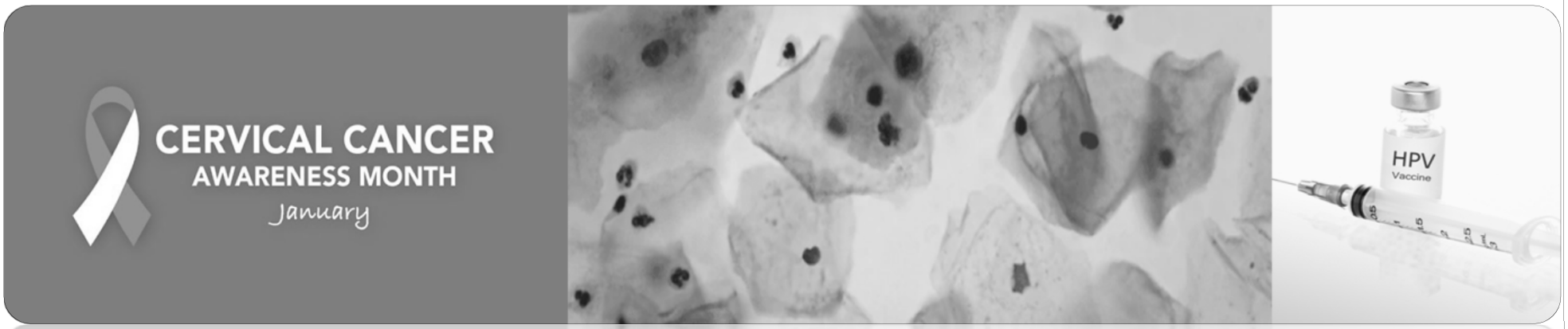

Screening of carcinoma cervix- an update

Dr. Debasis Gochhait
Associate professor, Dept. Of Pathology
Resident (PGIMER, Chandigarh)
PDCC (Cytopathology)(PGIMER)
PDCC (Renal and Transplant Pathology) (PGIMER)

JIPMER

DISCLAIMER

- CONFLICT OF INTEREST : NONE

DISCLAIMER

JIPMER

- DISCLOSURES : NONE

LEARNING OBJECTIVES

- CERVICAL CANCER STATISTICS
- ETIOPATHOGENESIS
- SCREENING MODALITIES AND MANAGEMENT
- UPDATE ON SCREENING RECOMMENDATIONS
- FUTURE DIRECTIONS

Cervical Cancer Statistics

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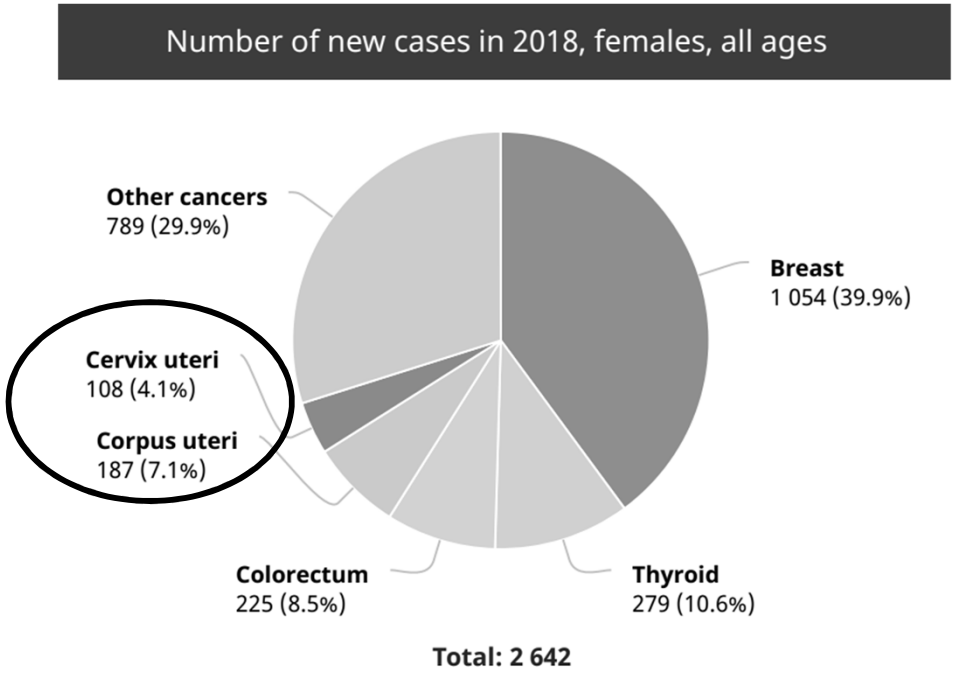
DISEASE FREQUENCY				
	Worldwide population	**India**	**United States of America**	**United Kingdom**
Incidence rate, age-standardized (per 1,00,000 women per year)	13.1	**14.7**	6.5	8.4
Cumulative risk (%) at 75 years	1.36	**1.59**	0.63	0.73
Mortality rate, age standardized (per 1,00,000 women per year)	6.9	**9.2**	1.9	1.7

ICO/IARC Information Centre on HPV and Cancer, 2020

UAE statistics:



- It is among the five cancers in females in the UAE .
- 74 new cases in 2015 (2.3% of all cancers) to 108 cases in 2018 (4.1%).
- 56 women died of cervical cancer in the UAE in 2018

- **GLOBOCAN- 2018**

Introduction

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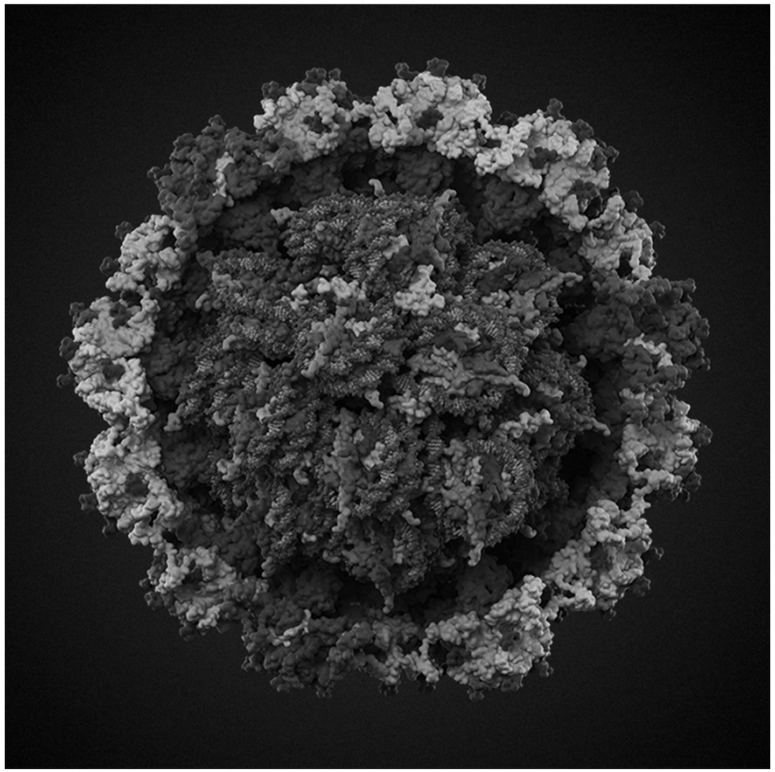
- Cervical cancer is the **fourth most common cancer** among women **worldwide**
- Almost all cases (99.7%) of cervical cancer are related to ***Human Papilloma Virus (HPV) infection***
- This association makes cervical cancer **preventable** and **treatable with early detection**

Etiopathogenesis



Etiology

- **Persistent infection** with **high risk oncogenic HPV virus (HR-HPV)**:

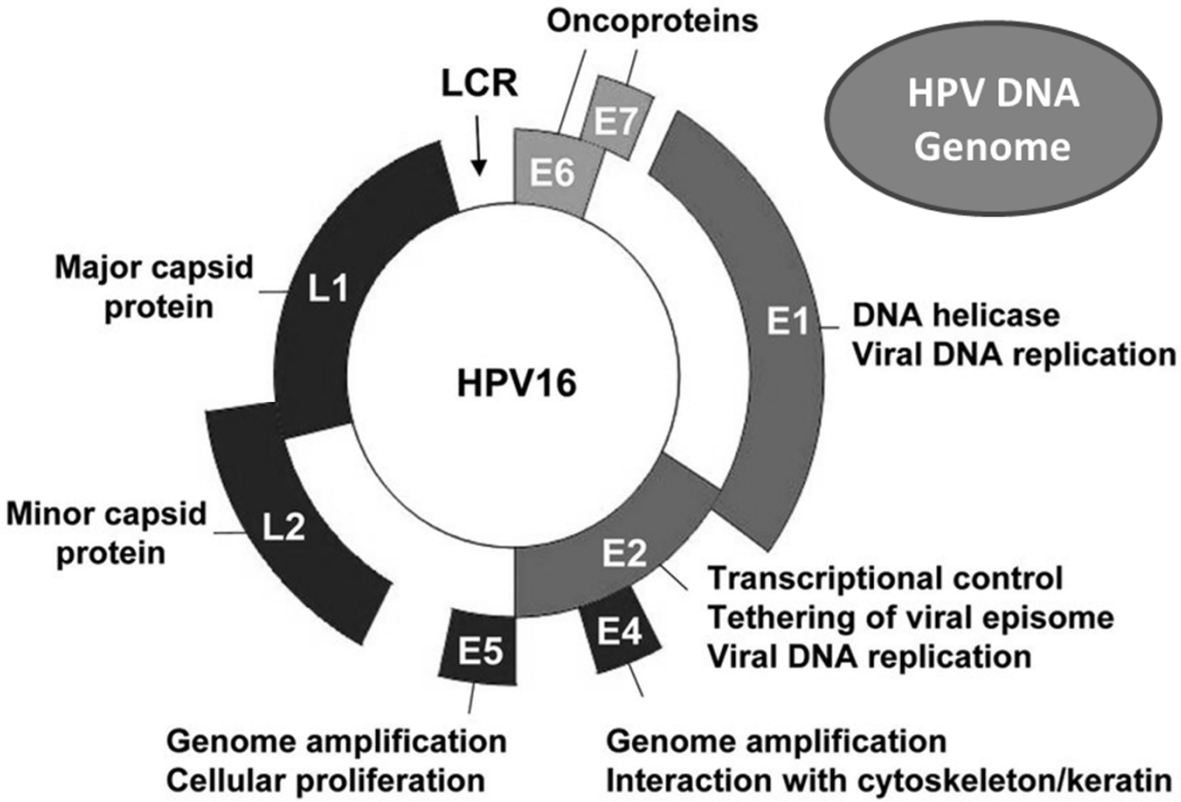
  ✓**Most common types (70%) - 16, 18**

  ✓Other types- 31, 45

- HR-HPV infection along with risk factors and co-factors result in **multistep oncogenesis**

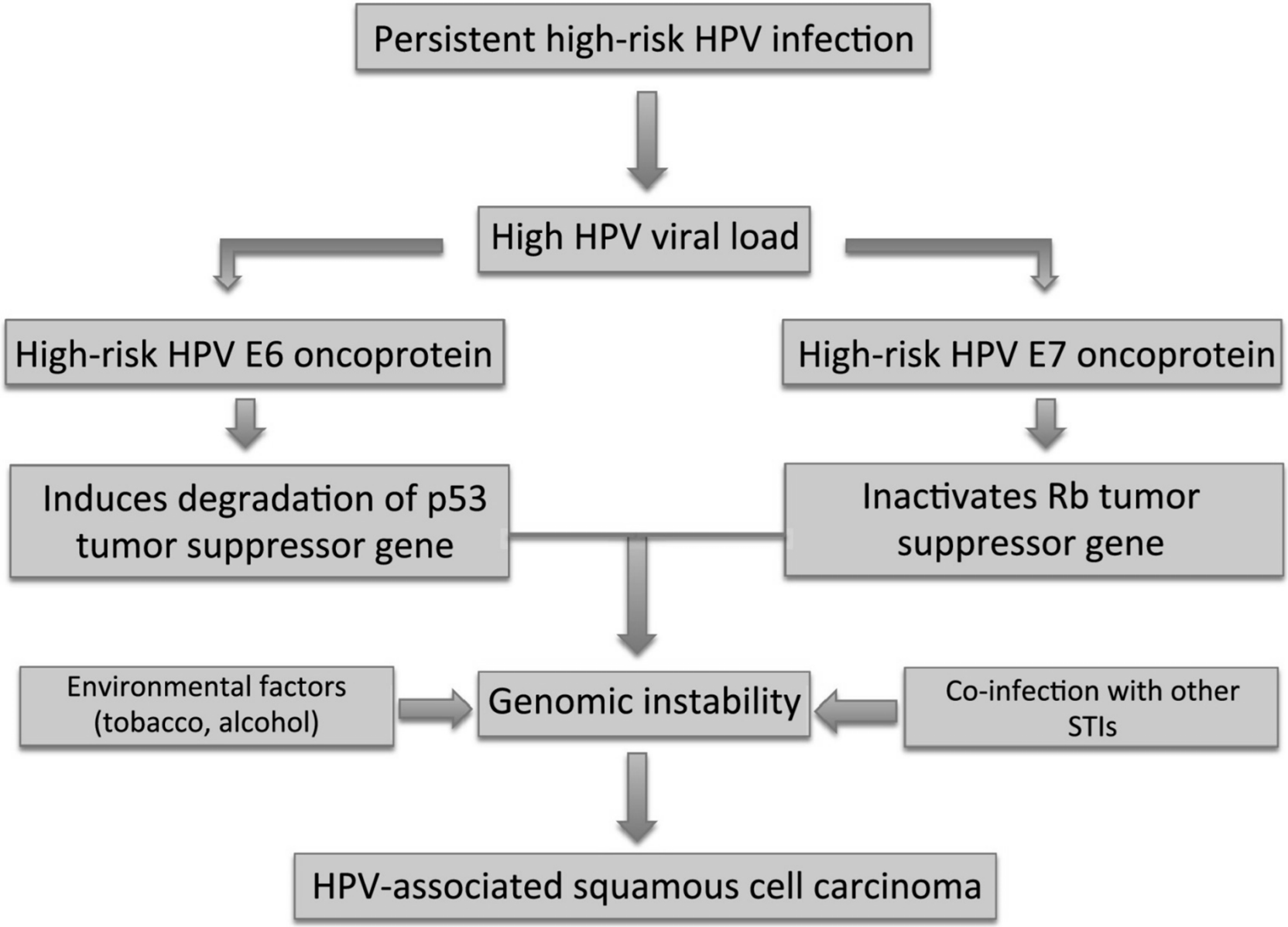
Human Papillomavirus (HPV)

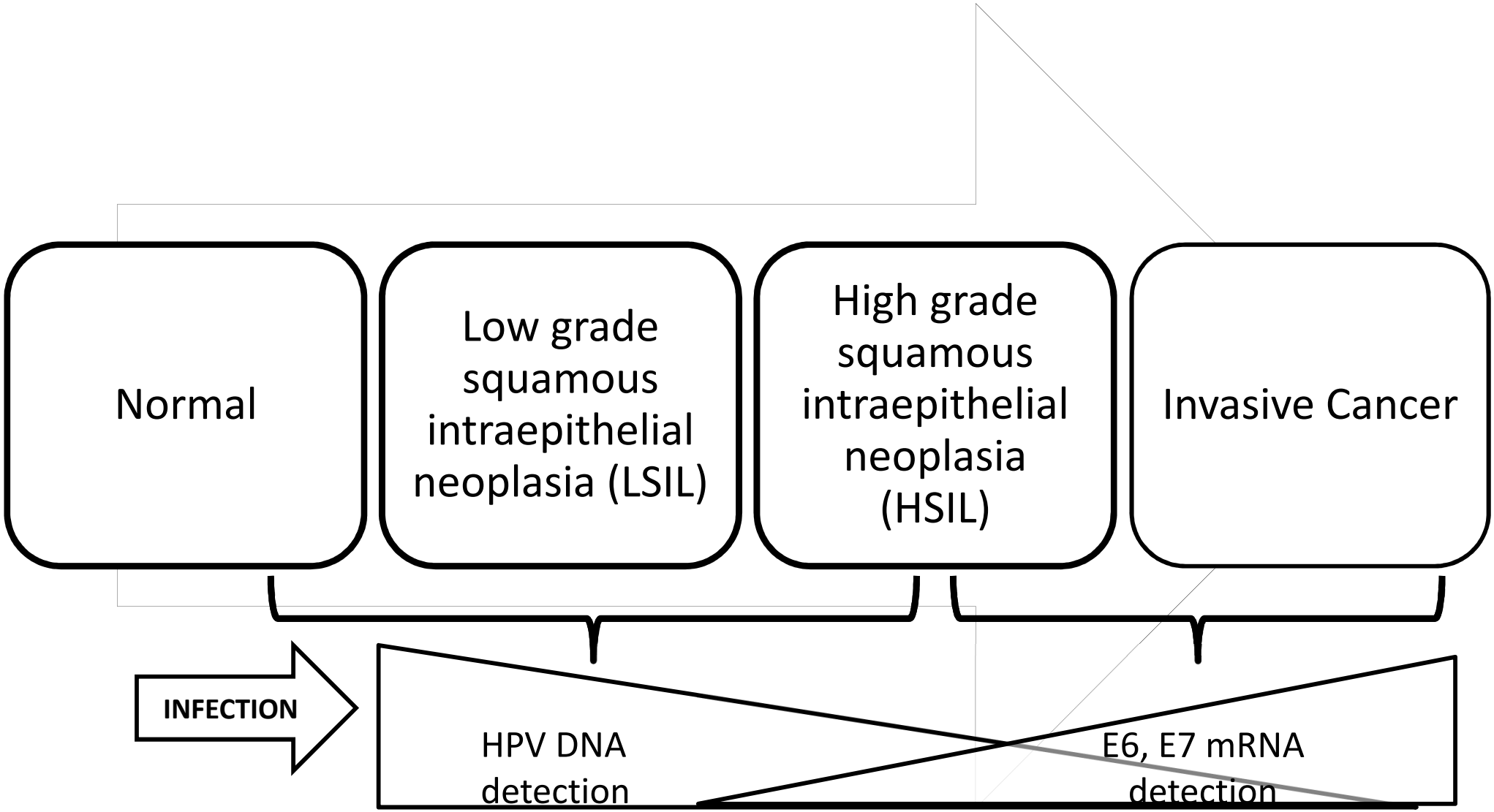
- **Human Papillomavirus (HPV)** belongs to the ***Papovaviridae*** family
- It is a **double stranded, circular DNA virus**
- HPV has a tropism for the **immature squamous cells** of the transformation zone
- Damage of surface epithelium facilitates viral access to the immature cells

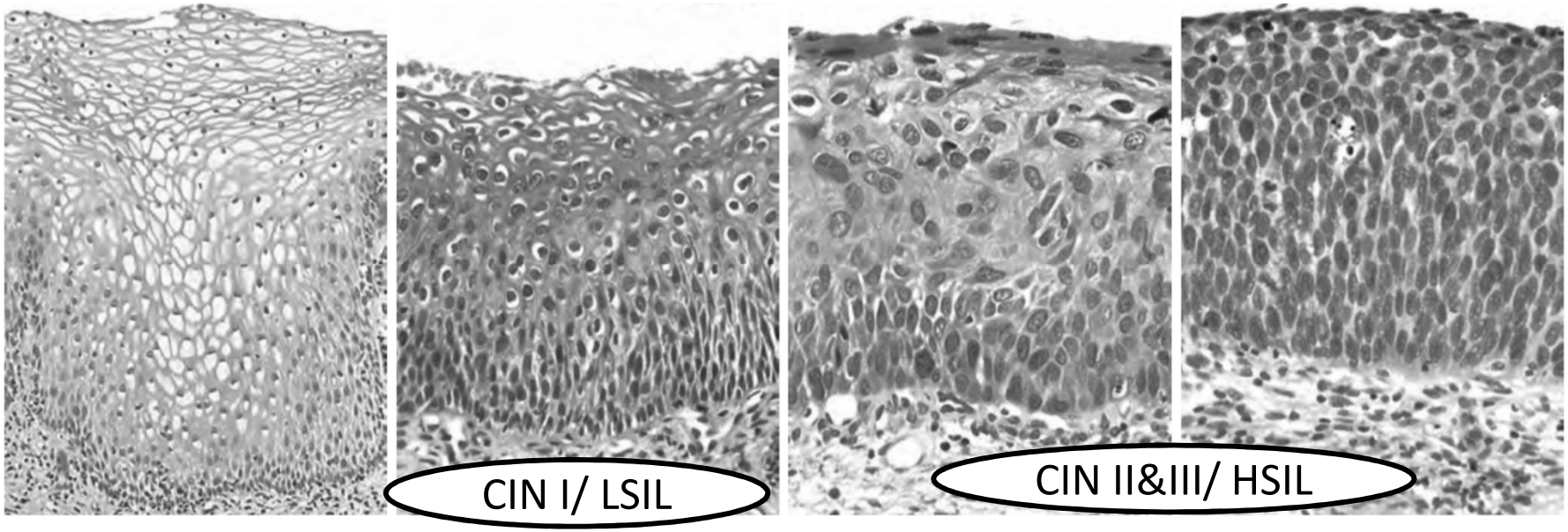


Pathogenesis of Cervical Carcinoma

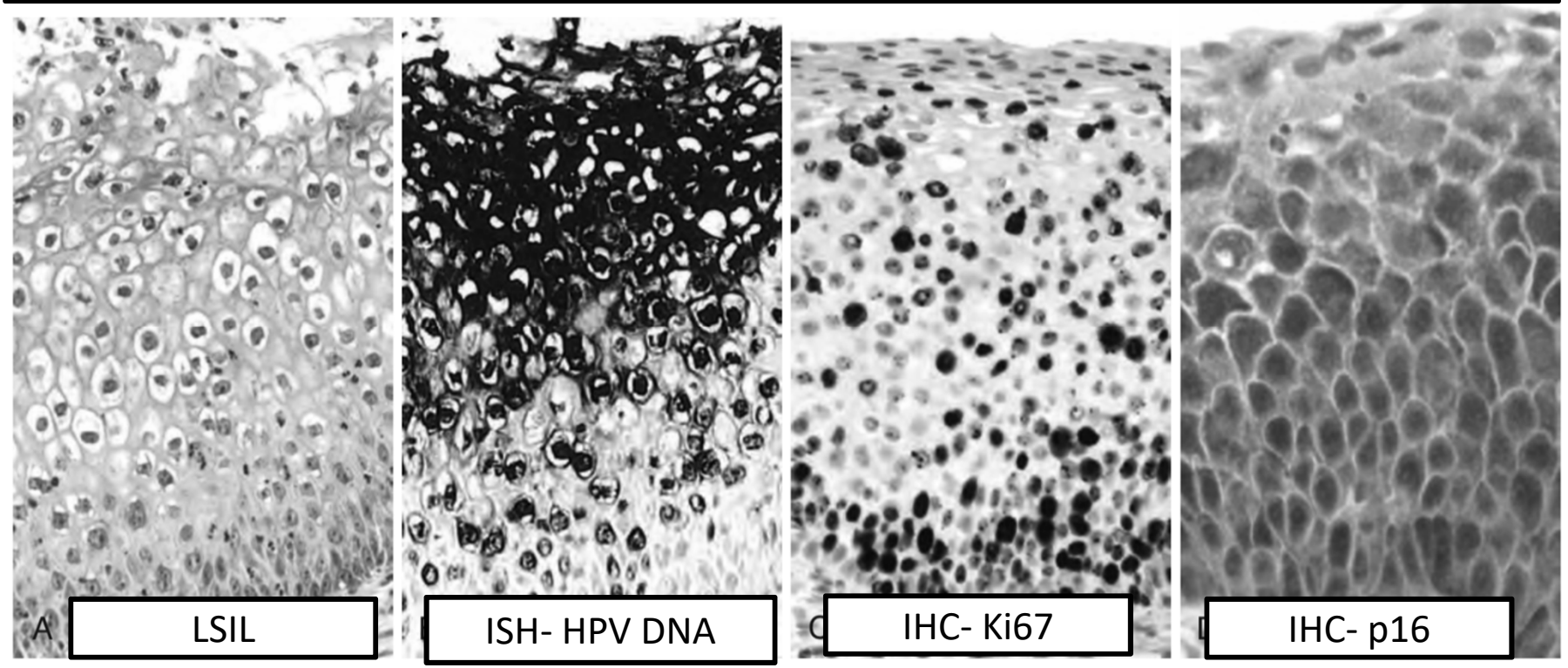
BIOLOGICAL PATHWAYS OF HPV INDUCED CARCINOGENESIS




Normal
Low grade squamous intraepithelial neoplasia (LSIL)
High grade squamous intraepithelial neoplasia (HSIL)
Invasive Cancer
INFECTION
HPV DNA detection
E6, E7 mRNA detection

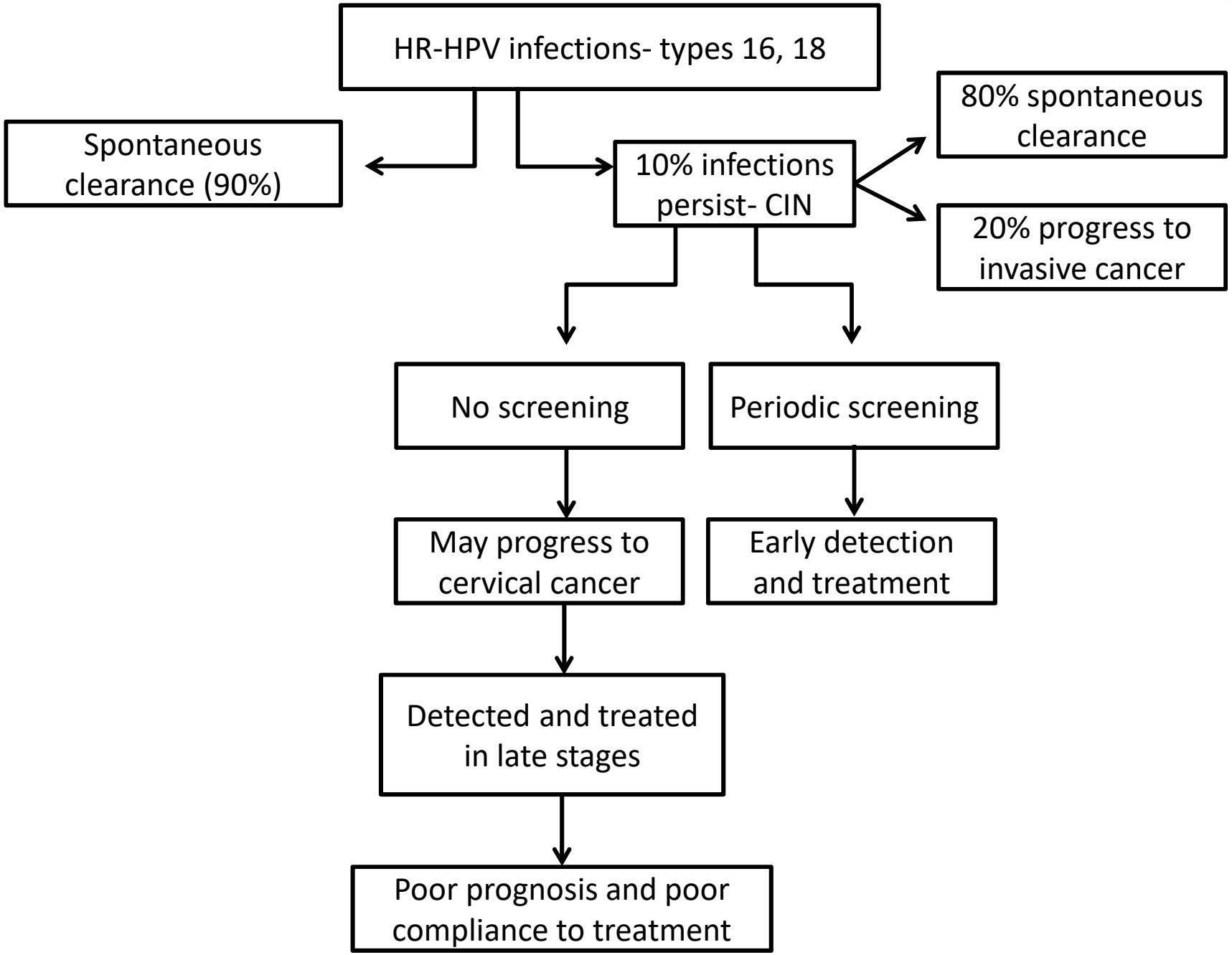


SPECTRUM OF CERVICAL INTRAEPITHELIAL NEOPLASIA

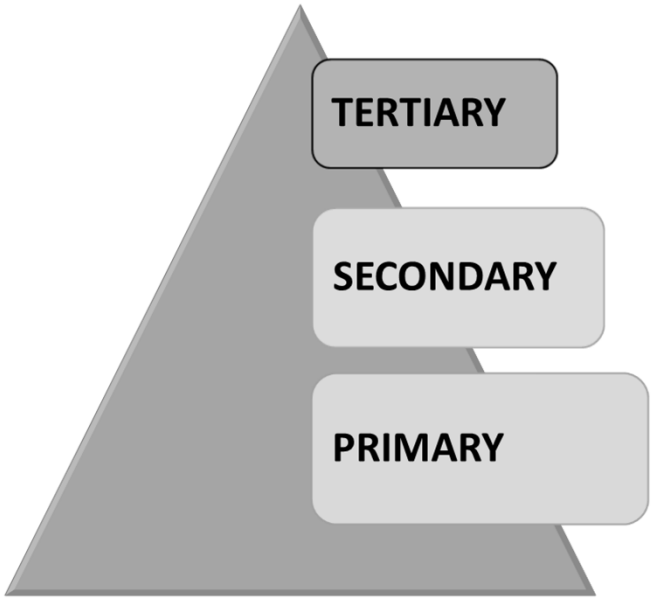


ISH- In situ Hybridisation, IHC- Immunohistochemistry

NATURAL HISTORY OF HPV INFECTION



Strategies in Cervical Cancer Prevention



SECONDARY PREVENTION

❖ ***To detect and treat the infection early***

Women aged >30 years

Screening and treating asymptomatic individuals

- ✓ Cervical cytology
- ✓ HPV testing
- ✓ Visual inspection of cervix with acetic acid (VIA)
- ✓ Colposcopy and biopsy

Rationale for screening

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- **Reduce the risk of disease** and associated **mortality** by detecting and treating precursor lesions – **primary goal.**
- Prolonged preinvasive stage of the disease permits **early detection** by proper screening.
- The **secondary goal** is the detection of ***invasive cervical cancer at an early stage.***
- Decline in incidence and mortality rates in **developed nations** is attributed to efficient screening programs.
- Implementation of effective screening programs in **developing nations** - availability of screening and treatment facilities

Screening modalities

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PRIMARY MODALITIES

- ✓ *Visual inspection of cervix with acetic acid (VIA)*
- ✓ *Cytology (Pap test)*
- ✓ *Primary HPV testing*
- ✓ *Co-testing (HPV testing + cytology)*

NEWER MODALITIES

- ✓ *DNA Methylation studies*
- ✓ *E6 and E7 mRNA testing*
- ✓ *p16 and ki67 as biomarkers*

RESOURCE BASED CERVICAL CANCER SCREENING RECOMMENDATIONS

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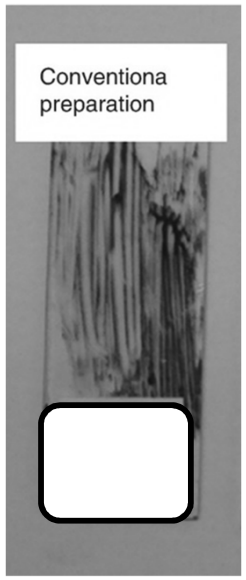
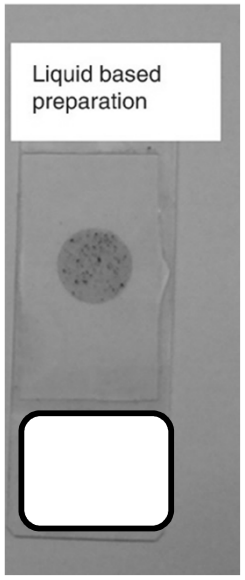
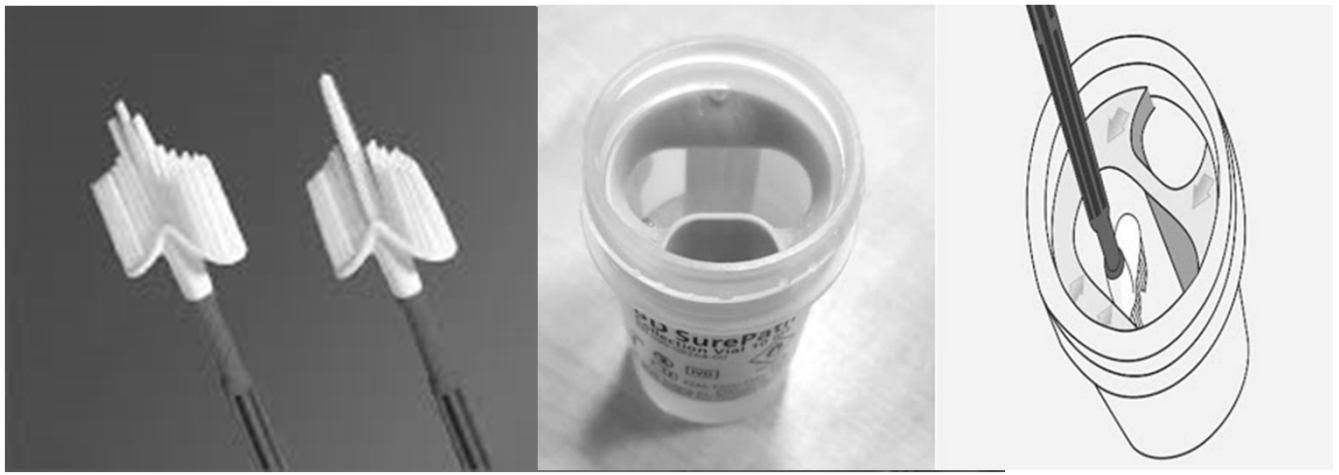
	GOOD RESOURCE SETTINGS	LIMITED RESOURCE SETTINGS
MODALITIES	✓ **HPV testing** (primary and co-testing) ✓ Cytology ✓ Colposcopy and biopsy ✓ VIA	✓ VIA ✓ Cytology ✓ Colposcopy ± biopsy

Federation of Obstetric and Gynaecological Society of India (FOGSI) - Good Clinical Practice Recommendation Screening and Treatment of Preinvasive Lesions of Cervix and HPV Vaccination, 2018

Cytological Sample collection & devices







Which method is better ?

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Conventional smear:

- Material may be lost and sample is haphazard.
- Obscuration by inflammation, necrosis.
- HPV testing cannot be done.
- Easy and Cheap….no spl training required

LBC method

- All material collected and homogenized during processing.
- Minimal obscuration of morphology.
- HPV testing can be done.
- Costly, cumbersome and training

Screening age and periodicity

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Recommended age to start screening:

- **At settings with good resources**- from 25 years
- **At settings with limited resource-** from 30 years

Periodicity:

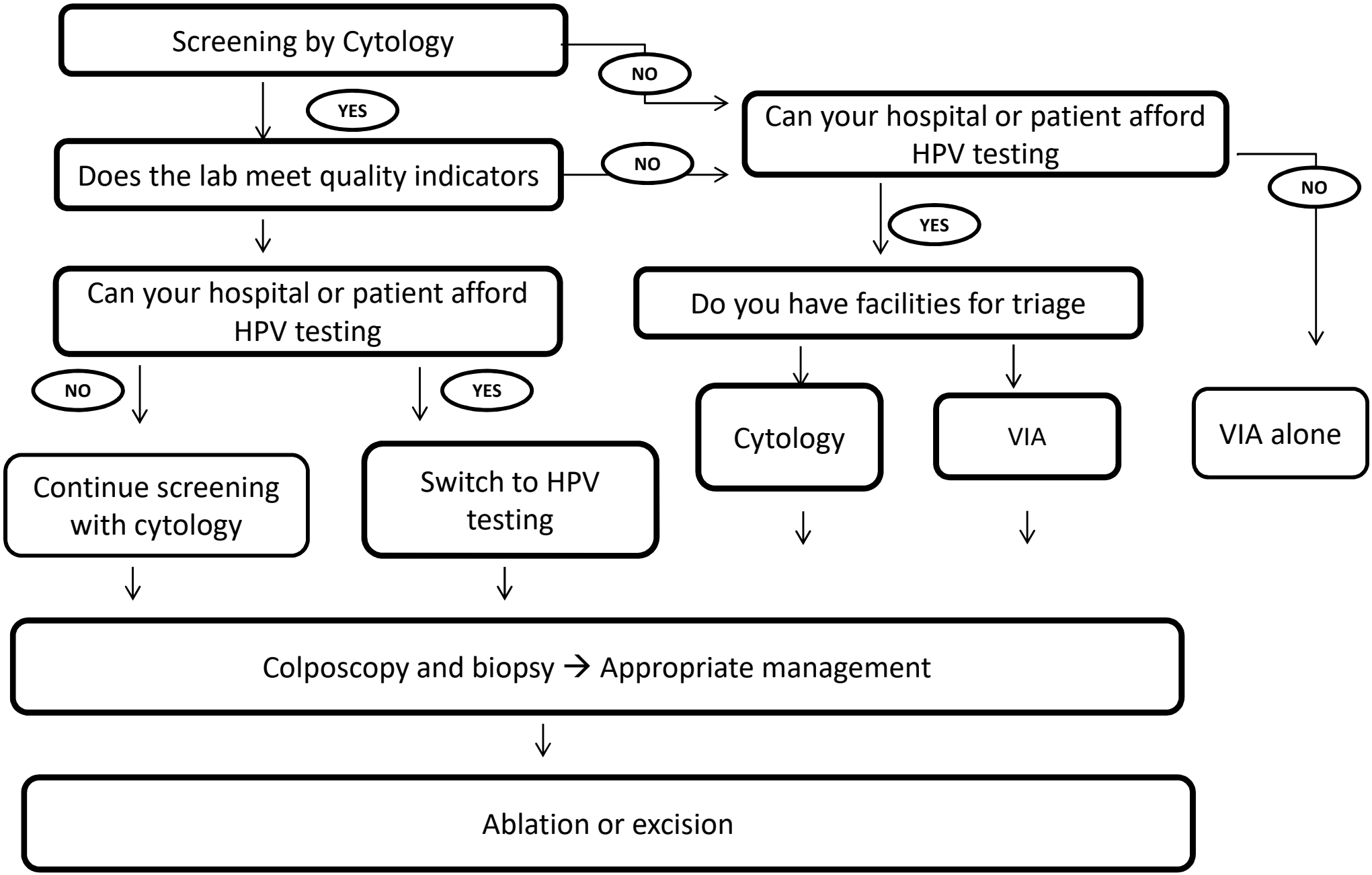
- **At settings with good resources- HPV testing or Co-testing every 5 years** or **Cytology every 3 years**
- **At settings with limited resource- VIA every 5 years**

Age to stop:

- ***At 65 years*** if there were consistent negative results in the last 15 years

2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2020;24: 102–131)

Algorithm to select the most appropriate screening modality based on resources

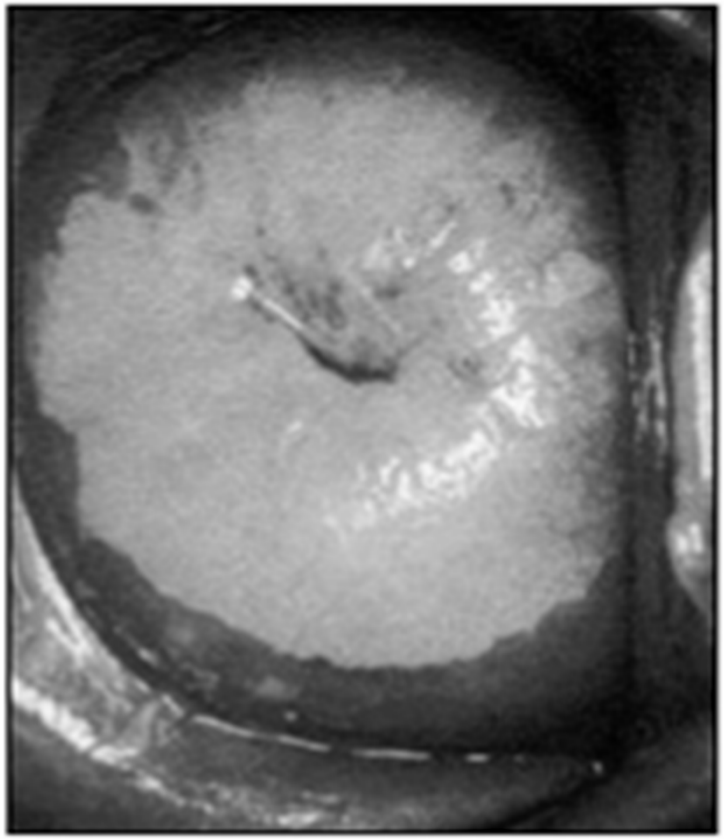


WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013

Visual inspection of cervix with acetic acid (VIA)

- It is a useful screening tool in ***resource poor settings*** which lack an organised screening program
- Indicated in the age group of ***30-65 years***
- It is ***economical*** and provides useful results
- Test results are available **immediately**
- Requires a ***single visit*** by the patient
- ***Mass screening*** in resource limited settings is feasible

- It involves application of **dilute acetic acid** (3-5%) to the cervix
- **Rapid uptake** of acetic acid by abnormal areas (<20 seconds) which appear glazed white
- The abnormal areas have **irregular surface** and **sharp raised edges**



VIA positive area

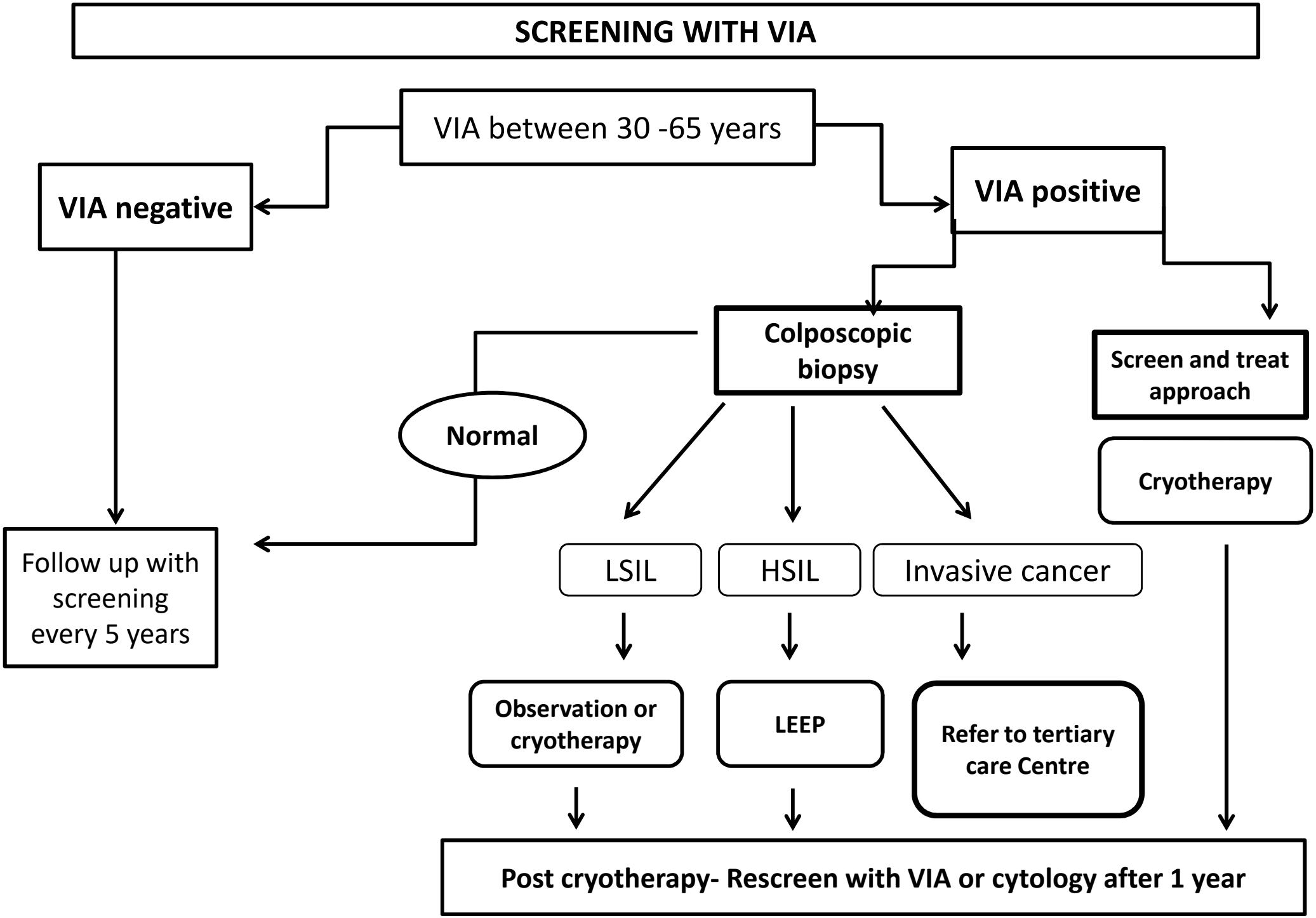
VIA

ADVANTAGES

- Simple, feasible and affordable
- Minimal resources are required
- Results are immediately available
- Permits a Screen and treat approach in a single visit (cryotherapy)

LIMITATIONS

- Visual inspection is subjective
- Requires supervision for quality control
- Not a reliable test in post menopausal women



Federation of Obstetric and Gynaecological Society of India (FOGSI) - Good Clinical Practice Recommendation Screening and Treatment of Preinvasive Lesions of Cervix and HPV Vaccination, 2018

Cytology- '*Pap test*'

- It is the ***most commonly used diagnostic method***
- The reporting format has been standardized by *The Bethesda system for Reporting Cervical Cytology*
- Cervical cytology **cannot be used to make a definitive diagnosis or start treatment**, except when it is HSIL
- The results are used to **guide further evaluation** with colposcopy and or biopsy
- The treatment decisions are based upon the results of further diagnostic tests

Cervical epithelial abnormality report categories

Adequate: based on no of cells (Conventional/ LBC).

Representative: based on transformation zone sampling (endocervical/metaplastic cells)

Squamous Cell abnormalities

- ✓ *Low grade Squamous Intraepithelial Lesion (LSIL)*
- ✓ *High grade Squamous Intraepithelial Lesion (HSIL)*
- ✓ *Atypical squamous cells (ASCUS, ASC-H)*

Glandular abnormalities

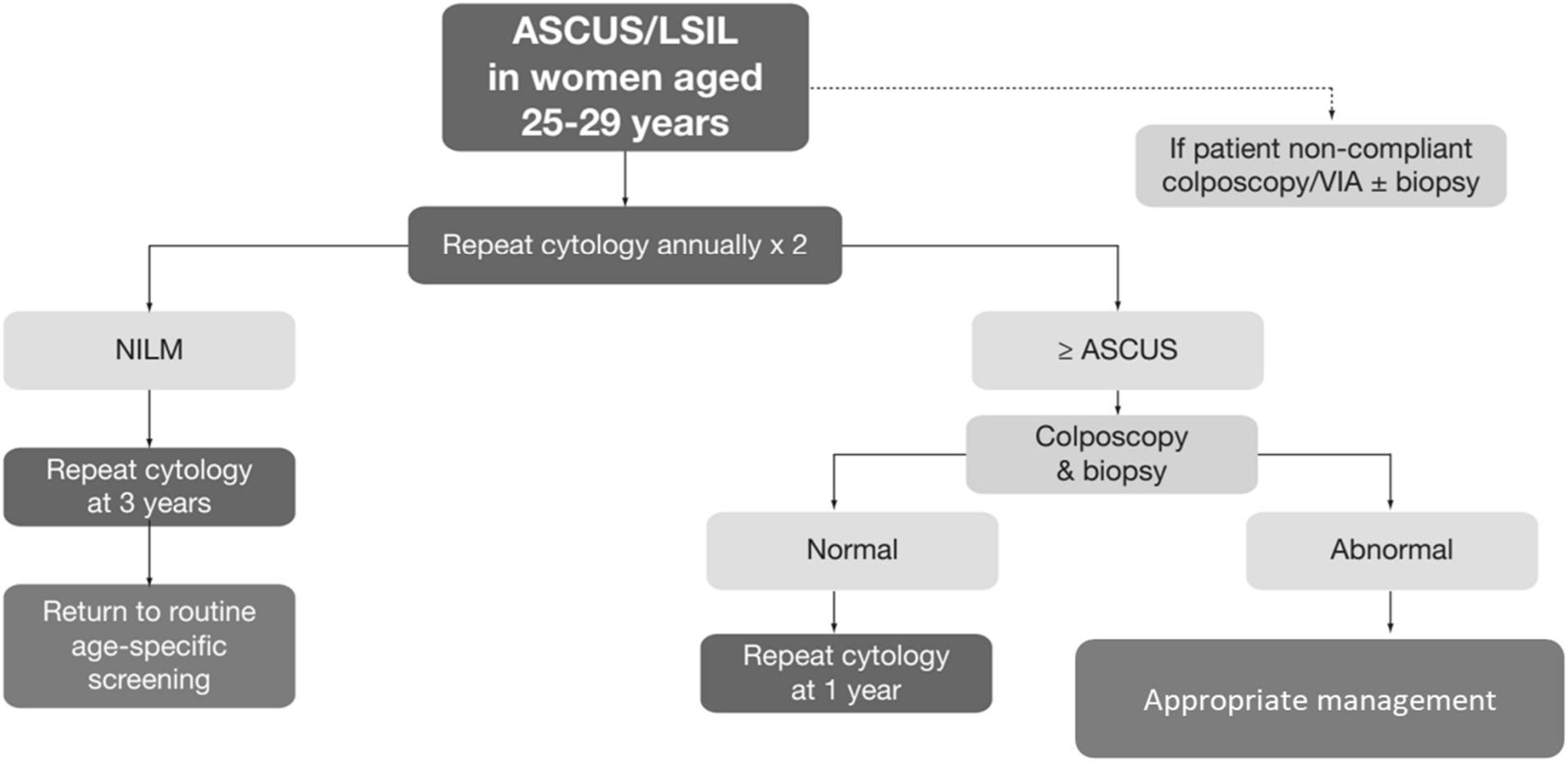
- ✓ *Atypical glandular Cells (AGC)*
- ✓ *Atypical glandular Cells, favour Neoplasia (AGC-FN)*
- ✓ *Endocervical adenocarcinoma in Situ (AIS)*
- ✓ *Adenocarcinoma*

Unsatisfactory sample/report:

- Unknown or negative HPV- repeat age based screening (cytology, primary HPV or cotesting).

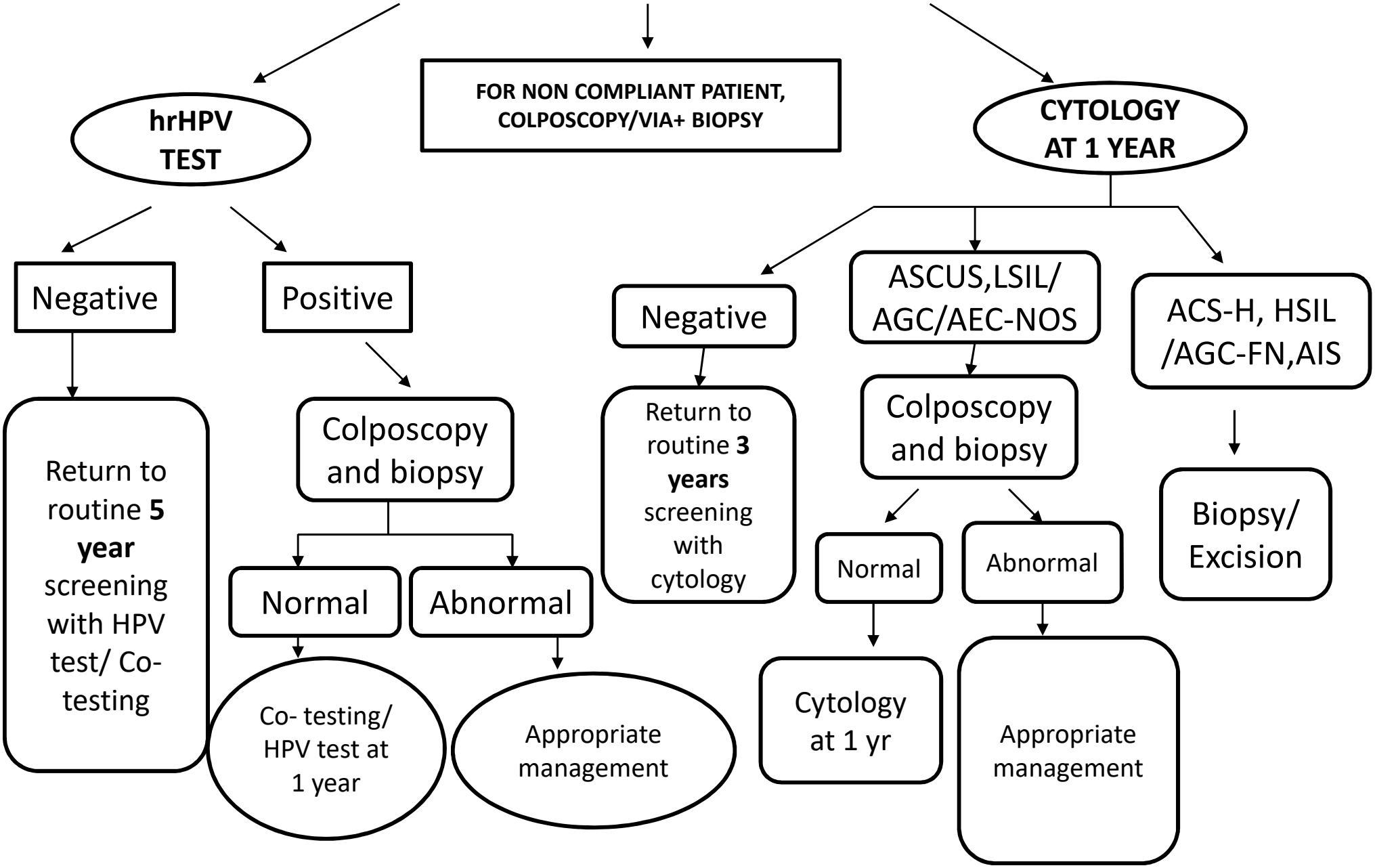
Benign endometrial cells in premenopausal patients: no further screening.

- Benign endometrial cells in post menopausal patients: endometrial assesment.



Federation of Obstetric and Gynaecological Society of India (FOGSI) - Good Clinical Practice Recommendation Screening and Treatment of Preinvasive Lesions of Cervix and HPV Vaccination, 2018

ASCUS/AGC in women aged 30-64 years



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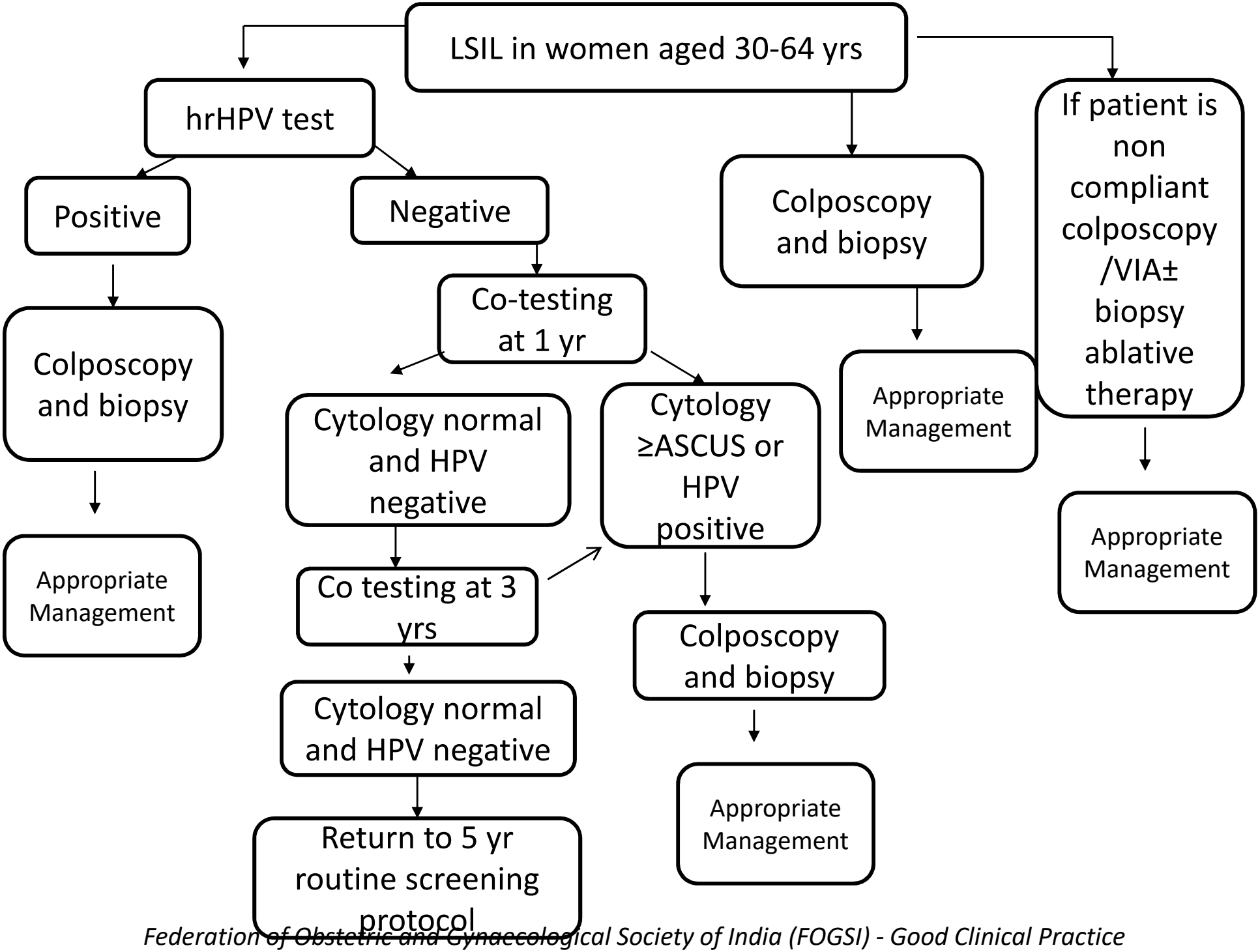

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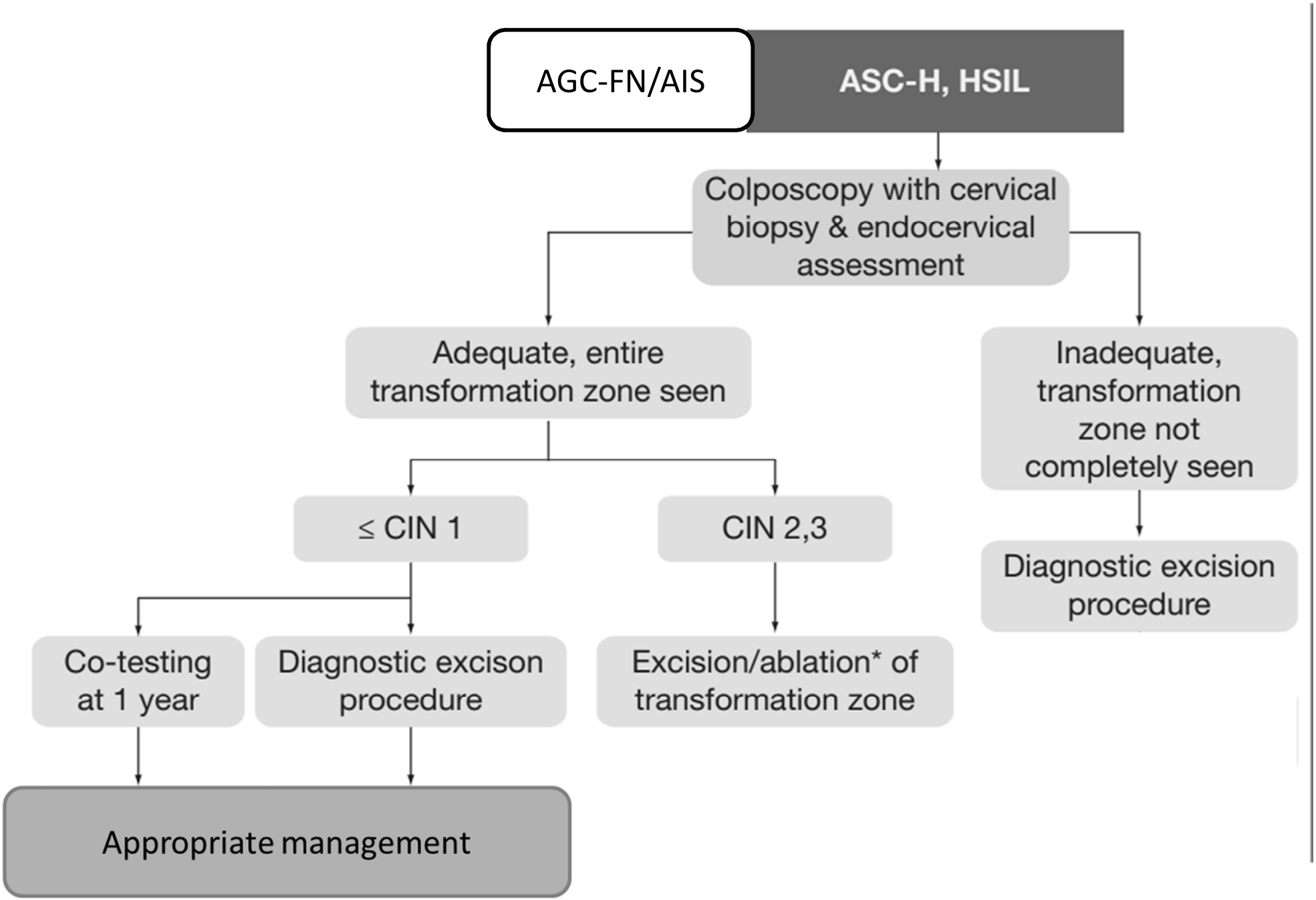

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Primary HPV testing

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- The understanding of natural history of cervical cancer and strong causal association with HPV has paved way for inclusion of HPV testing methods in screening
- It is recommended in women ***≥ 30 years of age***
- It has **high sensitivity** and **negative predictive value** and allows safe prolongation of screening intervals
- A negative HPV test provides **greater reassurance** against HSIL in the subsequent five to seven years than cytology alone
- HPV testing can not differentiate between persistent and transient infection, therefore it has 3%–4% **lower specificity than cytology**

HPV Testing Methods

DNA TESTING METHODS:

- It detects one or more high risk oncogenic HPV types with **direct genomic detection** or by **amplification of viral DNA fragment** using PCR

TECHNIQUE	NAME OF THE TESTS
Direct genome detection	• Hybrid Capture 2 • care HPV test
Amplification	• Cervista HPV HR • GP5+/GP6+ bio PCR EIA
Amplification and Genotyping of HPV-16 and HPV-18	• Cervista HPV 16/18 • Cobas HPV test • Xpert HPV • Abott Real time high risk HPV assay • Papillo check

HPV Testing Methods

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RNA TESTING METHODS:

- The mRNA tests detect expression of **HPV E6 and E7 oncoproteins**

TECHNIQUE	NAME OF THE TESTS
Amplification of E6 and E7 oncoproteins	• Aptima HPV assay • PreTect HPV-Proofer HPV
Monoclonal antibodies	• Advantage HPV E6 Test

HPV Co-testing

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- This **combines cytology (pap test) along with HPV testing**
- For women aged **30-65 years**, co-testing every five years is the **preferred method** of screening presently
- The **negative predictive value is high** when both the test results are negative and there is a very high level of reassurance that they will not be at risk for cervical cancer for a long time
- A negative co-test allows **spacing of screening** in every five years

Newer modalities of screening

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- ✓ ***DNA Methylation studies***
- ✓ ***E6 and E7 mRNA testing***
- ✓ ***p16 and ki67 as biomarkers***

Update on Screening recommendations

WHO guidelines

- Change in age to start screening from 21 years to 25 years
- Patients younger than 25 years do not require screening
- Screening can be discontinued at 65 years of age

WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013

Screening and management for special Categories

4 special categories are considered:

- Pregnant women:
- Immunosuppressed patients:
- Older than 65 or younger than 25:
- Patients after hysterectomy:

Pregnant women:

- Endocervical and endometrial biopsies are unacceptable.
- Only if cytology suggestive for cancer- colposcopy and biopsy.
- However it can be deferred till 4 weeks after delivery.
- HPV testing if age > 30 years.

Immunosuppressed patients:

- HIV, SLE, RA,IBD, organ transplant.
- Screening within 1 year of first sexual exposure.
- Annually for 3 years- every 3 years up till 30.
- Then cytology and contesting every 3 years.
- Any lesion LSIl or worse -> colposcopy

Older than 65 and younger than 25:

- Only in cases with abnormal screening result or treated for precancer.
- Less than 25 years: repeat cytology alone at 1 and 2 year for low grade lesions.
- Colposcopy is recommended only for high grade lesions.
- No HPV testing less than 25 years

Patients after hysterectomy/ surgical procedures:

- 3 consecutive annual hr HPV based tests.
- Long term – hr HPV based tests every 3 years up to 25 years.

Methods to improve screening

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- Organizing community out reach camps
- Screening pregnant ladies.
- Awareness creation
- Removing stigma associated with positive result
- Instill knowledge about screening and treatment options

Future directions

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- WHO's strategy for elimination rests on **three main pillars**:

✓ *Prevention through vaccination*

✓ *Screening and treatment of precancerous lesions*

✓ *Treatment and palliative care for invasive cervical cancer*

- *To eliminate cervical cancer, all countries must reach and maintain an incidence rate of below four per 100 000 women*

Targets or milestones that each country should meet by 2030 to get on the path to eliminate cervical cancer:

90:70:90

- ✓**90%** of girls fully **vaccinated** with the HPV vaccine by the age of 15
- ✓**70%** of women **screened** using a high-performance test by the age of 35, and again by the age of 45
- ✓**90%** of women identified with cervical disease receive **treatment** (90% of women with pre-cancer treated and 90% of women with invasive cancer managed).

References

1. *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013.*
2. *2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2020;24: 102–131)*
3. India Against Cancer" National Institute of Cancer Prevention and Research database
4. ICO/IARC Information Centre on HPV and Cancer, 2020
5. Federation of Obstetric and Gynaecological Society of India (FOGSI) - Good Clinical Practice Recommendation Screening and Treatment of Preinvasive Lesions of Cervix and HPV Vaccination, 2018
6. *The U.S. Preventive Services Task Force (USPSTF), clinical guidance, practice advisory, 2018*