GUIDELINE DOCUMENT CERVICAL CANCER SCREENING IN SOUTH AFRICA 2015

Cervical cancer remains an important cause of morbidity and mortality in South Africa. At present the national cervical cancer prevention programme offers three cervical cytology smears per lifetime, starting after the age of 30 at 10-year intervals. In the private sector, cytology based opportunistic screening is well accepted but not uniformly implemented. However, the incidence of invasive cervical cancer remains unacceptably high, cases are often diagnosed late, and many patients have poor response to treatment. [1]

A uniform screening program in all health cate settings may not be the best way forward and individual districts may need differing screening solutions.

Screening with HPV testing will replace traditional cervical cytology in the next few years. The possibility of patient-collected (self-sampling) specimens will cater for a large number of women who may not have access to healthcare facilities.

INTERNATIONAL SUPPORT FOR HPV BASED PRIMARY SCREENING

World Health Organisation (WHO)

A Guideline Development Group (GDG) was established by the WHO to consider screening and treatment for cervical pre-cancer that included experts, clinicians, researchers in cervical cancer prevention and treatment, health programme directors and methodologists. This 2013 guideline provides recommendations for strategies for a screen-and-treat programme. [2] Among other findings, the following recommendations were made.

- Use a strategy of screen with an HPV test and treat, over a strategy of screen with VIA and treat.
- Use a strategy of screen with an HPV test and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat.
- Use either a strategy of screen with an HPV test followed by VIA and treat, or a strategy of screen with an HPV test and treat.

United States of America

Primary screening for human papilloma virus (HPV) using a DNA test can be considered as an alternative to current US cytology-based cervical cancer screening strategies, according to new interim guidance from multiple USA societies.[3]

In 2011, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology updated their screening guidelines. At that time, these groups recommended cytology alone and in combination with high-risk

HPV testing (co-testing) as primary screening strategies, but not the use of high-risk HPV testing alone.

However, more recently, representatives from the Society of Gynecologic Oncology, American Society for Colposcopy and Cervical Pathology, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology, convened to provide guidance for primary hrHPV screening. [3] Guidance was based on literature review and review of data from an FDA registration study, supplemented by expert opinion. They concluded *Primary hrHPV screening is an important scientific and clinical advance in cervical cancer screening since it offers better reassurance of low cancer risk compared to cytology-only screening* conducted at the same interval. Primary hrHPV screening can be considered as an alternative to current US cytology-based cervical cancer screening approaches including cytology alone and co-testing.

United Kingdom

In a large study, HPV testing as an initial screen was *significantly more protective* over three screening rounds (6 years) than the current practice of cytology. The use of primary HPV screening could *allow a safe lengthening of the screening interval*. Modelled analysis predicts that primary HPV screening would be both *more effective and cost saving* compared with current practice with cervical cytology. This study and the economic evaluation lend support to convert from cytology to HPV-based screening. [4]

Australia

In April 2014, the Medical Services Advisory Committee recommended that Australia move to a five yearly screening program using an HPV test with partial genotyping for HPV16/18 as the primary screening test, commencing at age 25 and with an exit test between the age of 70 and 74. [5] Following a comprehensive review of the current evidence for cervical screening, MSAC has recommended for both HPV vaccinated and unvaccinated women that:

- an HPV test should be undertaken every five years
- cervical screening should commence at 25 years of age
- women should have an exit test between 70 and 74 years of age
- women with symptoms (including pain or bleeding) can have a cervical test at any age.

- An HPV test every five years is *more effective at protecting against cervical cancer and is just as safe as, screening with a Pap test every two years*.
- *An HPV test every five years can save more lives* and women would need fewer tests than in the current two-yearly Pap test program.
- HPV vaccinated women will still require cervical screening as the HPV vaccine does not protect against all the types of HPV that cause cervical cancer.
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Acceptable technology

Arbyn et al published a review on the HPV assays that fulfil the criteria for use in primary screening. [6] More than 125 HPV assays (and over 80 variants of the original assays) have been developed, but evidence of their clinical utility has been demonstrated for relatively few. A group of experts suggested criteria for test requirements in 2009. [7] At present only seven HPV DNA tests fully meet the requirements. [6] One mRNA test may also meet the criteria but longer term follow-up data is needed.

Due to the particular oncogenic importance of type 16 as well as other types like 18, 31, 45 and 52 (sometimes referred to "highest risk HPV"), there is interest in (partial) HPV genotyping which may add specificity to the result. An HPV-16 positive result has a higher likelihood of being associated with a high risk lesion than other types. Individuals test positive for these highest risk types are considered to be in the high risk category.

GENERAL CONSIDERATIONS FOR SOUTH AFRICA

- Cytology based screening services are well established in the private sector and certain provinces of the public sector. The change to HPV primary screening will take time and this document will consider ways to improve on cytology where it is still used. However, the HPV advisory Board is of the opinion that HPV based primary screening is more *sensitive* to detect pre-cancer and cancer and also has a *better negative predictive value (NPV)* than cytology and that funders and providers must migrate to HPV primary screening in the near future.
- The degree of sophistication of health systems in different geographical areas of South Africa are dissimilar and the same solutions will not be applicable in all settings. The HPV advisory Board supports health systems assessments to determine the best screening algorithm for each district.
- The HPV advisory Board supports the development of treatment facilities for cervical cancer and pre cancer at the same time as improved screening.
- Liquid based samples has the advantage that it can be used for primary HPV test and triage tests.
- Patient self-sampling may be an option

DEVELOPMENT OF THE GUIDANCE

- The HPV advisory Board is a multi-disciplinary group of experts including professionals from the disciplines of public health, virology, gynaecological oncology, anatomical pathology and cytology.
- The activities and opinions of the Board is independent of pharmaceutical and diagnostic industries.
- This guidance was drafted after careful literature review and discussion, and is the third guideline published by the group and will be reviewed from time to time.
- Guidelines for screening in low and high resource settings still needed to be different due to affordability but are more similar than before.
- Users and readers are encouraged to enter the debate on ideal screening strategies for South Africa.

PRIMARY SCREENING TESTS:

- Screening aims to detect women with unsuspected cancer risk by testing asymptomatic women
- Screening facilities must choose the most appropriate test
- Management of positive tests follows guidelines set in regions
- Screening interval can be longer in resource poor environments and where more sensitive tests are used

	LOW RESOURCE:	**HIGH RESOURCE:**
Initiate screen:	Age 25 At diagnosis of HIV positivity	Age 25 At diagnosis of HIV positivity
End screen:	Age 55 or hysterectomy Only after previous negative tests Never end if HIV positive	Age 65 or hysterectomy Only after previous negative tests Never end if HIV positive
Interval - HPV test	10 years if HIV neg or unknown 5 years if HIV pos	5 years if HIV neg or unknown 3 years if HIV pos
Interval - cytology	5 years if HIV neg or unknown 3 years if HIV pos	3 years if HIV neg or unknown Yearly if HIV pos
Timing:	Ten-yearly: At ages 25, 35, 45, 55 Five yearly: Also at ages 30, 40, 50. Three yearly: At ages 25, 28, 30, 33, 36, 40, 43, 46, etc.	Five yearly: Also at ages 30, 40, 50. Three yearly: At ages 25, 28, 30, 33, 36, 40, 43, 46, etc. Yearly: each year
Follow-up:	After single abnormal screening test or after treatment: • HIV negative and < 35 years: 5 yearly until normal. • HIV positive or > 35 years: yearly until normal. Back to SCREEN when normal Treat after second abnormal test	After single abnormal screening test or after treatment: • HIV negative and < 35 years: yearly until normal. • HIV positive or > 35 years: yearly until normal. Back to SCREEN when normal Treat after second abnormal test

SECONDARY / TRIAGE TESTS:

- Triage aims to avoid overtreatment of women with abnormal screening test which may not confer a high risk for severe dysplasia.
- Triage is therefore a way to manage “intermediate risk” results
- Treatment facilities should choose the most appropriate triage test.
- Triage must be done with a different test from the initial screening test.

Visual inspection with Lugol’s iodine or acetic acid (VILI or VIA)

When: Low resource settings
Medium risk result on cytology or HPV test

Results:	Possible invasive lesion:	Biopsy
	No lesion:	Do not treat
	Small lesion:	Cryo-treatment or LLETZ
	Large lesion:	LLETZ

Cytology using either conventional or liquid based cytology

When:	Low or high resource settings As alternative to treatment Medium risk result on HPV test	
Results:	Normal:	Do not treat
	ASCUS or worse:	Treat with cryo-treatment or LLETZ

Cytology stain or similar biomarker

When:	High resource settings Medium risk result on cytology or HPV test	
Results:	Normal:	Do not treat
	Positive:	Colposcopy and biopsy

HPV test triage with or without partial genotyping

When:	High resource settings Medium risk result on cytology	
Results:	Normal:	Do not treat
	Positive:	Colposcopy and biopsy

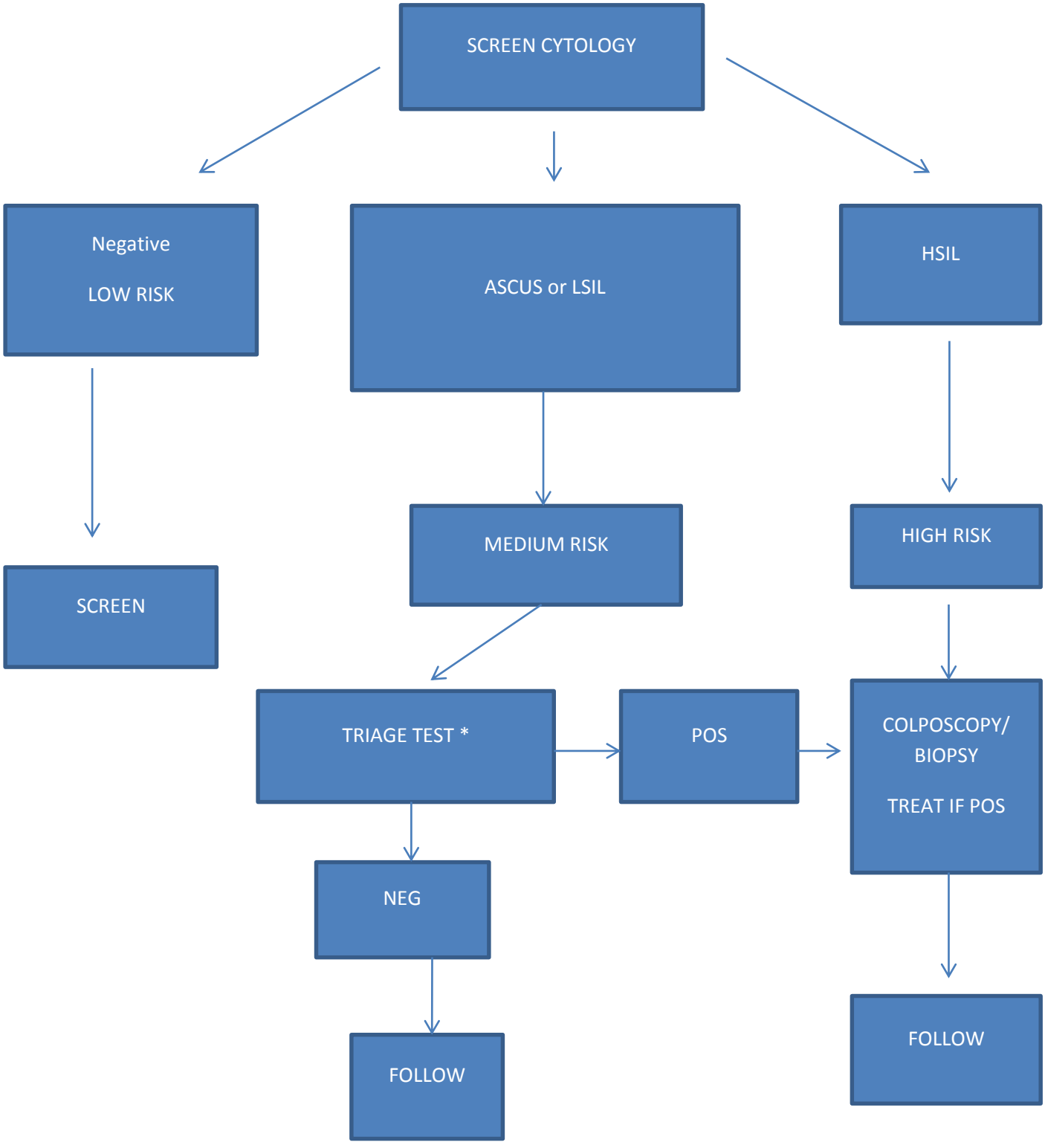
Management of non-squamous cytological abnormalities

Atypical glandular cells on cytology needs adequate investigation of the endocervical canal and endometrium. In young women (less than 30 years of age) a single AGC result may be treated with antibiotics and the cytology repeated. In all women with AGC over the age of 30 or where a repeat cytology again shows AGC result an endocervical and endometrial sample should be obtained for cytology and/or histology.

Treatment options

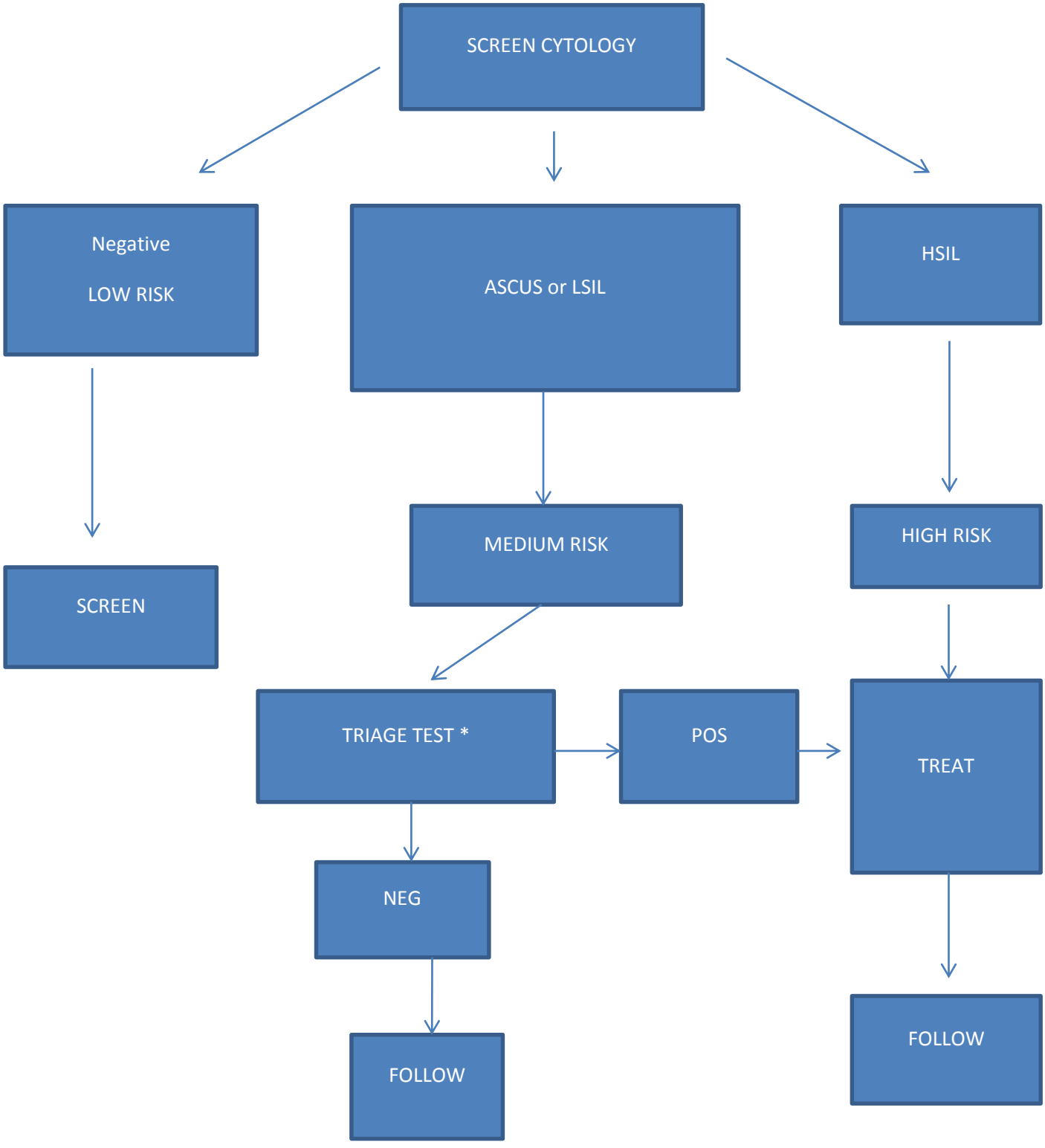
Excisional treatment with a loop procedure is the preferred treatment option for an abnormal screening test. The cervical surface must be stained with iodine before the procedure to identify all the abnormal epithelium. Histology of the excised specimen is preferred. In selected cases where an infiltrating cancer has been excluded, the transformation zone is visible and resources for histology is limited, ablative therapy with cryosurgery or cauterisation acceptable.

CYTOLOGY PRIMARY SCREENING – SA HIGH RESOURCE SETTINGS (TO BE PHASED OUT):



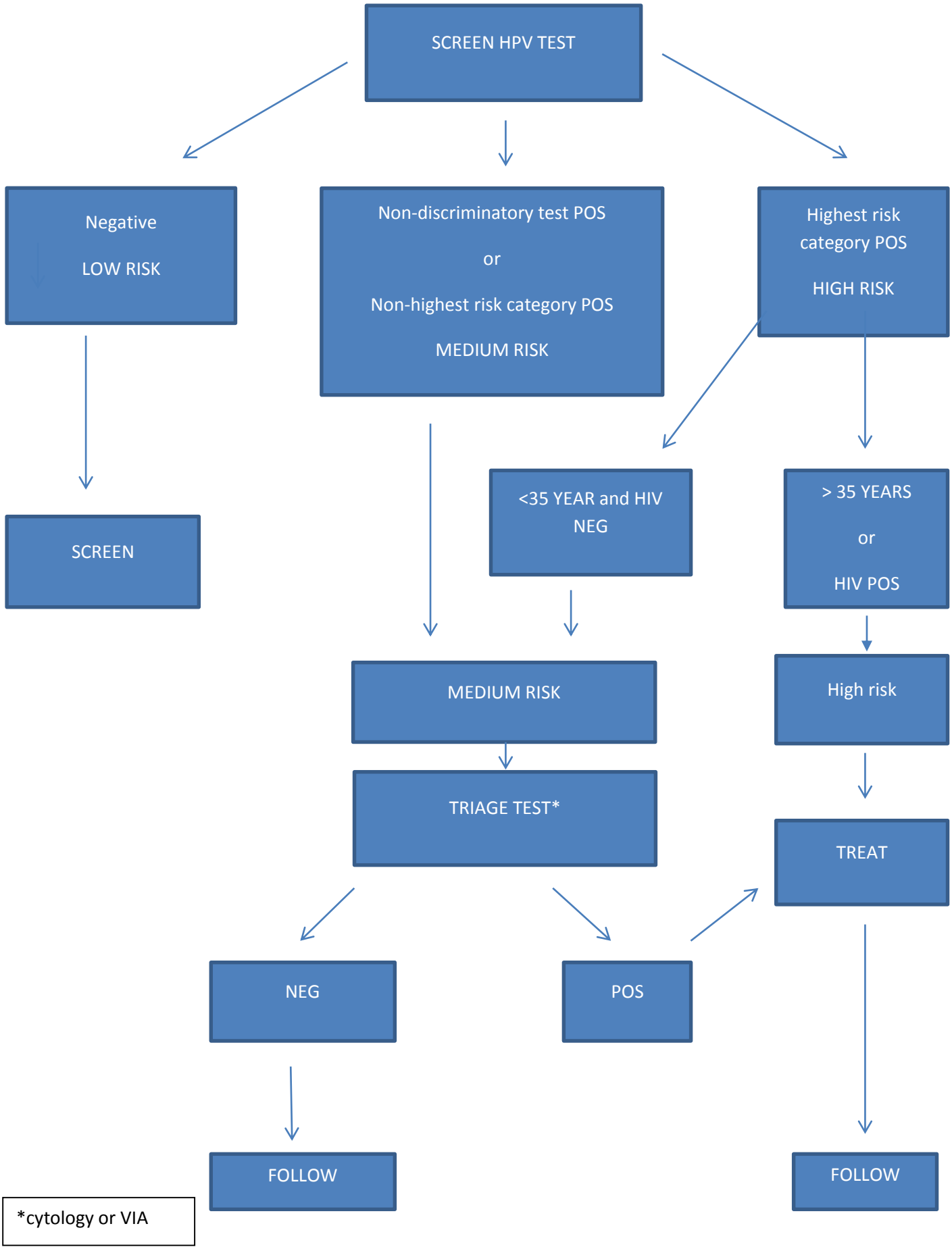
*HPV test or cytology stain

CYTOLOGY PRIMARY SCREENING – SA LOW RESOURCE SETTINGS (TO BE PHASED OUT):

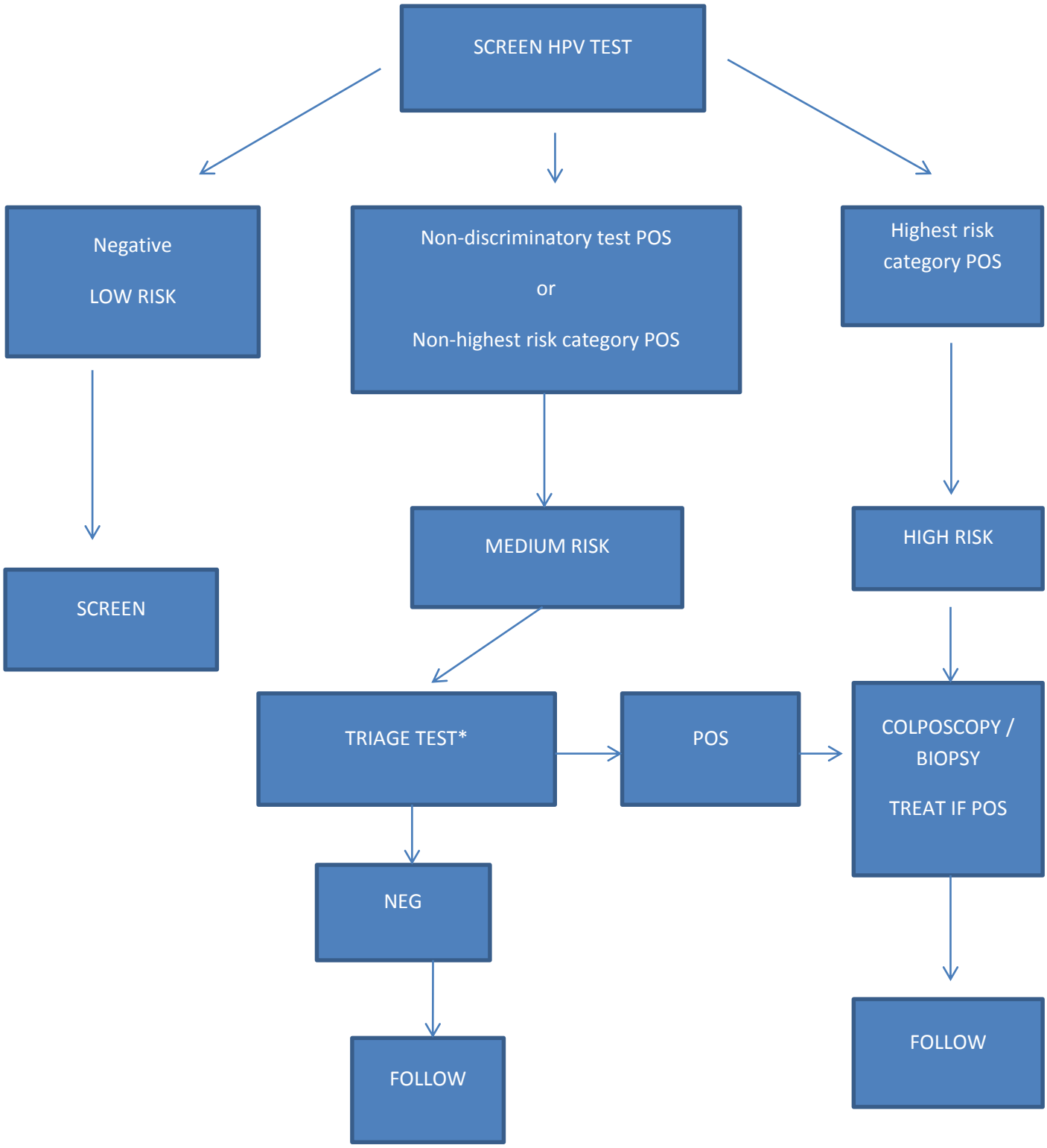


*HPV test

HPV PRIMARY SCREENING – SA LOW RESOURCE SETTINGS:



HPV PRIMARY SCREENING – SA HIGH RESOURCE SETTINGS:



* HPV partial genotyping or cytology

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2. WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. Geneva; 2013.
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4. H CK, Canfell K, Gilham C, Sargent A, Roberts C, Desai M, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess. 2014; **18**(23): 1-196.
5. Medical Services Advisory Committee. National Cervical Screening Program Renewal: Executive summary. 2013 [cited 205; Available from: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/MSAC-recommendations
6. Arbyn M, Snijders PJ, Meijer CJ, Berkhof J, Cuschieri K, Kocjan BJ, et al. Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening? Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2015; **21**(9): 817-26.
7. Meijer CJ, Berkhof J, Castle PE, Hesselink AT, Franco EL, Ronco G, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. International journal of cancer Journal international du cancer. 2009; **124**(3): 516-20.