



SULLIVAN NICOLAIDES
PATHOLOGY

Cervical Screening Update

CST Self-collect
CINtec PLUS
Latest guideline update

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The Global Effort to Eliminate Cervical Cancer

The global strategy to eliminate cervical cancer proposes:

- a vision of a world where cervical cancer is eliminated as a public health problem;
- a threshold of 4 per 100,000 women years for elimination as a public health problem;
- the following 90-70-90 targets that must be met by 2035 for countries to be on the path towards cervical cancer elimination:

90%

of girls have received at least one dose of HPV vaccine by age 15

70%

of women aged 25-49 years have received at least one cervical screening test

90%

of women aged 25-49 years have received at least one HPV test

- a mathematical model that illustrates the following interim benefits of achieving the 90-70-90 targets by 2035 in low and lower-middle-income countries:
 - median cervical cancer incidence rate will fall by 40% by 2045, and by 90% by 2050, averting more than 76 million new cases of cervical cancer;
 - median cumulative number of cervical cancer deaths averted will be 300,000 by 2035, over 14 million by 2050, and over 62 million by 2100.



WHO
UNAIDS
GAP
IOTD495
ROSE

Australia making advances...

2020

- 80.5% girls fully vaccinated by 15 yrs
- 62% women aged 25-74 yrs participated in cervical screening (2018-2021), 67.3% 45-49yrs
- 85.8% of those with pre-cancer treated within 6 months (QLD data showed over 90% treatment rates for cervical cancer - no national data)

Sadly, Australian women are still dying of cervical cancer

- In 2021 in Australia, there were **851 new cases** of cervical cancer
- In 2020 there were **209 deaths** attributable to cervical cancer



Equity – screening participation

~80% women diagnosed with invasive cancer are under/never screened

- Indigenous – 2 x develop and 3.8 x likely to die from cervical cancer
- Geographical – NT, outer regional/remote/very remote
- Age 25-29 and >70 years
- Socioeconomic disadvantage
- Cultural and linguistic diversity
- LGBTIQ+
- Gender (versus sex) identify as male; assigned female at birth
- Disability
- History of sexual violence



Ref: C4 2021 Cervical Cancer Elimination Progress Report
VICCR Statistical Report - Victorian Cervical Cytology Registry, 2015.

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Cervical Screening Test Self-collection (CST Self-collect)

CST Self-collects

Initial hesitancy and mistrust combined with (extremely) restricted access – very low uptake (0.1%); minimal labs accredited.

2018 meta analysis showed equivalence in accuracy between self-collection and clinician collection for PCR results.

2022 offered as a **choice** for all participants, except for the small number who are ineligible (i.e. those who need a co-test)

Ref: Inamura F, Aiken CA, Melchers WJG, et al. Clinical performance of high-risk HPV testing on self-samples versus clinician samples in routine primary HPV screening in the Netherlands: An observational study. *Lancet Reg Health Eur*. 2021;11:100235. Published 2021 Nov 9. doi:10.1016/j.lanpep.2021.100235



Original modelling estimated 6% by mid 2025 but anticipation from the NCSP was that **universal self-collection** from July 2022 would do much better than that.

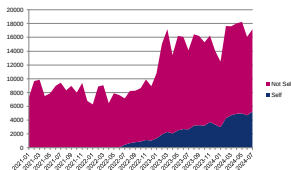


Fig. 1 Sullivan Nicolaides Pathology proportion self collects vs all collects 2021 - current

Nationally:
Increased numbers of self collects in rural/remote areas, Northern Territory residents, 70+ yrs, financially disadvantaged, never screened and under screened populations

Patient Eligibility

Eligible:

- Anyone who is eligible for cervical screening (women and people with a cervix aged 25-74 yrs who have ever had any sexual contact) and *asymptomatic*
- Follow-up HPV testing at 12 or 24 months after an intermediate risk result
- Cervical screening during pregnancy
- Previous hysterectomy for benign reasons without history of cervical pathology or screening history unknown

Ineligible:

- Symptomatic (e.g. PCB, IMB, PMB, unexplained persistent unusual vaginal discharge)
- Undergoing Test of Cure (TOC) surveillance after treatment for HSIL or history of glandular abnormality
- Total hysterectomy with past history of HSIL
- Diethylstilbestrol (DES) exposure in utero



CINtec PLUS... why?

- Vaccinated cohorts are now entering the screening system
- HPV subtypes are changing and moving towards less aggressive types with non 16/18 HPV subtypes increasing
- Colposcopy versus surveillance poses a challenge to follow up, for which HPV genotyping together with *dual staining* (*alias CINtec*) may provide a potential efficient strategy for stratification
- Allows to increase interval between colposcopies or to identify women that may benefit most from immediate colposcopy

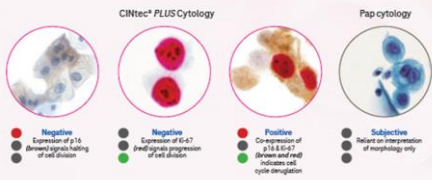
CINtec PLUS... What is it?

- Dual-stain cytology performed as on a liquid based cytology (LBC) slide to detect presence of two proteins: p16 and Ki-67.
- P16 protein expressed in cells that have been transformed by high-risk HPV due to actions of the HPV oncoprotein E7. Overexpression is shown in most cervical pre-cancer lesions and cancers, but is rarely observed in normal tissue.
- Co-expression of p16 protein and proliferation marker Ki-67 within the same cervical epithelial cell can be used as a surrogate marker for cell-cycle dysregulation mediated by HPV oncoproteins.
- Positive test = co-staining of p16 (brown, cytoplasmic) and Ki-67 (red, nuclear) in same cell means increased risk that CIN2/3 lesions are present.

CINtec® PLUS Cytology increases clarity

Identify transforming HPV infections with p16 and Ki-67

CINtec® PLUS dual stain technology based on immunocytochemistry staining, provides objective and enhanced visual clarity. This is in comparison to Pap cytology, where disease identification is based on morphological characteristics which can be difficult to assess objectively.



Preliminary COMPASS result findings

- COMPASS is a randomised controlled trial of primary HPV versus cytology screening in unvaccinated and vaccinated populations and a secondary comparison between LBC vs cintec to triage HPV other positive women
- DS can improve risk stratification in conjunction with HPV genotyping
- Potentially more effective than LBC as a triage (that is, following positive HPV result). Interestingly more so in young vaccinated cohort than older age group.
- Negative DS is a very strong marker of safety in non HPV 16/18 positive patients.

Ordering CINtec PLUS

- Offering test for persistent HPV (any type) and negative/pLSIL/LSIL cytology
- CINtec PLUS cytology should be requested by, or in consultation with, a gynaecologist
- The request must be placed **within four weeks** of receiving the CST report, as LBC material is discarded after four weeks. Cannot be performed on a self collect sample.
- Write 'CINtec' on the standard pathology request form and send a copy of your request to:
F (07) 3377 8278 E: DL.SNPcintecplus@bri.sonichealth.com.au
- There is an out of pocket fee of \$100

Latest Update

Key changes already in place

Intermediate risk tests must have a positive HPV test (not 16/18) and are no longer triggered by LBC of possible LSIL or LSIL alone:

- Ø Changes required to both 'Risk' and 'Recommendation' for HPV not detected + LBC PLSIL or LSIL = Low risk & Rescreen in 5 years
- Ø This change does not apply to TOC, DES & AIS patients

Clarification

Non – concurrent COTEST results:

As per NCSR metrics and the NCSP guidelines committee, it is acceptable for non-concurrent negative HPV and LBC results to be used together as a COTEST. The NCSP guideline committee give no timeframe recommendation for combining tests, but SNP has considered tests done after the NCSP guidelines renewal, in December 2017, to be reasonable.

Negative LBC tests and negative HPV tests collected after December 2017 may be combined to form a negative COTEST.

There must be no intervening positive HPV or positive LBC tests, effectively following the same rules as a traditional Test Of Cure.

The tests may be collected in any order

There must be 12 months since curative surgery

There must be 12 months between tests.

COTEST (performed as requested) after HR HPV detected on self-collected sample:

If a COTEST has been requested after HPV has been detected on a Self-collected sample, the test is to be performed as requested.

SELF COLLECT HPV (not 16/18).

CO-TEST HPV NOT DETECTED; LBC NEG/PLSIL/ LSIL

Where the self-collected sample had HPV (not 16/18) detected, the report issued can be based on the findings in the COTEST. Therefore if HPV was NOT DETECTED; the test can be considered LOW RISK and rescreening in 5yrs recommended.

Clearing of the virus - This is the expected outcome from the vast majority of HPV infections. The timeframe for this to happen is expected to be within a year, but can happen at any time.

Sampling differences - The same area may not have been sampled

Key Changes to Program Guidelines:

- The new program Guidelines will be available to view from Monday 6 January 2025.
- There is a need for the laboratories and the National Cancer Screening Register (NCSR) to have time to technically align with the new guidelines, the launch date of the new guidelines is scheduled for March 2025.

Key Changes to Program Guidelines:

INCLUSION OF SELF-COLLECTION OPTION:

Screening participants with HPV (not 16/18) detected on a self-collected sample who do not return until 9 months or more after the HPV test can be offered a follow-up self-collected HPV test, rather than LBC.

POST-TREATMENT MANAGEMENT ("TEST OF CURE"):

People treated for HSIL are recommended to have annual HPV tests (rather than co-tests) until tests are negative on two consecutive occasions, at which point they can return to routine screening.

People with HPV not 16/18 detected on three consecutive annual post-treatment tests, should be referred for colposcopy.

Key Changes to Program Guidelines:

AFTER TOTAL HYSTERECTOMY:

This has been simplified to annual testing (co-testing or HPV testing, depending on cervical pathology and history) until oncogenic HPV is not detected on two consecutive occasions

Key Changes to Program Guidelines:

SURVEILLANCE AFTER AIS:

Follow-up testing after completely excised AIS (annual co-tests) can be extended to 3-yearly testing if all tests have been negative for 5 years, and can cease 25 years after completely excised AIS if all tests have been negative, the recommendation depends on the screening participant's age:

- Those aged less than 70 years can return to routine screening.
- Those aged 70 years or older can exit screening if they have had at least one co-test when aged 70 years or older, with no oncogenic HPV detected and LBC report of negative.

Key Changes to Program Guidelines:

COLPOSCOPY-RELEVANT CHANGES:

- To assist colposcopists in the situation where screening participants have HPV (16/18) detected but no LBC results are available prior to colposcopy or there is no visible lesion on colposcopy, information has been provided about the likely underlying disease risk for different combinations of test results, screening history and age, based on data from the NCSR.
- In some circumstances, recommendations now state that endocervical curettage could be considered by those who are confident and trained in the technique and have appropriate equipment.
- There is now an option to defer re-referral for those with HPV (16/18) detected, LBC report of negative, and normal colposcopy, if 12-month follow-up results are again HPV (16/18) detected and negative LBC: the HPV test could be repeated in another 12 months, rather than immediate referral to colposcopy.
- The recommendation against diagnostic excision of the transformation zone (TZ) in the absence of high-grade cytology or histology has been clarified.
- Loop electrosurgical excision procedure (LEEP) is now recommended in preference to cone biopsy in some circumstances, due to the evidence of reduced post-surgical complications. Compared with cone biopsy, LEEP is associated with a lower rate of post-surgery complications but has the same margin success rate. The evidence for effectiveness of cone biopsy or LEEP, however, has not changed.

Self-collect HVP Test Clinical Audits

