Cervical Cancer Screening Guidelines for South Africa

Background

Cervical cancer is largely preventable but remains a major public health problem in South Africa. The age-standardised incidence rate was three times the global average at 35.3/100 000 women in 2020, and it was the leading cause of female cancer deaths in 15 to 44-year-olds with a mortality rate of 19.6/100 000.

- Persistent viral infection with high-risk human papillomavirus (hrHPV) genotypes causes nearly all cervical cancers and in South Africa around 64.2% of invasive cervical cancers are attributed to HPV16 or HPV18.
- School-based HPV vaccination was introduced in 2014, but until herd protection is reached, screening remains essential.
- Women living with human immunodeficiency virus (HIV) (WLWH) have a six-fold increased risk of developing pre-cancerous cervical lesions, cervical cancer and early-age disease. Currently nearly 25% of South African women between 15 and 49 years are living with HIV.
- In May 2018 the World Health Organization (WHO) announced a global strategy to eliminate cervical cancer and published an updated WHO Guideline, recommending HPV DNA detection as preferred screening test.
- Among general populations, screen-and-treat approaches are strongly recommended, but a screen-triage-and-treat approach is recommended for WLWH.

Guidelines for screening

Age at initiation of screening is *generally age 25 years* for all sub-populations due to our country's disease profiles.

- First screening at age of 30 for women at lower risk will reduce false positive screen results and overtreatment.
- Screening of women younger than 25 years is not recommended but can also be individualized if a particular risk exist, in which case cervical cytology is the preferred test.

Age at exit of screening is *generally age 60 years* after a normal test, but depends on previous screening history.

- Any woman over 25 years who had never been screened should be offered screening.
- If an individual had three negative screening tests, screening can be stopped at 50 years of age.
- In individuals with any previous abnormal results, screening can be stopped at 60 years of age after a normal test.

The primary test of choice is *high risk HPV testing* (hrHPV) for all women, including high (WLWH) and lower risk.

- Cervical specimen collected with a cytology brush from the transformation zone by a health care worker is preferred.
- This specimen is placed and transported in liquid medium which enables both HPV testing and reflex cytology.

The recommended screening interval is between *five and ten years* when using HPV testing, because of the superior sensitivity of molecular screening.

- The interval can be varied depending on risk profile, previous test results and resources.
- HIV-positivity and previous HPV-positivity are the most important risk factors requiring a shorter screening interval.

Risk-based interpretation according to the risk for current or future pre-cancer or cancer lesions is supported.

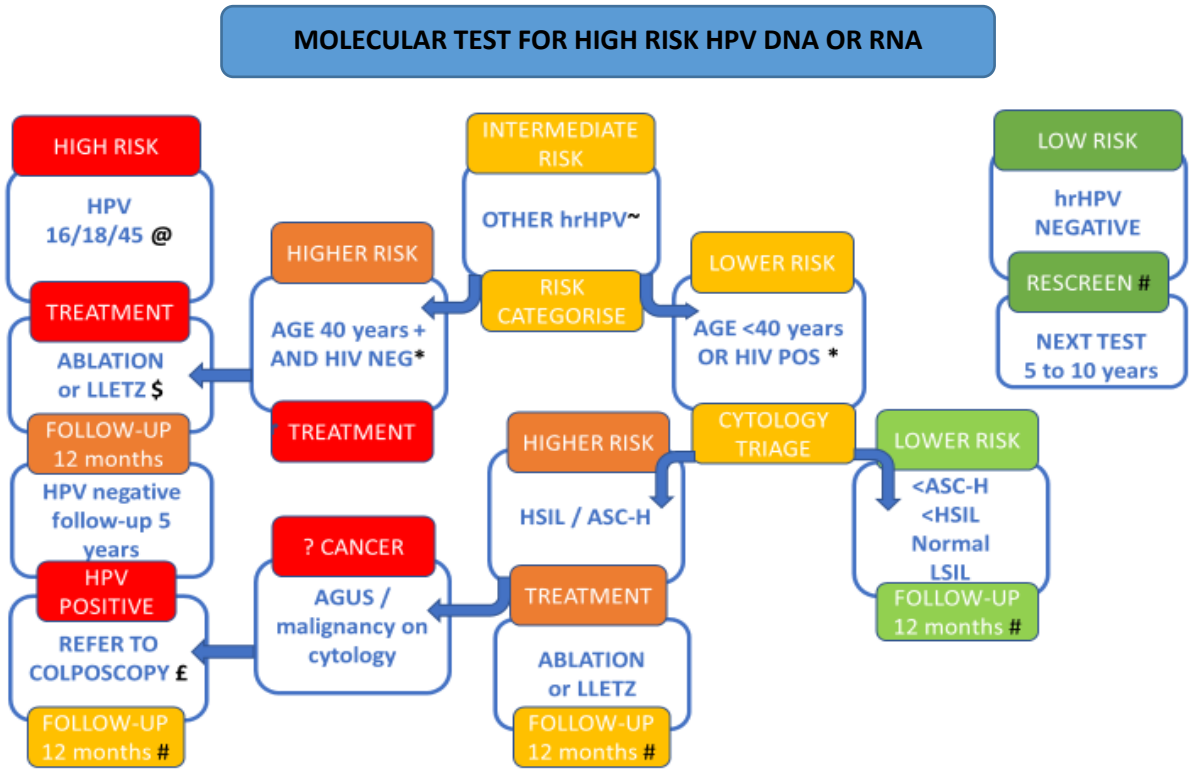
- **Low risk** women [high risk HPV (hrHPV) negative] should return for the next screening round
- **Intermediate risk** women [hrHPV non-16/18/45 positive, intermediate risk HPV-types positive] can have triage test, earlier follow up, or treatment. Risk categorizing these women using HIV-status and age can save resources.
- **High risk** women [HPV 16, 18 or 45 OR triage test positive] should receive treatment, then followed until HPV negative.

Clinical Guideline

This document is intended to guide clinical care without changing the responsibility of the health care team or the patient.
It never replaces clinical judgement and individualised care.

Developed and endorsed by SASOG as part of the BetterGyn® programme

Screening and treatment algorithm:



EXPLANATORY NOTES:

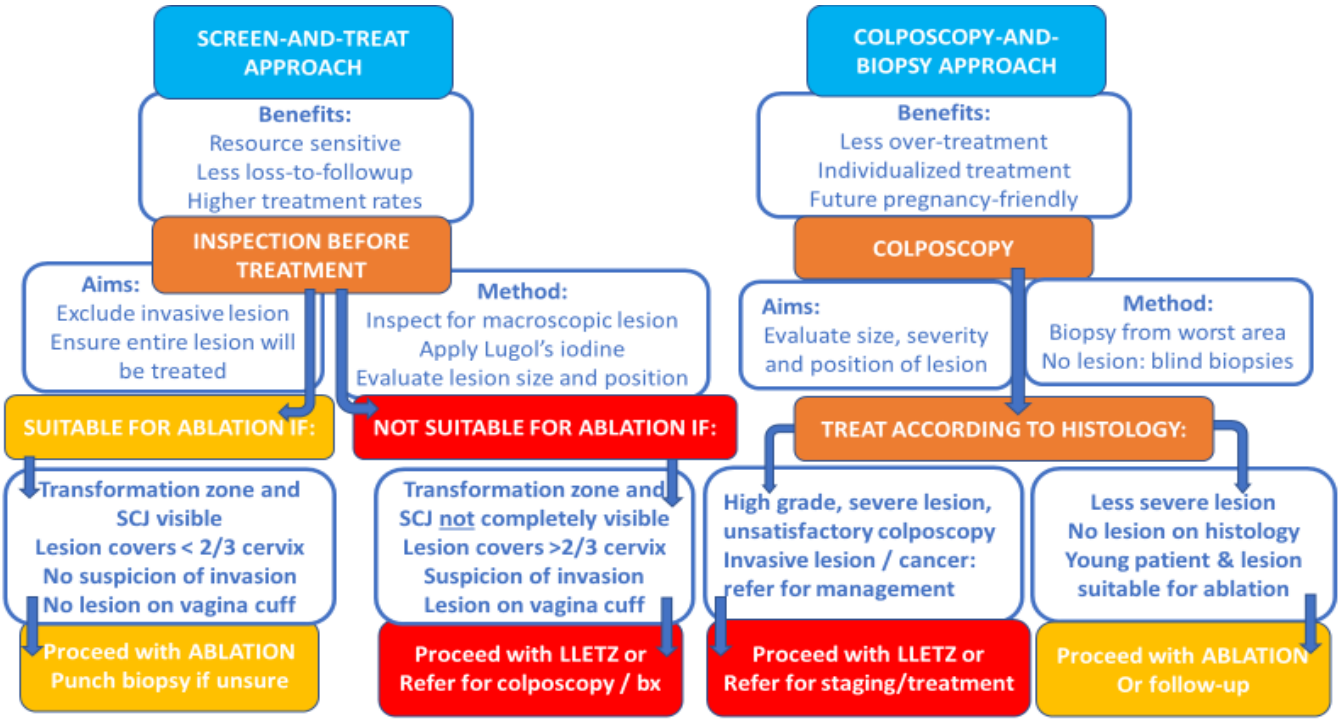
@	Although HPV45 is not included in all tests, it should be consider as high risk result if reported.
~	All high risk HPV types other than HPV16/18/45, or all intermediate risk HPV types (some tests).
$	Colposcopy and biopsy before treatment is allowed in young women with reliable follow-up.
*	Among older women who are HIV negative, high risk HPV is more predictive of a pre-cancer lesion.
	Among HIV-positive women, intermediate risk HPV-types are less predictive of pre-cancer or cancer.
	Women younger than 40 years has a lower risk for a lesion, and the treatment threshold should be higher.
£	Colposcopy referral is referral for specialist diagnosis and possible retreatment
#	The low risk population should be rescreened after 10 years
	Higher risk population should be rescreened after 5 years
	After treatment yearly follow-up continues until HPV-negative results, then 5 yearly

Guidelines for treatment

Indications for treatment

- Immediately refer for treatment
- all women who test positive for **HPV types 16, 18, and 45**. Immediate treatment using thermal ablation is preferred for all who qualify. At the treatment visit, colposcopy and biopsy-based management is allowed provided follow-up is guaranteed.
- Immediately refer for treatment those women who test positive for "**other high risk HPV**" positive who are *HIV-negative and 40 years* and older.
- Offer cytology triage to women who test positive for "**other high risk HPV"** who are *HIV-positive OR HIV negative and younger than 40* years.
  - Triage cytology should be done as a reflex test in the laboratory, treat only those with **ASC-H or HSIL**.
  - Triage negative women return for a follow-up HPV test in one year and are referred for colposcopy or treatment if a second test is still positive. High risk cytology (AGUS, etc.) requires further diagnostic work-up.

Treatment Algorithm:



*SCJ = Squamo-columnar junction of cervix

Choice of treatment method

- At the treatment visit, the recommended option is to offer immediate treatment, called "screen-and-treat", because it enhances program effectiveness and risk reduction.
- For higher resource environments where colposcopy is readily available and clinically indicated, it will reduce the number of women treated, but must be used in conjunction with biopsy to confirm the screening results and to guide treatment and follow-up must be guaranteed.
- Both types of treatment methods available to treat cervical cancer risk and pre-cursor lesions can be used for patients with positive screening tests.
    - Excisional methods provide a histology sample and is suited for lesions suspicious of cancer or extending into the endocervical canal. Large loop excision of the transformation zone (LLETZ or LEEP) is widely offered and effective; cold knife cone should not be used routinely as it causes significant shortening of the cervix and reproductive failure.
    - Ablative methods include cryotherapy and, more widely available, thermo-ablation which cause limited loss of cervical stroma but does not provide tissue for histology. These methods are not suited to treat lesions that are suspicious for invasion, very large (>2/3 or > three quadrants) or stretching into the canal and there may be higher recurrence rates.

Follow-up after treatment

Follow up after excisional or ablative treatment for precancer is essential due to the risk of treatment failure and subsequent development of pre-cancer and cancer. Women who have a negative HPV-test during follow-up can return

to the low-risk group with a longer interval. The management of individuals with repeated abnormalities after previous treatment should be individualized and falls outside the scope of these guidelines.

Conclusion

- We recommend a universal screening strategy for South Africa based on primary HPV-screening, with partial genotyping, starting from 25 years, varying screening interval between five and 10 years based on risk and exiting at the age of 50 years only after three negative tests.
- There is now sufficient evidence to recommend treatment for everyone with the highest risk HPV-types, and for intermediate types, or "other HPV-positive" women who are above the age of 40 years and HIV-negative.
- Reflex cytology should be offered to increase the specificity of screening for women with non-16/18/45 HPV types who are HIV-positive or younger than 40 years.
- We recommend nationwide development of screening and treatment facilities and wide implementation of thermo-ablation and LLETZ treatment on indication. After treatment, women need yearly follow-up until HPV-negative.
- The validity and feasibility of HPV testing on cervico-vaginal specimens collected by the patient has been accepted world-wide and may increase uptake of screening significantly. Self-screening cannot be used for cytology
- Treatment options for pre-cancer must be scalable in a country with huge health care disparities between urban and rural environments and include ablative options like thermal ablation or cryotherapy. Strengthening of policy, programs, treatment capacity and adequately training of healthcare workers are all integral to the success of secondary prevention of cervical cancer.

References:

This is a summary of the published guidelines:

Botha MH, Mabenge M, Makua M, Mbodi ML, Rogers LJ, Sebitloane M, Smith TH, van der Merwe FH, Williamson AL, Whittaker J, Dreyer G. *Cervical cancer screening guidelines for South Africa*. Afr J Obstet Gynaecol. 2023; 1(1): Published online.

Writing team: Botha MH, Dreyer G.

Contributions & review: Mabenge M, Makua M, Mbatani N, Mbodi L, Rogers L, Sebitloane T, Smith T, Van der Merwe FH, Williamson AL, Whittaker J.

The guidelines were developed and workshopped during an in-person meeting of the South African HPV Board working group on screening, where there was representation from the national Department of Health, SASOG and SASGO. The Board is independent from industry sponsors and guidelines are based on the opinions of Board members only, without influence from pharmaceutical and diagnostic industry sponsors. The Board and its working groups are multidisciplinary in nature, and works in collaboration with and supported by the South African Society of Obstetricians and Gynaecologists (SASOG) and the South African Society of Gynaecologic Oncology (SASGO). All members gave input into the final document, which is the fourth updated guideline from the group.

All previous members of the HPV Advisory Board are acknowledged for their vision, support and input into previous guidelines forming the basis of the current work:

- South African HPV Advisory Board. *Cervical cancer and human papillomaviru: South African guidelines for screening and testing.* South Afr J Gynaecol Oncol 2010;2(1):23-26.
- South African HPV Advisory Board. *Guideline document. Cervical canecr screening in South Africa 2015.* https://www.sasog.co.za/images/SASOG_screening_for_cervical_cancer_November-final.pdf
- Botha MH, Dreyer G. *Guidelines for cervical cancer screening in South Africa. S*outh Afr J Gynaecol Oncol 2017; 9(1):28-32.

Clinical Guideline

This document is intended to guide clinical care without changing the responsibility of the health care team or the patient.
It never replaces clinical judgement and individualised care.

Developed and endorsed by SASOG as part of the BetterGyn® programme

These guidelines should be considered as a simplified practice guide for clinicians in public and private sector healthcare environments, working in a middle-income country with high rates of HPV and HIV.

Guidelines are works in progress. The authors welcome any contributions which should be sent to the SASOG secretariat.