CervixCheck program. 4. Describe CervixCheck Operations.

Cervical Cancer

Cervical cancer is the 13th most frequently diagnosed cancer amongst Canadian women.[1] On average in Canada, 1,500 women are diagnosed with invasive cervical cancer, and 475 women die each year.[1] Most women are diagnosed between the ages of 40 and 44. Figure 1 shows the invasive cervical cancer incidence for women by age group, in eight Canadian provinces, for January 2011 – December 2013.[2]

Figure 1. Invasive cervical cancer incidence rate per 100,000 women, by age group, January 2011 to December 2013.

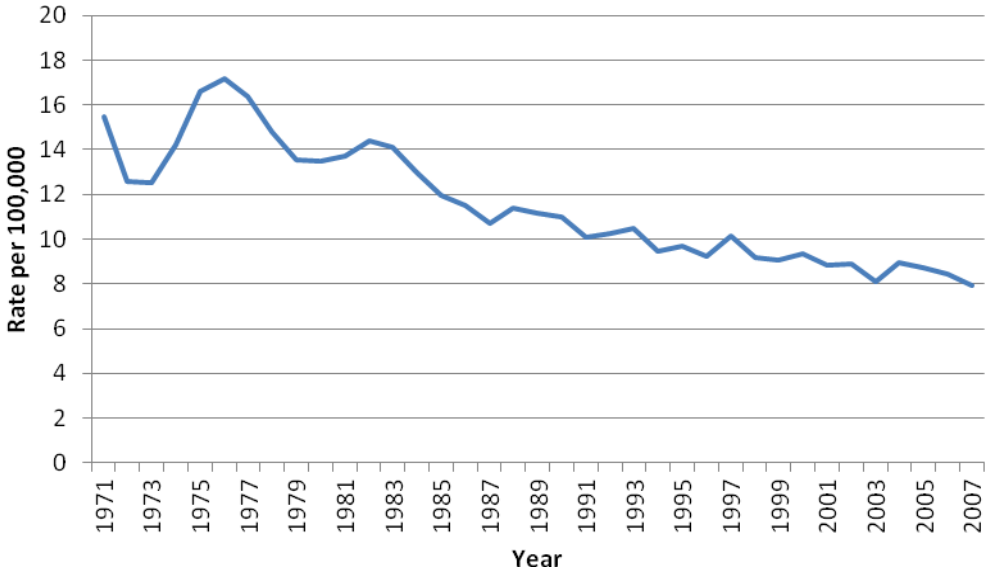


Includes BC, AB, SK, MB, NB, NS, PE, and NL and Labrador. British Columbia includes data from 2011 and 2012. Age standardized to the 2011 Canadian population

In Manitoba in 2016, 50 women were expected to be diagnosed with cervical cancer, and 20 women were expected to die from cervical cancer.[1]

Since the incept of the Pap test in Canada, the incidence of cervical cancer in Manitoba has reduced over time. Reduction in rates of cervical cancer are due to increased participation in screening by Manitobans. Figure 2 shows the age-standardized cervical cancer incidence rate per 100,000 for Manitoba between 1971 to 2007.[3] However, recently the Canadian Cancer Society published their 2016 Canadian Cancer Statistics report which revealed that age-standardized incidence rates of cervical cancer in Canada have increased by 0.5% since 2005, and the age-standardized mortality rates have increased by 1.8% since 2008. Although low, these changes remind us of the continued efforts required by all partners to increase screening participation rates.[1]

Figure 2. Age-standardized cervical cancer incidence rate per 100,000 for Manitoba, 1971 to 2007.



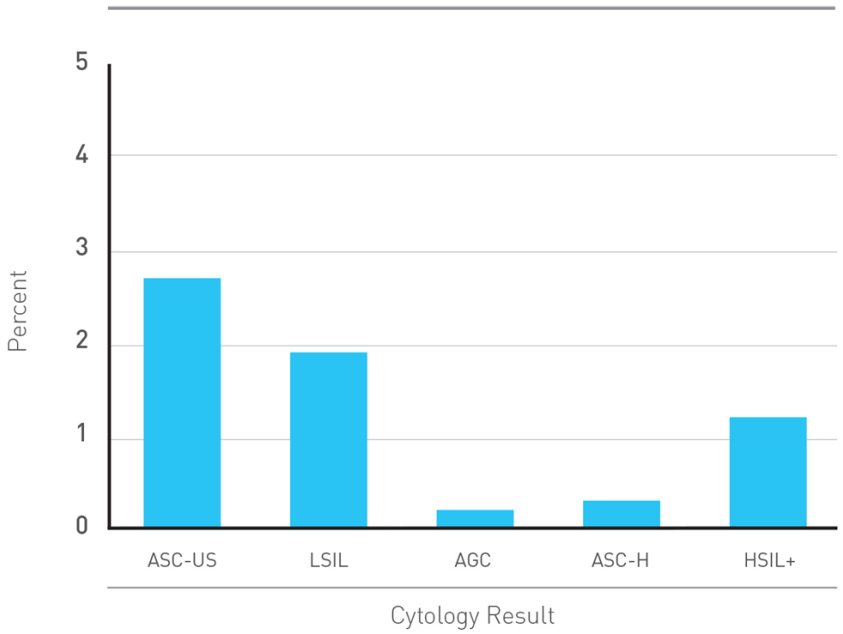
HPV Disease Burden

Infection with human papillomavirus (HPV) is recognized as the causal factor for cervical cancer and it's precursors, genital warts, as well as other anogenital and oral cancers.[1,4] Transmission of HPV occurs through skin-to-skin or skin-to-mucosa contact with more than 40 types of HPV known to infect the skin of the penis, vulva, and anus, and the lining of the vagina, cervix and rectum, as well as the lining of the mouth and throat including the oropharynx, base of tongue and tonsil.[1] HPV is estimated to be the most prevalent sexually transmitted infection in the United States and Canada.[5] Most sexually active individuals will have an HPV infection at some point during their lifetime, including over 80% of sexually active women.[1,]

Almost all cervical cancers can be traced to oncogenic HPV types, with over 70% being traced to HPV 16 and 18. These HPV types are considered high risk (HR) due to their link to cervical cancer. Other HPV types are considered low risk (LR) for causing cancer, and are primarily associated with genital warts (HPV types 6 and 11).[1]

The incidence of cervical dysplasia in Manitoba is significant. 1 in 4 women will have an abnormal Pap test in her lifetime.[5] Between January 1st, 2012 to December 31st, 2014, 4.6% of women had a low-grade Pap test (ASC-US or LSIL), and 1.7% had a high-grade (AGC, ASC-H, HSIL) or more severe Pap test (Figure 3). [6] Each year in Manitoba about 12,000 colposcopies are performed in response to persistent low-grade Pap tests or high-grade Pap test results.[7]

Figure 3. Percentage of women who had an abnormal Pap test result by diagnostic category from January 2012 to December 2014 (n = 16,119).



NOTE: ASC-US (Atypical squamous cells of undetermined significance), LSIL (Low-grade squamous intraepithelial lesion); AGC (Atypical glandular cells); ASC-H (Atypical squamous cells, cannot rule out high-grade); HSIL+ (High-grade squamous intraepithelial lesion or more severe).

A recent study that looked at 100% of the U.S. population between 2004 and 2008, found HPV to be responsible for:

- over 90% of anal cancers,
- more than 50% of vaginal, vulvar and penile cancers, and
- 60-70% of oropharyngeal cancers.[8]

In Manitoba between 1985 and 2004, HPV was responsible for approximately 25,000 cases of anogenital warts.[9]

The psychological impact of an abnormal cervical cancer screening test result, colposcopy procedure, genital warts and/or cancer diagnosis on the individual is significant. This, coupled with the financial burden to the healthcare system, makes the disease burden of HPV an important healthcare issue in Canada.

Natural History

The peak incidence of HPV occurs in women under 25 years of age, shortly after the onset of sexual activity.[10] However, over 90% of cervical HPV infections spontaneously regress within 24 months without symptoms or intervention.[11] [12] It is not clear if "*Viral "clearance"* means that an individual's immune system completely eliminates HPV infection or reflects *Latency* where the amount of virus reduced to levels undetectable with current diagnostic methods. HPV infections are very common in the lifespan of any individual with a lifetime probability of over 80% (*Koutsky)*. Persistent infection with the same HPV genotype is a necessary risk factor to develop a high-grade cervical precancer abnormality.[13]

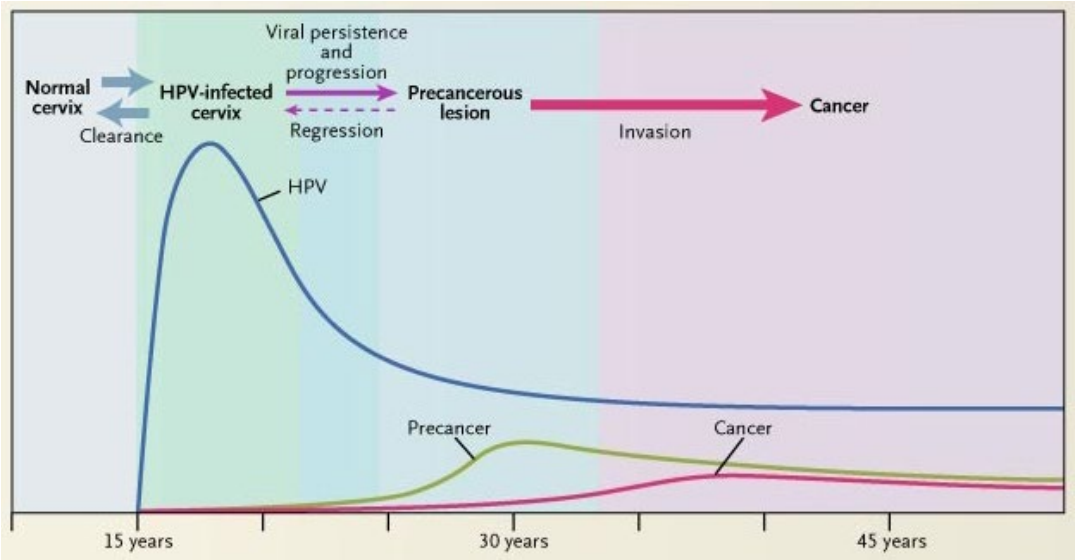
It is not clearly understood why HPV infections "resolve" in certain individuals and disease (cervical abnormalities) develops in others. "Disease is a rare consequence of a common infection"

When progression occurs, it happens over a long period of time. One study showed that the mean time for progression to HSIL was as long as seven years.[14] As well, an average of 20 years may be required for low-grade lesions to develop into invasive squamous cell carcinoma (Figure 4).[15] Having a HSIL does not necessarily mean that progression to cancer is inevitable.[16]

Occasionally cervical cancer appears to progress more rapidly. This may be due to:

- inadequate specimen collection and preparation (hence the importance of HCPs to learn the proper technique for Pap test), and/or
- lab misinterpretation.
- Limitation of cytology to identify certain cancers like adenocarcinomas
- Rapidly biological cancer

Figure 4. The natural history of HPV infection and cervical cancer.



Schiffman M. Castle PE. The promise of global cervical-cancer prevention. N Engl J Med. 2005:353(20):2101-4. doi:10.1056/NEJMp058171

Risk Factors for HPV and Cervical Cancer

Risk Factors for HPV

Genital HPV is transmitted by:

- **Current and previous sexual activity including sexual intercourse and skin-to-skin genital touching (including oral, genital and/or rectal sex and sex with toys).** HPV can be transmitted between any two people regardless of sexual orientation or gender identity. It is not possible to identify the origin of an individual's HPV infection.

Occasionally, HPV can be transmitted by:

- **Vertical transmission.** HPV has been shown to transmit non-sexually through vertical transmission. HPV infections that are transmitted from a mother to her baby in utero and/or during childbirth are uncommon, and often rarely persist beyond six months after birth.[17] [18]

Factors that may put a person at increased risk for HPV include:

- **Number of sexual partners.** Increasing the number of sexual partners one has can increase the risk of acquiring HPV infection. However, HPV transmission can occur with only one sexual encounter. Some research indicates that up to 60% of women were infected with HPV by their first partner.[19]
- **Early age of onset of sexual activity** has been identified as a possible co-factor for HPV infection due to the probability of an increase in the number of sexual partners. Potential for initial infection begins with onset of sexual activity, and each sexual encounter augments the risk of infection.[20 21 22]
- **The sexual behavior of the woman's male partner.** Studies have indicated that the risk of HPV infection and cervical cancer incidence in women increased with the number of her male partner's sexual partners, and with the male partner's early age at first intercourse.[23]
- **Male partners who are not circumcised** have more HPV infections than men who are circumcised.[24] Uncircumcised men are also more likely to be infected with carcinogenic HPV types compared to circumcised men.[25] HPV infection in uncircumcised men is also more likely to persist when compared to HPV infections in circumcised men.[26] As well, the incidence of high-risk HPV infection among women is lower among those who have circumcised male partners.[27]

Specific HPV genotypes cause genital warts while others cause abnormal cervical changes. HPV types 16 and 18 cause 70% of cervical cancer. HPV 6 and 11 cause over 90% of genital warts.	Important Information

Risk Factors for Cervical Cancer

Factors that can contribute to the development of cervical cancer include:

- acquisition of high-risk HPV
- persistent high-risk HPV infection
- not having Pap tests and/or not having Pap tests for 5 years or more

Other contributing factors that may act together with HPV and affect the development of cervical cancer include:

- smoking
- infection with other sexually transmitted agents

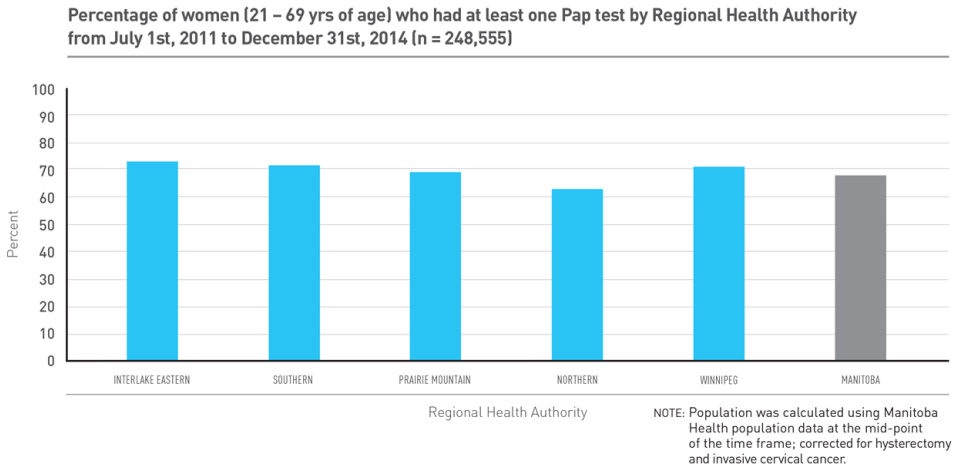
- immunodeficiency

High risk groups include those who are less likely to be screened. Therefore, it is valuable to focus our recruitment efforts on underserved clients who are eligible for screening. These populations include:

- older women, post-menopausal
- women of low socioeconomic status
- immigrant women
- Aboriginal women
- women who live in rural, remote and isolated areas
- women who have poor access to Pap test providers
- providers not offering cervical screening
- poorly educated and illiterate women
- women who have sex with women
- women with disabilities
- women with no family physician
- women with persistent HPV infection
- women who smoke and/or exposed to second-hand smoke
- women who are immunosuppressed
- women infected with HIV and have a CD4 count lower than 400
- women who have been victim to childhood sexual assault
- transgender/non-binary individuals

In Manitoba, between July 1, 2011 to December 31, 2014, 67.7% of women had at least one Pap test. The Northern Regional Health Authority (formerly Burntwood and Nor-Man) had the lowest screening rate, with 62.7% of women having had at least one Pap test between July 2011 and December 2014.[8]

Figure 5. Percentage of women (21-69 years of age) who had at least one Pap test by Regional Health Authority from July 1st, 2011 to December 31st, 2014 (n = 248,555).



Organized Cervical Cancer Screening in Manitoba: CervixCheck, CancerCare Manitoba

Cervical cancer screening may be opportunistic or organized. Opportunistic screening depends on the individual eligible client and/or their HCP's initiative, and does not achieve optimal screening coverage of the eligible population.

Manitoba's organized screening program allows a standardized approach to screening, follow-up, and treatment, and requires a registration database of eligible clients. The database of an organized screening program enhances participation by identifying and recruiting underscreened and unscreened clients, as well as facilitating the recall of those who may be overdue for routine screening. A registry also enables the program to facilitate follow-up for abnormal results where the appropriate management may not have occurred. It further provides Quality Assurance at all levels of screening.

What is CervixCheck, CancerCare Manitoba?

CervixCheck was established in January of 2000 with a mandate to ensure that eligible Manitobans receive organized, high quality cervical cancer screening services. CervixCheck is supported by Manitoba Health and managed by CancerCare Manitoba. On April 27, 2001, an amendment to the Public Health Act requiring the reporting of all cervical cancer screening tests to CervixCheck commenced operation of the CervixCheck registry. The registry is a central and confidential record of Pap tests, colposcopy, and biopsy results.

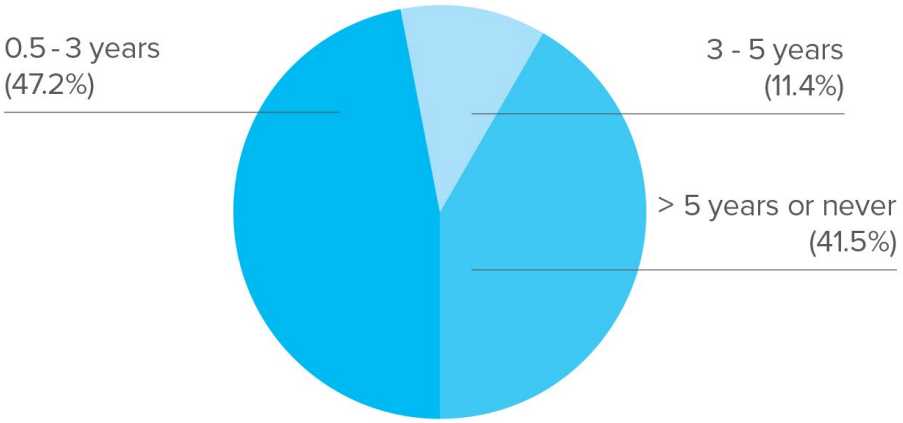
The goal of CervixCheck is to reduce the incidence of and mortality from invasive cervical cancer. To accomplish this goal, CervixCheck is guided by the following five objectives:

1. Maximize screening uptake in the eligible population
2. Operate and enhance a population-based information system and Registry
3. Facilitate and support quality assurance activities for cervical cancer screening services
4. Monitor and evaluate CervixCheck
5. Participate in review, evaluation and implementation planning of new technologies

Why is the program needed?

Cervical cancer is largely preventable, yet each year in Manitoba, 50 women are diagnosed with invasive cervical cancer and approximately 20 women die from their disease. Surveillance of cervical cancer and Pap test utilization in Manitoba has confirmed that individuals diagnosed with invasive cervical cancer have not ever had a Pap test or have had significantly fewer Pap tests in the 5 years before their diagnosis (Figure 6).[8]

Figure 6. Percentage of women diagnosed with invasive cervical cancer by time since last Pap test, from January 2011 to December 2013 (n = 123). *Note: more than 5 years includes women who had a Pap test more than 5 years prior to diagnosis, women who had no record of a Pap test, and women whose only Pap test was during the 6 months prior to diagnosis (because this Pap test was likely performed for diagnostic rather than screening purposes).*



Research from around the world shows that organized cervical cancer screening programs like CervixCheck reduce the rates of cervical cancer by:

- Educating the public and HCPs about the importance of regular Pap tests for the prevention of cervical cancer,
- Inviting eligible unscreened clients to participate in screening,
- Reminding eligible clients when they are overdue for a Pap test,
- Informing patients when they have high-grade Pap test results, and
- Sending letters to HCPs and patients when the appropriate follow-up has not occurred for low-grade abnormal Pap test results.

What is a client's role in this program?

A client's role in the program involves participating in her own healthcare by participating in regular cervical cancer screening and recommended follow-up. The client may contact the program to request a copy of a test result or receive information about screening for cervical cancer.

What is the CervixCheck Registry?
The Registry is a central and confidential record of Pap tests and follow-up test results for all eligible Manitobans. It was established in 2001. Personal health information is collected according to the cervical cancer screening regulation of the Public Health Act. The Registry contains:

- the client's name, address and date of birth
- the client's Personal Health Identification Number (PHIN) and Manitoba Medical Number (MHSC)
- the date(s) and results of cervical cancer screening and colposcopy test(s)
- the name, address and provider number of the HCP who did the test(s)
- the name of the laboratory where each test was read
- HPV vaccine information for females age 18 or older (dates and number of doses)
- hysterectomy status (if completed after 1985 and in Manitoba) for females 18-69 years of age
- in-situ cervical cancer, invasive cervical cancer and invasive gynecologic cancer information for all women between 18 and 69 years of age

Who has access to the information in the Registry?

- The individual woman can access her own results
- The HCP who did the Pap test
- A HCP who provides the woman care where a woman's cervical screening history is relevant to the care being provided
- The laboratory that reads the Pap test
- CervixCheck staff involved in the Registry

Everyone who has access to a client's health information is bound by the Personal Health Information Act (PHIA) of Manitoba and has signed a Pledge of Confidentiality.

What does CervixCheck do with the information in the Registry?
The information in the Registry enables CervixCheck to send HCPs and clients letters where appropriate. The Registry allows the program to determine where underscreened communities exist and focus recruitment efforts in those regions. HCPs may also access the screening histories of clients in their care in order to facilitate appropriate and efficient screening (see Appendix 2 for a

screening histories request form). CervixCheck also uses information in the Registry to measure the performance of the program.

Can a woman opt out of the CervixCheck Registry?
Yes. To opt out, a client must complete an opt out form available at https://www.cancercare.mb.ca/screening. A client's HCP will continue to receive test results from the lab, but CervixCheck will no longer collect any Pap test or follow-up test results for the client. As well, letters will no longer be sent to the client or the client's HCP. A client can choose to opt back into the registry by calling the CervixCheck office, however, historical results will not be accessible.

Does a client's HCP continue to communicate with her regarding Pap test results?
Yes, a client's HCP retains responsibility to communicate Pap test results, provide follow-up care and arrange for any medical follow-up procedures. The program does not replace communication requirements between a client and the client's HCP.

Can a client choose not to receive letters from CervixCheck?
Yes, a client can choose not to receive correspondence from the program. A client may in the future want to receive correspondence from CervixCheck.

What kind of correspondence does the program send in the mail?
To follow is a summary chart and more specific detail below the chart for each letter type. Note: Specimen collectors will always receive a lab report for each result.

LETTER TYPE	PURPOSE	TIMING
Patient - Invite	▪ Notify patient they are eligible to be screened for cervical cancer ▪ Encourage patient to make a cervical cancer screening appointment.	Send to patient when they become eligible for cervical cancer screening. Eligibility criteria includes: • Age 24-69 • Existed in the registry for at least 5 years • Manitoba resident with a current MB Health number • No history of a Pap test, colposcopy, gyne cancer, or hysterectomy
Patient – Invite Reminder	▪ Remind patient they are eligible to be screened for cervical cancer ▪ Encourage patient to make a cervical cancer screening appointment.	Send to patient 3 months after initial invite is sent.
Patient - Recall	▪ Notify patient they are due to be screened for cervical cancer ▪ Encourage patient to make a cervical cancer screening appointment.	Send to a patient 36 months after last Pap test or colposcopy result.

LETTER TYPE	PURPOSE	TIMING
Patient – High-Grade Result	▪ Notify patient of their recent high-grade cervical cancer screening result ▪ Encourage patient to contact their healthcare provider to ensure a colposcopy appointment has been made	Sent to patient within 4 weeks of a high-grade Pap test result.
Provider – Repeat Pap test	▪ Notify the healthcare provider (HCP)their patient has not had their repeat Pap test.	Send to HCP: • 6 months after Unsatisfactory result. • 9 months after last ASCUS or LSIL result.
Patient –Repeat Pap test	▪ Notify the patient they are due for a repeat Pap test after a low grade or unsatisfactory result. ▪ Encourage the patient to make a Pap test appointment.	Send to patient 8 weeks after HCP notification letter and no update/response is received.
Provider – Pending 2nd negative	▪ Notify the (HCP) their patient has not yet had their second negative Pap test.	Send to HCP 9 months after last negative result.
Patient – Pending 2nd negative	▪ Notify the patient they are due for a repeat Pap test after a recent low grade or unsatisfactory results.	Sent 8 weeks after HCP notification letter and no update/response is received.

LETTER TYPE	PURPOSE	TIMING
Provider – Pending colposcopy	▪ Notify the HCP their patient has not yet been seen in colposcopy due to persistent low grade or unsatisfactory results. ▪ Encourage HCP to make colposcopy referral if not already done.	Send to HCP: • 6 months after unsatisfactory result • 9 months after last ASCUS or LSIL result.
Patient – Pending colposcopy	▪ Notify the patient they should be seen in colposcopy due to persistent low grade or unsatisfactory results. ▪ Encourage the patient to contact their HCP to ensure a colposcopy appointment has been made.	Send to patient 8 weeks after HCP notification letter and no update/response is received.
Provider – High-Risk HPV (hrHPV) Result	▪ Notify the provider of their patient's recent cervical cancer screening result including the Pap test interpretation and a positive hrHPV test result	Within one week of CervixCheck receiving the result.

LETTER TYPE	PURPOSE	TIMING
Patient – High-Risk HPV (hrHPV) Result	▪ Notify patient of their recent cervical cancer screening result including the Pap test interpretation and a positive hrHPV test result ▪ Encourage patient to contact their healthcare provider to ensure a colposcopy appointment has been made	Sent to patient within 4 weeks of a hrHPV result.

Abnormal Follow-Up (Fail-Safe) Letters

Follow-up or fail-safe letters are correspondence sent by the screening program to health care providers, patients or both to ensure appropriate investigation of abnormal screening results occurs. Correspondence is sent when the appropriate investigation is overdue.

i. **Follow-Up Letters to Primary HCPs:** A letter will be sent to the HCP when the necessary follow-up is not evident within 6 – 9 months.
ii. **Follow-Up Letters to Patients:** A letter will be sent directly to the patient when:
    a. CervixCheck does not receive a response from the provider eight weeks from the date when the follow up letter was generated,
    b. CervixCheck is informed by the provider that the individual could not be located and, hence, has not been informed of the abnormal cervical cancer screening result,
    c. The provider is no longer practicing and the follow up letter to the provider is returned to the program.
    d. The patient has a high-grade cytology result or a high-risk HPV result.

Follow-up letters to patients notify them of their abnormal cervical cancer screening test result and encourage follow-up with their HCP.

High-Grade Result Letters

Result letters are sent directly to patients with a high-grade cytology result test result four weeks after the specimen date to notify patients of their high-grade test result and need for colposcopy. Patients are encouraged to contact their health care provider to arrange an appointment for colposcopy. Information about abnormal results, colposcopy and the importance of cervical cancer screening are also provided in the letter. The specimen taker is still responsible to notify patients of all abnormal cervical cancer screening test results.

High-Risk HPV Result Letters

Result letters are sent directly to patient with a high-risk HPV (hrHPV) test result. Patients are encouraged to ensure their healthcare provider has made them a colposcopy appointment. Information about high-risk HPV and colposcopy are also provided in the letter package.

Invitation Letters
An invitation letter is correspondence from a cervical screening program to a never screened client informing the client about screening and their eligibility to participate in screening. Invitation letters notify clients on their screening status and encourage clients to make an appointment with their health care provider for cervical cancer screening. Information about the importance of cervical cancer screening and where a client may access service are also provided in the letter.

Recall Letters
A recall letter is correspondence from a cervical screening program to a previously screened client to inform the client that they are due for repeat routine screening. Recall letters notify clients on their screening status and encourage clients to make an appointment with their health care provider for a Pap test. Information about the importance of Pap tests and where a woman may access service are also provided in the letter. A phrase translated into several languages is also included.

Recommended Reading

CervixCheck Resources:
https://www.cancercare.mb.ca/screening/resources

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1. Describe human papillomavirus, cervical cancer incidence, precursors, natural history and risk factors. 2. How does CervixCheck operate? 3. Why is the CervixCheck program needed? 4. Who are the most important high-risk groups for HCPs to target?	Chapter 2 Self-Test

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