

## THE VIRUS, THE TEST, AND SINGAPORE NATIONAL CERVICAL CANCER SCREENING GUIDELINE – IMPLEMENTATION OF HPV TESTING IN AN OPPORTUNISTIC SCREENING PROGRAMME

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### ABSTRACT

Cervical cancer is a highly preventable disease, yet it remains the 10th most common cancer among Singaporean women. This paper examines the evolution of Cervical Screen Singapore (CSS), which was launched in 2004. In view of the emerging evidence on the advantages of HPV primary screening compared to cytology-only screening for primary cervical cancer screening, the guideline underwent a major update in 2019.

1. Use only liquid-based cytology (LBC) and abolish the conventional pap smear method
2. To screen women aged 30 to 69 with HPV test every 5 years
3. A more frequent screening schedule for immunocompromised women
4. Cytology triage for HPV non-16/18 positive result
5. HPV triage for women aged 25 to 29 whose cytology result is ASCUS

The paper highlights several recommendations to eliminate cervical cancer in Singapore, such as improving awareness and knowledge for women and primary healthcare providers and the potential role of HPV tests using vaginal self-sampling for under screeners. The importance of collaboration among key stakeholders is emphasised to enhance the effectiveness of the national screening programme and better public health outcomes.

**Key Words:** Uterine Cervical Neoplasms; Human Papillomavirus Viruses; Mass Screening; Secondary Prevention, Practice Guideline

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### INTRODUCTION

Cervical cancer is a preventable cancer.<sup>1</sup>

Ever since the discovery of High-risk Human Papillomavirus (hrHPV) as the cause of cervical cancer by Harald Zur Hausen in 1976, leading to his Nobel Prize award, the world has been able to better understand cervical cancer. Various effective screening tools and preventive strategies have been developed to detect and prevent persistent hrHPV infection, leading to the prevention of future cervical cancer.

Organised national cervical cancer screening programmes were initiated especially in high-income countries such as the United Kingdom, Australia, and the Netherlands. These programmes had shown effectiveness in preventing cervical cancer. The introduction of school-based HPV vaccination programmes brought these countries even closer to eradicating cervical cancer.

### THE GLOBAL BURDEN OF CERVICAL CANCER

Globally, cervical cancer was the fourth most common cancer in women, making up 6.9 percent of the total number of new cervical cancer cases diagnosed in 2022,<sup>2</sup> despite the ability for this disease to be effectively screened, in addition to the availability of an effective HPV vaccine.

The World Health Organization (WHO) has recognised the impact of cervical cancer globally and the importance of eliminating this terrible preventable disease. The COVID-19 pandemic further aggravated the efforts to eliminate cervical cancer globally by diverting screening resources and halting cervical cancer screening measures worldwide.<sup>3</sup>

In November 2020, WHO launched a call for action on a global strategy for cervical cancer elimination.<sup>1</sup> The strategy called for all countries to reach and maintain a cervical cancer incidence of below four in 100,000 women, by adopting three key pillars to elimination:

- **Vaccination:** 90 percent of girls fully vaccinated with the HPV vaccine by the age of 15
- **Screening:** 70 percent of women screened using a high-performance test by the age of 35, and again by the age of 45
- **Treatment:** 90 percent of women with pre-cancer treated and 90 percent of women with invasive cancer managed

Each country should be on target for this 90-70-90 goal by the year 2030 in order to eliminate cervical cancer from their country by the next century.

## THE EVOLUTION OF THE SINGAPORE NATIONAL CERVICAL SCREENING PROGRAMME

Singapore's national cervical cancer screening programme (Cervical Screen Singapore, CSS) was introduced in 2004. The aim of this programme is to reduce the incidence of cervical cancer in Singapore, which in 2004 was 16.7 per 100,000 women compared to countries with resource settings such as Australia (4.9 per 100,000) and Finland (4.7 per 100,000).<sup>2,4</sup>

The initial CSS programme, launched in 2004, was designed as an opportunistic cytology-only primary cervical screening programme inviting women from the age of 25-69 years old who had ever had sex to undergo screening using a Papanicolaou (Pap) smear once every three years.<sup>5</sup>

A steady decline in cervical cancer incidence has been observed, with the incidence falling to the tenth most common female cancer in Singapore four years after the introduction of the CSS. Similar to other countries that adopted an opportunistic approach to screening, the incidence of cervical cancer in Singapore has not improved further and has plateaued at this level.<sup>4</sup>

There have been emerging worrying trends in Singapore's cervical cancer screening population. Uptake in screening has not improved since CSS introduction, with only 10 percent of women reporting regular triennial screening.<sup>6</sup> The 2011-2015 Singapore cancer registry reported an increasing trend in cervical cancer incidence, with an increase in the incidence of stage 3 and stage 4 cervical cancer diagnosed in women 30 years and above.<sup>4</sup> The most recent Singapore national cancer registry reported cervical cancer being the fourth most common cancer in young women aged 30 to 40 years old.<sup>7</sup> The Singaporean Malay population remains the community with the highest incidence of cervical cancer with the least uptake in screening.<sup>4</sup>

The identification of hrHPV as a causative agent for cervical cancer prompted the development of the HPV DNA test. This test was more sensitive than cytology alone in cervical cancer screening. Consequently, it offered Singapore the opportunity to adopt a more effective screening strategy compared to the existing CSS.

This paper outlines the evolution and implementation process of introducing HPV primary screening in Singapore's national cervical screening programme and future efforts and opportunities to continue cervical cancer elimination in Singapore.

## THE HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER

Persistent infection with hrHPV is central to the pathogenesis of cervical cancer. The development of cervical cancer is closely linked to the age at first sexual intercourse, which often correlates with the age at first HPV infection. The typical age for contracting HPV closely follows the onset of sexual activity, similar to other sexually transmitted

infections, with the peak incidence occurring shortly after the average age of sexual initiation. This timing varies across cultures, influencing the age at which subsequent stages of infection and precancer occur.

Most cervical HPV infections do not lead to immediate cytological abnormalities and are typically cleared or suppressed within 1-2 years by cell-mediated immunity. For instance, CIN1 (Low grade CIN, mild cervical dysplasia) often represent transient infection or infections with non-carcinogenic HPV types (low-risk HPV), and thus do not always indicate a high risk of progression to more severe disease. The majority of HPV infections (90 percent) resolve within two years; however, the 10 percent that persist are significantly associated with the development of precancer and future cervical cancer.

The progression from persistent hrHPV infection to cervical cancer involves hrHPV-infected cervical epithelial cells overtaking the cervical epithelium, initially leading to the development of preinvasive cervical disease (cervical pre-cancer), more commonly known as CIN2/CIN3 (High Grade CIN, moderate/severe cervical dysplasia).

Cervical pre-cancers are not cervical cancer but are abnormal or dysplastic cervical cells that have the potential to develop into cervical cancer in future. Cervical pre-cancer is asymptomatic and can only be diagnosed using colposcopy and cervical biopsy. Treatment of cervical pre-cancer exposes the woman to a significantly minor impact compared to the impact of cervical cancer treatment.

## THE HPV TEST

Several clinical trials investigating the performance of primary HPV screening have been pooled, confirming the safety and efficacy of this approach.<sup>11-13</sup> The sensitivity of HPV DNA testing surpasses that of conventional cytology-based methods (Pap smear), although it exhibits lower specificity. HPV testing is highly sensitive but cannot discriminate between transient and persistent infections. A negative test result indicates a low probability of developing CIN3+ disease within the next 5-10 years with accuracy, but a positive result only indicates the presence of an essential risk factor.<sup>14</sup>

Consequently, if all HPV-positive cases are referred for colposcopy, the burden of colposcopy referrals and associated procedures will be very high, with 57.2 colposcopies per 1,000 tests, raising concerns, particularly in younger women.<sup>14-15</sup> Therefore, a triage strategy is essential to differentiate clinically low-risk lesions that do not require immediate colposcopy.<sup>16</sup>

The high specificity of cytology makes it suitable for triaging HPV-positive cases. The combination of HPV test and cytology (co-testing) for primary cervical cancer screening has not been shown to be more beneficial than HPV primary screening. Arbyn et al reviewed 48 studies, including eight RCTs, and concluded that adding cytology

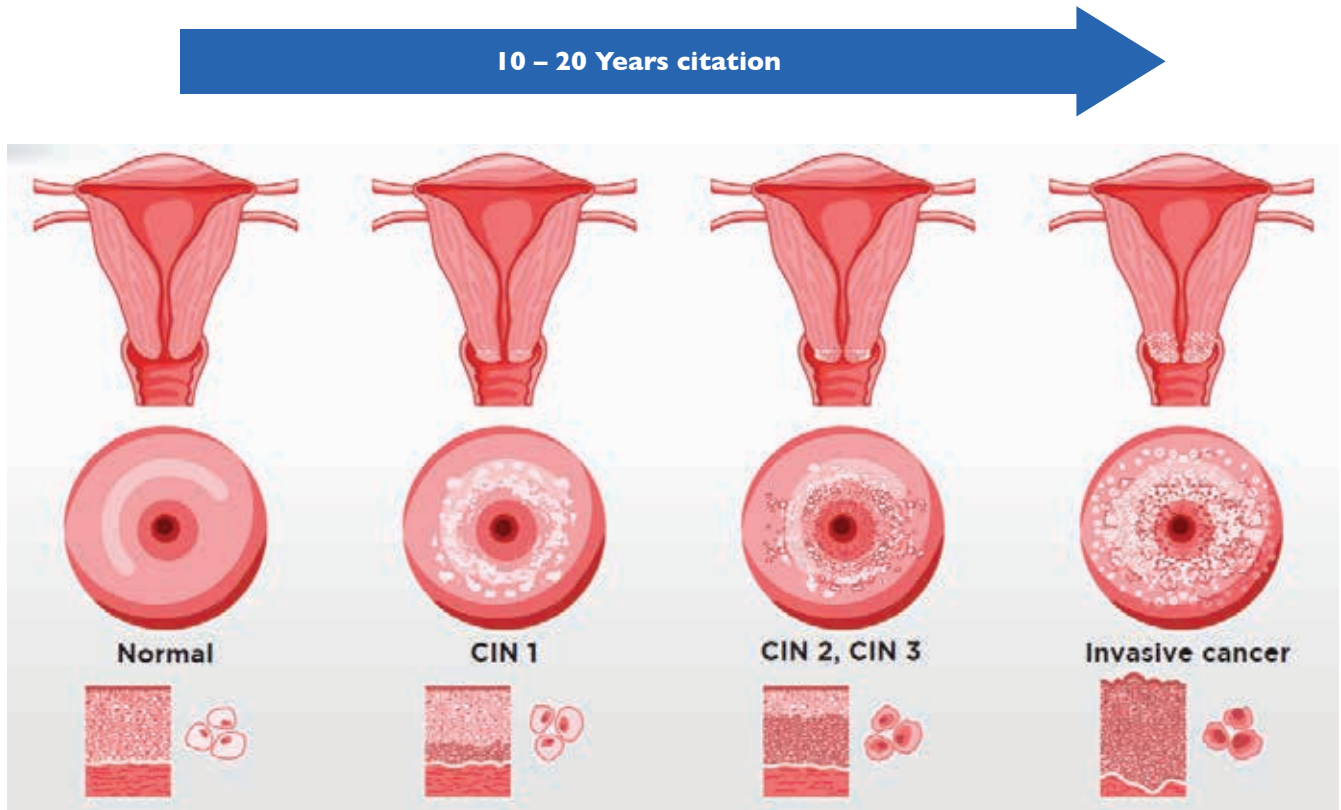
to HPV testing (co-testing) increased sensitivity by only 5 percent for CIN2+ and 2 percent for CIN3+, at the expense of a considerable loss of specificity.<sup>17</sup>

It is crucial to maintain a balance between sensitivity and specificity to avoid over-detecting benign infections, which can lead to unnecessary risks of overtreatment, and to ensure that testing identifies diseases that require intervention.

The HPV test uses the presence of hrHPV infection as a surrogate to predict the risk of future cervical cancer in a woman, allowing for earlier detection and treatment of preinvasive cervical disease (pre-cancer).

This paradigm shift in understanding the logic of a cervical screening tool requires all healthcare providers to have a deeper understanding of the goal of screening using the HPV test prior to offering the test to all eligible women.

**Figure 1: Major steps in the development of cervical cancer<sup>8,9</sup>**



**THE CHANGES INTRODUCED IN THE 2019 CERVICAL CANCER SCREENING GUIDELINE**

In view of the emerging evidence on the advantages of HPV primary screening compared to cytology-only screening for primary cervical cancer screening, the Singapore cervical cancer screening guideline underwent a major update in 2019 to incorporate HPV test into the national cervical cancer screening programme.

The main changes in the guideline are summarised in the table below.

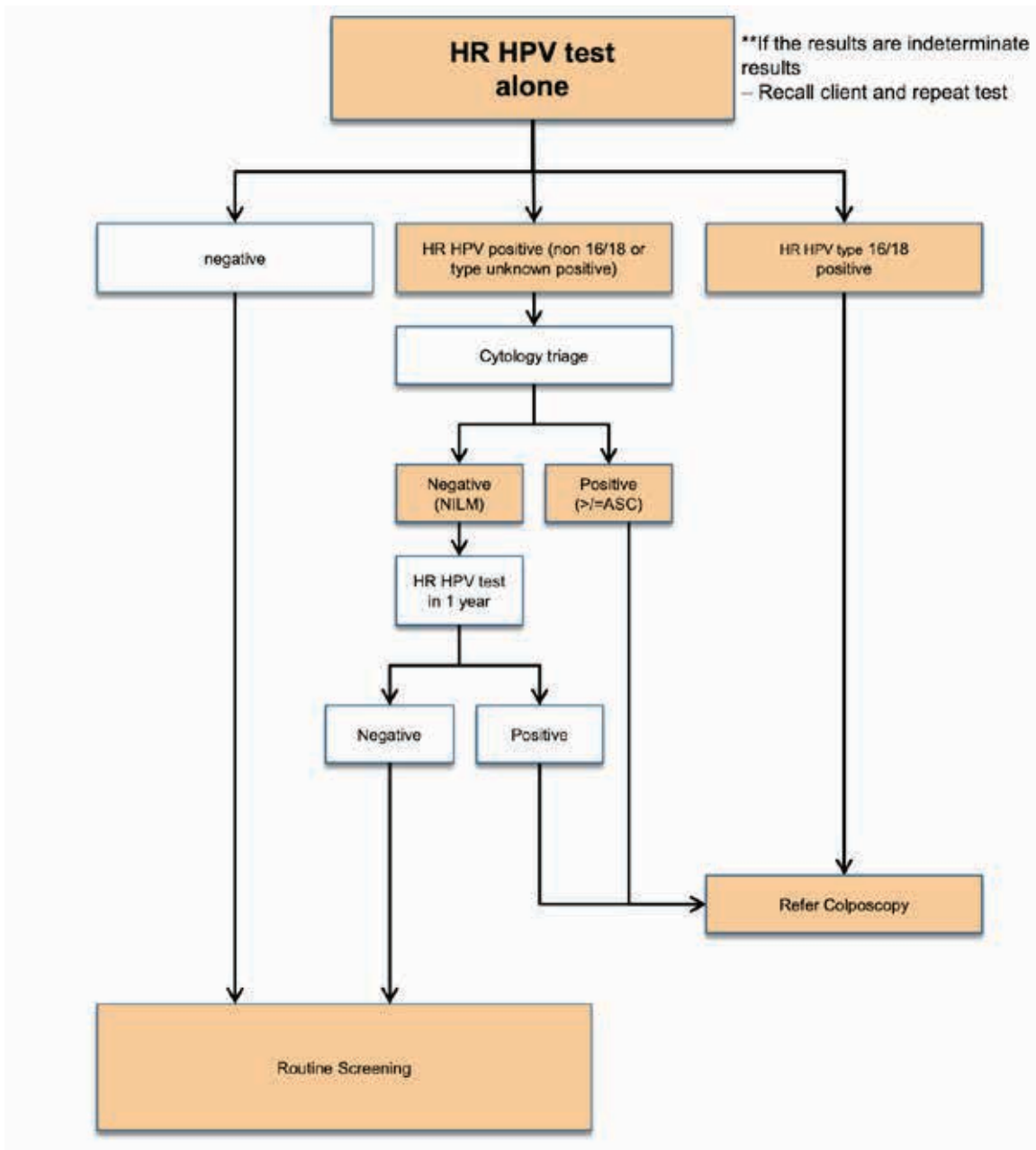
**Table 1: shows the main changes introduced in the 2019 updated national cervical cancer screening guideline.**

<p><b>Update 1:</b> Changing all screening modalities to liquid-based cytology (LBC) and abolishing the conventional pap smear method in all polyclinics and GP practices participating in the CSS national cervical cancer screening guideline.</p>	
<p><b>Update 2:</b> Changing the screening method and schedule for women 30-69 years old to HPV primary screening every 5 years.</p>	
<p>Before 2019 update</p> <p><b>Eligible criteria:</b> <i>All women 25-69 years old who have ever had sexual intercourse</i></p> <p><b>Screening frequency:</b> <i>Pap smear (cytology only method) every 3 years</i></p> <p><b>Discharge from screening criteria:</b> <i>69 years old with two normal pap smears 3 years apart</i></p>	<p>2019 update</p> <p><b>Eligible criteria:</b> <i>All women 25-69 years old who have ever had sexual intercourse</i></p> <p><b>Screening frequency:</b> <i>25-29 years old: Pap smear (cytology only method) every 3 years</i> <i>30-69 years old: HPV test only (HPV primary screening) every 5 years.</i></p> <p><b>Discharge from screening criteria:</b> <i>69 years old with 2 negative HPV tests 5 years apart</i></p>
<p><b>Update 3:</b> Recognition of the higher cervical cancer risk and introduction of a different screening schedule for the immunocompromised community.</p> <p><b>Definition of immunocompromised group:</b></p> <ul style="list-style-type: none"> <li>• All HIV-positive women</li> <li>• All women who are a recipient of solid organ transplant</li> <li>• All women who are taking 2 or more immunosuppressive medications</li> </ul> <p><b>Eligible criteria:</b> <i>All women 25 years old and above who have ever had sexual intercourse</i></p> <p><b>Screening frequency:</b> <i>25-29 years old: Annual Pap smear (cytology only method)</i> <i>≥30 years old: HPV test only (HPV primary screening) every 3 years</i></p> <p><b>Discharge from screening criteria:</b> <i>No discharge criteria. Screening is recommended to be done for life</i></p>	

**Update 4:**

Introduction of HPV partial genotyping and cytology triage for HPV non-16/18 positive result.

**Figure 3: Management of HPV test screening (Adapted from National Cervical Cancer Screening Programme<sup>5</sup>)**



**Update 5:**

Introduction of HPV triage for women 25-29 years old whose cytology result is Atypical Squamous cell of Undetermined Significance (ASCUS).

Before 2019 update

For ASCUS cytology result:



Repeat Pap smear in 6 months  
Result: NILM\*



Repeat Pap smear annually for 2 years  
Result: NILM\*  
Discharge to routine screening.

2019 update

For ASCUS cytology result:



HPV test^  
Result: Negative HPV test



Discharge to routine screening.

\*NILM: No intraepithelial lesion or malignancy

^HPV test for ASCUS triage is performed automatically by the lab without requiring healthcare providers to request it.

The updated 2019 guideline is available at the Society of Colposcopy and Cervical Pathology of Singapore (SCCPS) website at this link: <https://www.sccps.org/guidelines-and-updates/>.

**FUTURE PLANNING**

The national cervical cancer screening guideline will continue to evolve to guide all healthcare providers in Singapore on primary cervical cancer screening and management of abnormal cervical screening results.

Screening uptake is the first of the key pillars in in WHO global cervical cancer elimination strategy. It will continue to be one of the most important aspects of cervical cancer screening.

An effective cervical cancer screening strategy would require the uptake of at least 70 percent of its eligible women for screening. The uptake for cervical cancer screening in Singapore was 48.2 percent in 2019, 45.2 percent in 2020, and 41 percent in 2021.<sup>7</sup> The uptake rates were well below the recommended percentage and explains the current climate of cervical cancer incidence in Singapore.

The availability of the most effective and up-to-date screening, diagnostic, and treatment modalities would not be able to eradicate cervical cancer in Singapore without an improvement in screening uptake. Uptake starts in the community, with access to awareness and knowledge not only for the community but also for all primary healthcare providers. In order to increase uptake in screening, primary healthcare providers should continue to be supported in improving their knowledge, especially the continuous changes in the national cervical cancer screening guideline.

In addition to continuous medical education, primary healthcare providers should also be supported with the tools to overcome barriers so that they can offer cervical

screenings to every eligible woman they see in their clinic.<sup>18</sup>

HPV tests using vaginal self-sampling could be the innovation to overcoming such barriers in screening in the community, especially for the underscreeners, be it the woman or the healthcare providers.<sup>19</sup> HPV test using vaginal self-sampling is currently under review by the Cervical Screening Singapore Guideline Review Group, and the decision is highly anticipated in the near future.

**CONCLUSION**

Cervical cancer is preventable.

Singapore has an evidence-based, up-to-date national cervical cancer screening guideline to guide all healthcare providers in reducing the incidence of cervical cancer in Singaporean women.

Cervical cancer screening uptake is one of the key pillars of cervical cancer elimination and should start in the community, led by primary healthcare providers. In order for primary healthcare providers to continue to support and protect Singaporean women from cervical cancer, recognition of the barriers in screening for primary healthcare providers needs to be immediately addressed.

HPV tests using vaginal self-sampling will help to overcome some of the main screening barriers in primary healthcare providers.

Continuing medical education, with collaborations between the College of Family Physicians Singapore, the Health Promotion Board, and various cervical cancer screening

societies and advocacy groups in Singapore, is crucial for the sustainability of the national cervical screening programme.

In order to eliminate cervical cancer in Singapore, it is important that all implementers, decision-makers and stakeholders start working together to ensure an effective cervical cancer screening programme in Singapore that will protect every Singaporean woman from cervical cancer.

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## LEARNING POINTS

- **Preventability and Causation:** Cervical cancer is primarily caused by persistent infection with high-risk Human Papillomavirus (hrHPV). Cervical cancer can be effectively prevented through vaccination, screening, and effective treatment for precancerous conditions and invasive cancer.
- **Singapore's Screening Evolution:** Singapore's shift from a cytology-only screening approach to incorporating HPV testing offers a more sensitive method for detecting pre-cancerous conditions. However, healthcare providers need to understand the causation of cervical cancer and screening tests to refer treatment and counsel women.
- **Future Directions:** Ongoing updates to national guidelines and continuous medical education for healthcare providers are vital for improving screening rates and ultimately reducing cervical cancer incidence.