HPV & CERVICAL CANCER SCREENING

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Cervical cancer

- Worldwide cervical carcinoma continues to be a significant health care problem.
- Newly 500,000 new cases of cervical cancer and 274,000 deaths will occur throughout the world.
- Approximately 80% of these new cases occur in developing countries .
- In developing countries, cervical carcinoma remains a significant cause of mortality.

Cervical cancer

- Epidemiologic studies have identified the association of cervical neoplasia with sexual activity.
- The initial study suggested that this relationship is more than 150 years old.
- The sexually transmitted agent that could be related to the initiation or promotion of cervical neoplasia has been sought for many years.

Cervical cancer

- Since the mid-1970s, there has been an explosion of information concerning HPV.
- In the mid-1970s : Dr. Hauzen suggested that HPV is a likely candidate as a sexually transmitted agent may result in genital tract neoplasia.
- The development of immunoperoxidase techniques that can identify the HPV, confirmed these original observations.
- Subsequently, HPV has been isolated from genital lesions ; with the use of hybridization techniques, then HPV DNA can be typed.

Cervical Cancer Is Essentially Caused by Oncogenic HPV

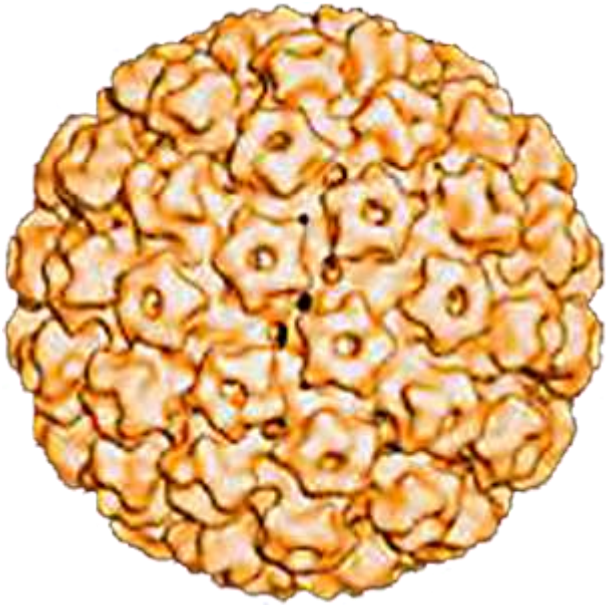
- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer etiology.[1]
  - HPV is a main cause of cervical cancer.[2]
- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = 99.7%.[2]
  - Tissue samples were analyzed for HPV DNA by three different polymerase chain reaction (PCR)–based assays, and the presence of malignant cells was confirmed in the same tissue sections.[2]

1. Muñoz N, Bosch FX, de Sanjosé, et al. *N Engl J Med*. 2003;348:518–527. 2. Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol*. 1999;189:12–19.

Human Papillomavirus (HPV)

HPV is a necessary cause of cervical cancer – 99.7%[4]

HPV



Cancer causing Types[1,2,4]

- HPV 16
- HPV 18

>75% of Cervical Cancer[5]•

>50% of Vaginal & Vulvar Cancer[5]•

Non-cancer causing types[1,2]

- HPV 6
- HPV 11

90% of Anogenital warts[5]

1.Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934. 2. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 3. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285. Reprinted from *J Virol.* 1994;68:4503–4505 with permission from the American Society for Microbiology Journals Department. 4. Walboomers JM, Jacobs MV, Manos MM, et al. J Pathol. 1999;189:12–19. 5. X. Castellsagué, S. de Sanjose, T. Aguado, K. S. Louie, L. Bruni, J.Muñoz, M. Diaz, K. Irwin, M. Gacic, O. Beauvais, G. Albero, E. Ferrer, S. Byrne,F. X. Bosch. HPV and Cervical Cancer in the World. 2007 Report. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Available at: www.who.int/hpvcentre

Human Papilloma Virus

Anogenital Disease: cervix, vulva, vagina, anus, penis

Condylomata accuminatum

Squamous intraepithelial neoplasia

Cancer

Head/Neck Disease:

Mouth, tongue, tonsils

Sinuses

Oropharangeal

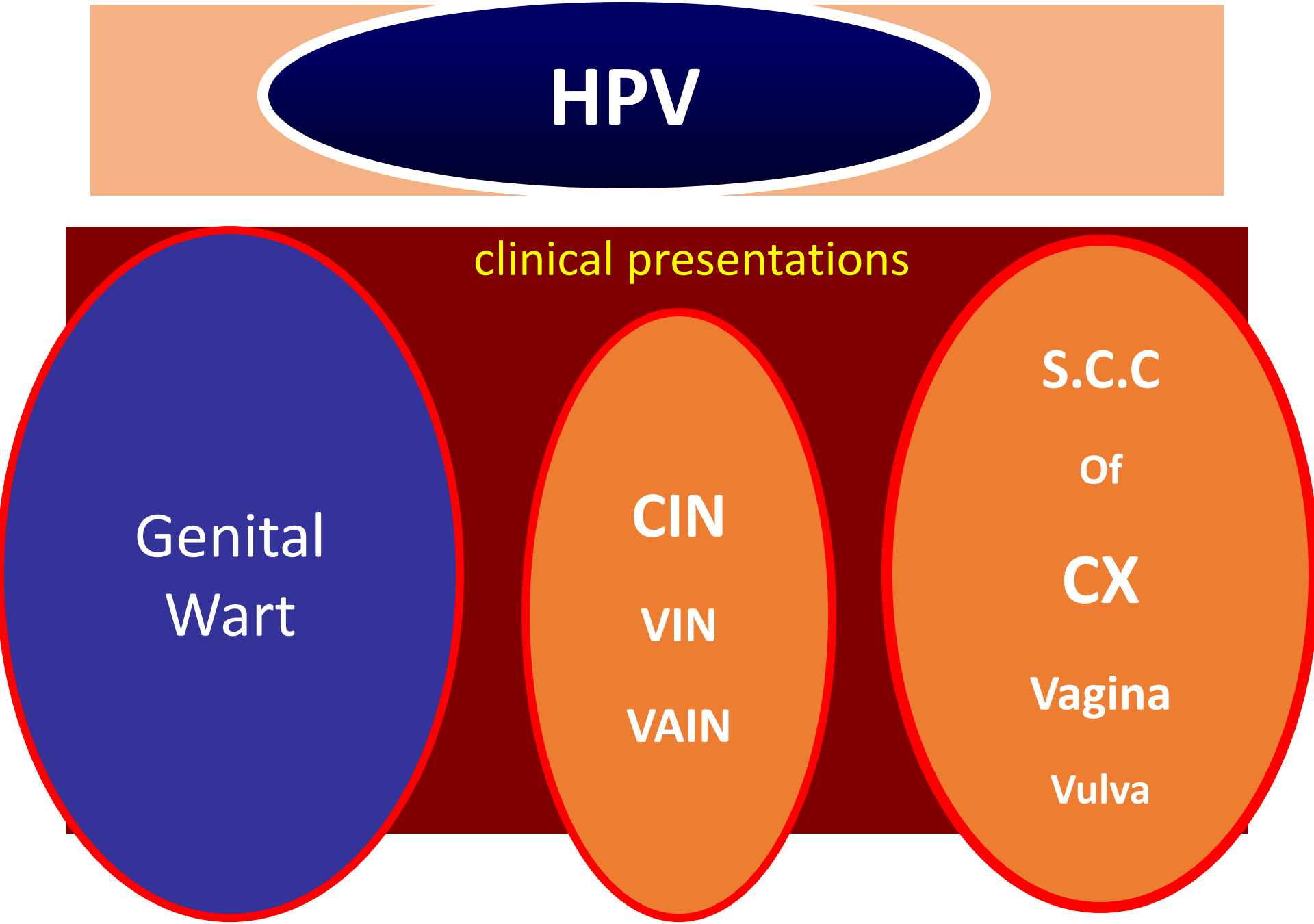
Respiratory mucosa (children; type 6, 11)

Cancer: usually HPV 16

Cofactors: Smoking, Alcohol

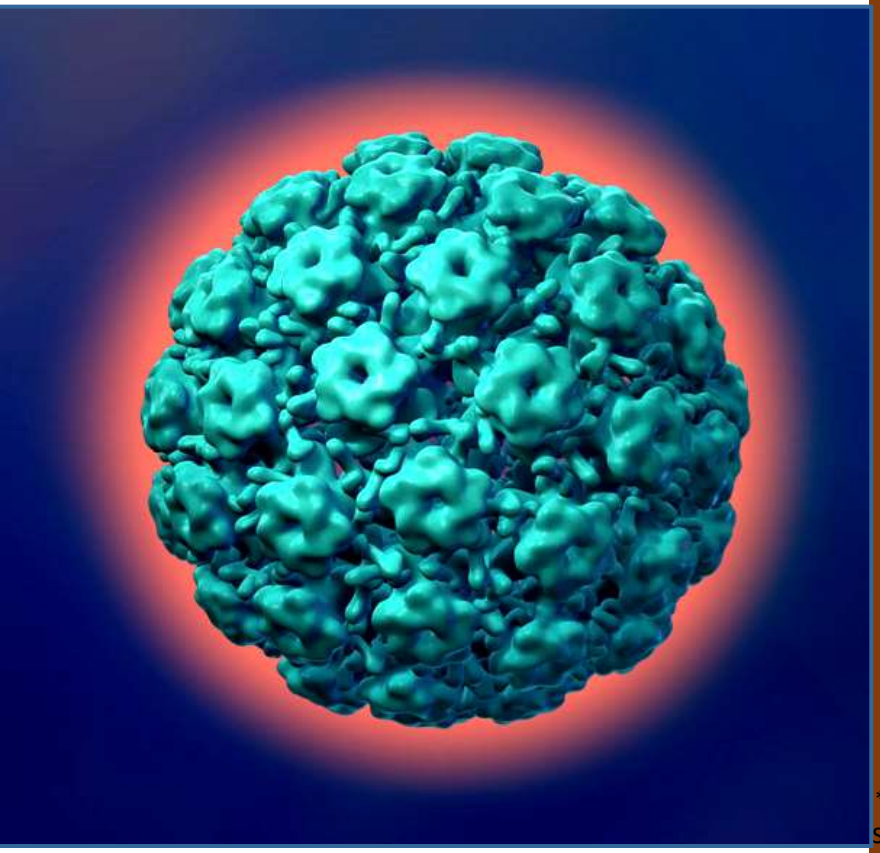
Cervical cancer
HPV

- The human papilloma virus is a necessary factor in the development of cervical cancer, and is one of the most common sexually transmitted infections throughout the world.
- The virus quite often display no early symptoms, and is the leading cause of vulvar, vaginal, cervical, anal, and penile cancers, as well the leading cause of anogenital warts.


HPV
clinical presentations
Genital Wart
CIN
VIN
VAIN
S.C.C
Of
CX
Vagina
Vulva

HPV

Nonenveloped double-stranded DNA virus



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sk

- ~100 types identified
- ~30–40 anogenital
  - ~15–20 oncogenic
    - HPV 16 and HPV 18 types account for the majority of worldwide cervical cancers.
  - Nononcogenic types
    - HPV 6 and 11 are most often associated with external anogenital warts.
    - These two types are responsible for >90% of genital warts.

1. Howley PM, Lowy DR. In: Knipe DM, Howley PM, eds. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229.
2. de Villiers E-M, Fauquet C, Broker T, et al. *Virology* 324:17-24, 2004. 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl

HPV

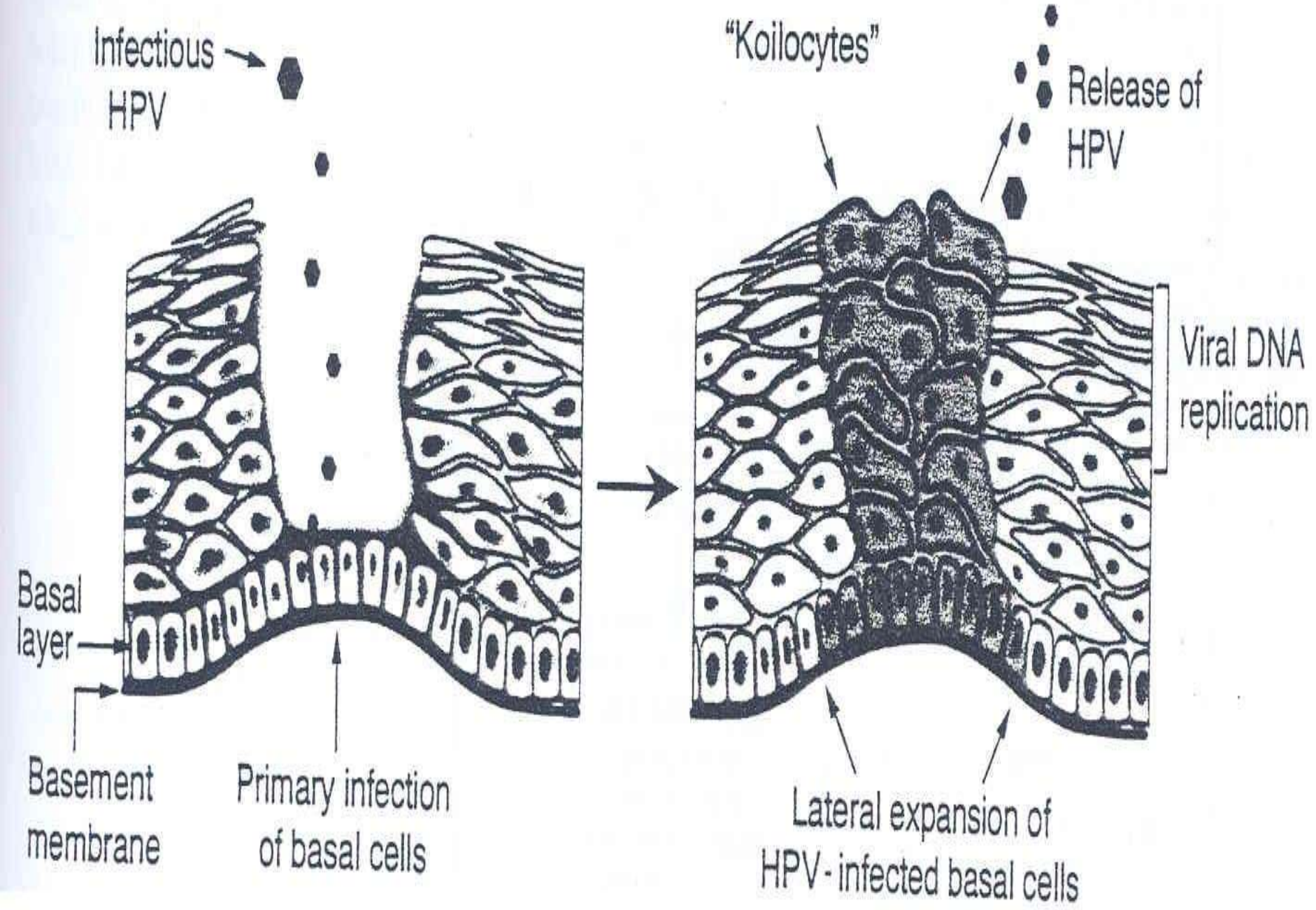
- The HPV virus is like a seed that is planted in soil, and need some co-factors to create cervical cancer
- Factors that may have a role in this progression include:

1. Smoking
2. Infection with other STDs
3. Immunosuppression
4. Nutrition

Mechanisms of HPV Transmission

- Sexual contact
  - Through sexual intercourse[1]
  - Genital–genital, manual–genital, oral–genital[2–4]
  - Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact.[2]
  - Proper condom use may help reduce the risk, but is not fully protective against infection.[5]
- Nonsexual routes
  - Mother to newborn (vertical transmission)[6]
  - Fomites (eg, undergarments, surgical gloves, biopsy forceps)[7,8]
    - Hypothesized but not well documented; would be rare
- Most infected individuals are unaware that they are infected and may unknowingly spread the virus.[9]

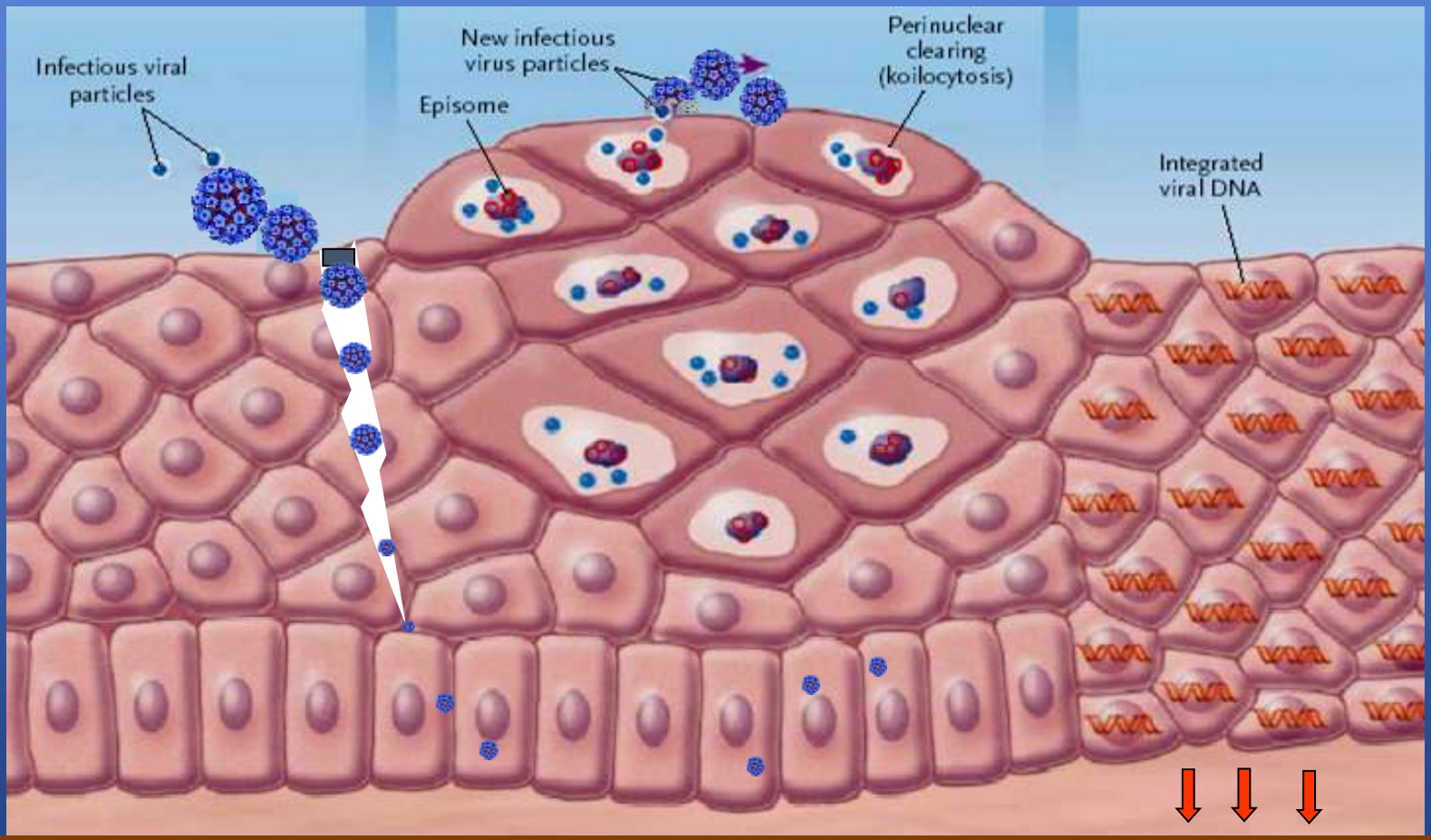
1. Kjaer SK, Chackerian B, van den Brule AJ, et al. *Cancer Epidemiol Biomarkers Prev*. 2001;10:101–106. 2. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. *Am J Epidemiol*. 2003;157:218–226. 3. Fairley CK, Gay NJ, Forbes A, Abramson M, Garland SM. *Epidemiol Infect*. 1995;115:169–176. 4. Herrero R, Castellsagué X, Pawlita M, et al. *J Natl Cancer Inst*. 2003;95:1772–1783. 5. Manhart LE, Koutsky LA. *Sex Transm Dis*. 2002;29:725–735. 6. Smith EM, Ritchie JM, Yankowitz J, et al. *Sex Transm Dis.* 2004;31:57–62. 7. Ferenczy A, Bergeron C, Richart RM. *Obstet Gynecol.* 1989;74:950–954. 8. Roden RBS, Lowy DR, Schiller JT. *J Infect Dis*. 1997;176:1076–1079. 9. Anhang R, Goodman A, Goldie SJ. *CA Cancer J Clin.* 2004;54:248–258


Infectious HPV
"Koilocytes"
Release of HPV
Viral DNA replication
Basal layer
Basement membrane
Primary infection of basal cells
Lateral expansion of HPV-infected basal cells

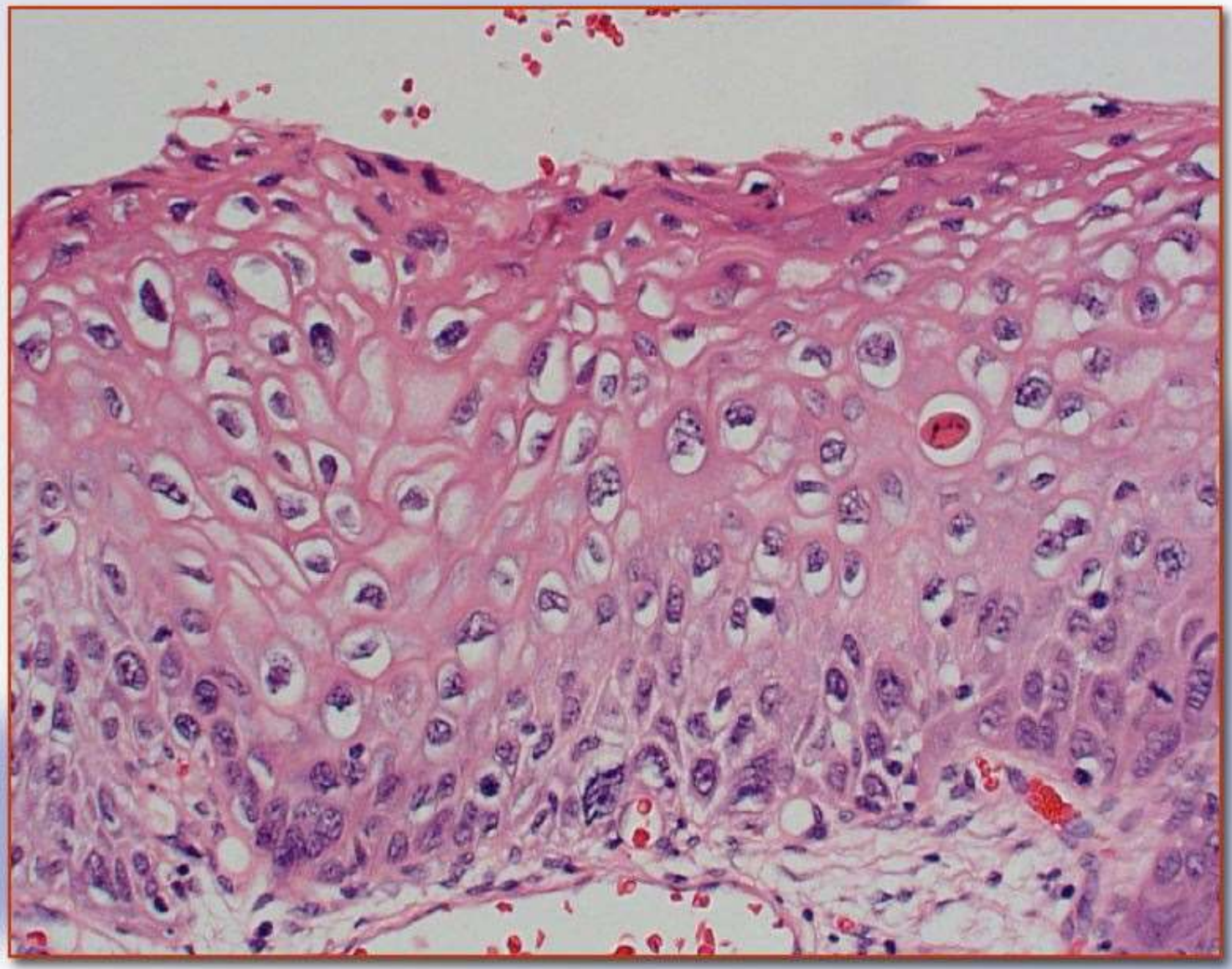
HPV

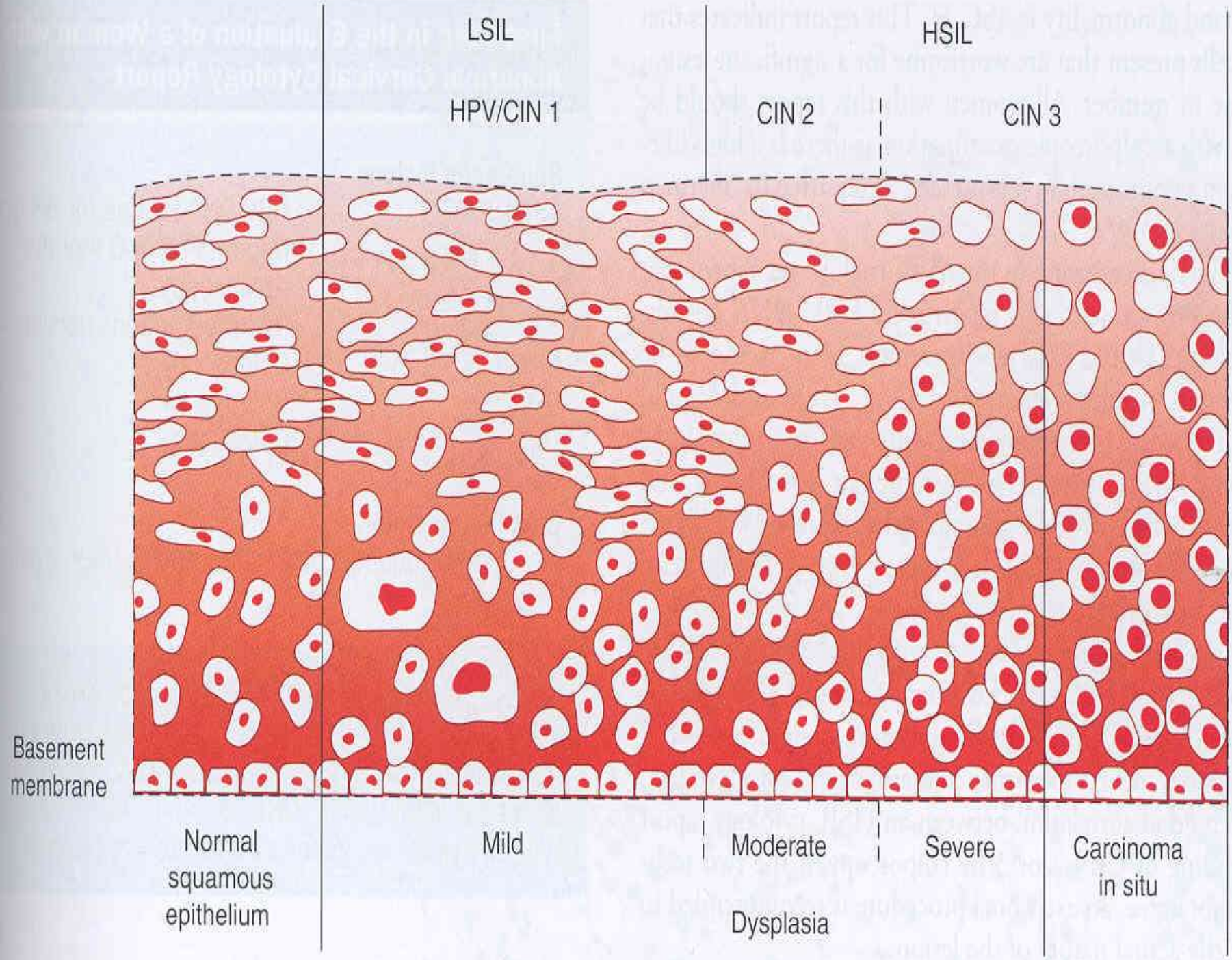
- The life cycle of HPV infections is tightly coupled with the differentiation of the stratified epithelium that is the target of infection.
- Infection requires access to the actively proliferating basal cells of the epithelium.
- This occurs usually at the site of microtrauma to the epithelium.
- As the infected basal cell proliferate, they migrate from the basal to the suprabasal compartment.

Spectrum of Changes in Cervical Squamous Epithelium Caused by HPV Infection



HPV Productive Infection or CIN 1

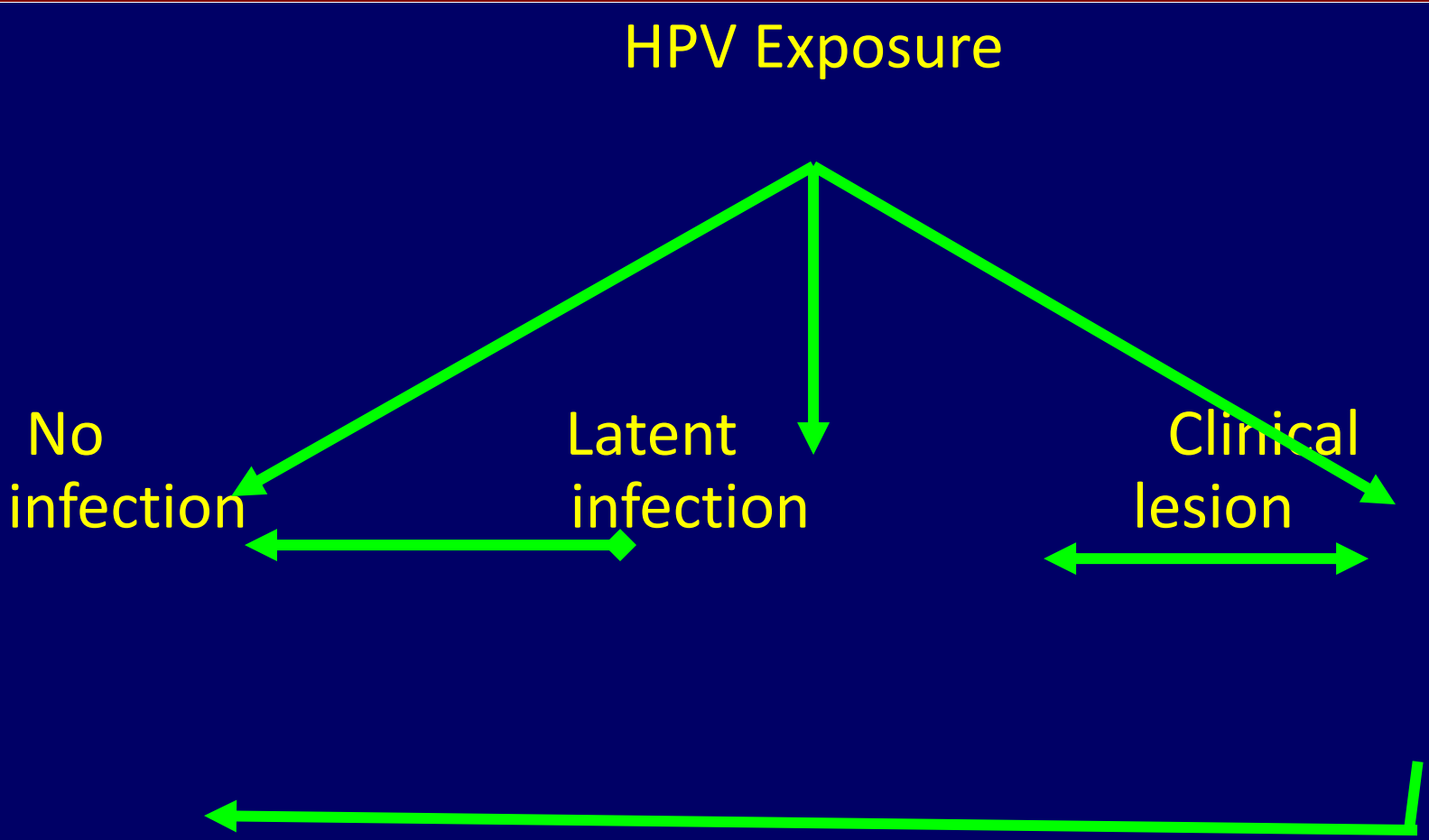



LSIL
HSIL
HPV/CIN 1
CIN 2
CIN 3
Basement membrane
Normal squamous epithelium
Mild
Moderate
Severe
Carcinoma in situ
Dysplasia

HPV

- Most women have no clinical evidence of disease, and the infection is eventually suppressed or eliminated.
- In most women, the infection will clear in 9 to15 months.
- A minority of women develop persistent infection that may progress to CIN.
- Persistent HR HPV infection increases the risk of HG lesions 300-fold, and is required for the development and maintenance of CIN3.

HPV


HPV Exposure
No infection
Latent infection
Clinical lesion

Acute (Incident) HPV Infection

5 – 10 years to develop cancer from time of infection

Infects only the epithelium – no viremia

Most cases – no histologic or cytologic changes (66% - 90%)

- Resolution of infection and cytologic changes occurs secondary to antibodies, and NKC, activated CD-4 and T lymphocytes

Cofactors for progression of cervical HPV infection to Cancer

Long term use of Hormonal Contraceptive
-> 5-9yrs :: 3 times Risk
-> 10yrs or more :: 4 times Risk

Other STI's
->Chlamydia Trachomatis
-> HSV 2

Early initiation of Sexual Activity

Immune Suppression

High Parity :: 4 times Risk

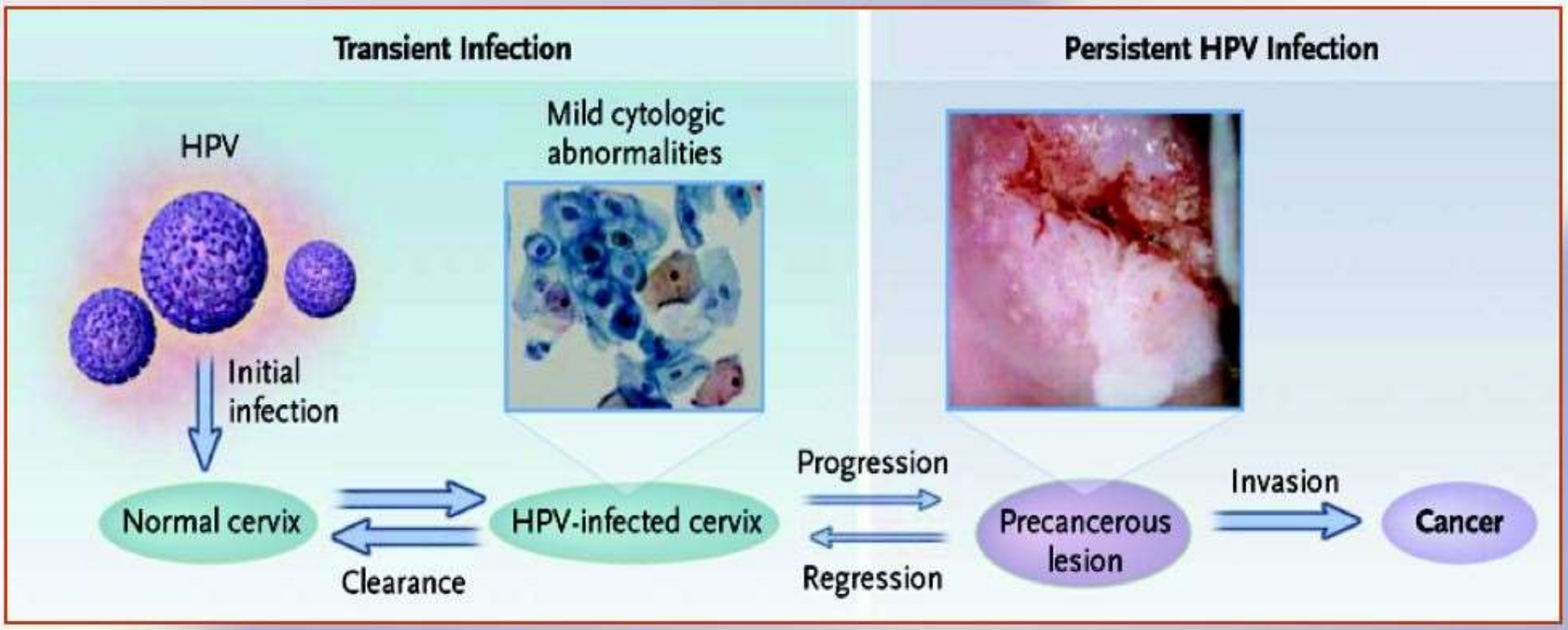
HIV Infection

Tobacco Smoking (Both active & passive)

Multiple Sex Partners

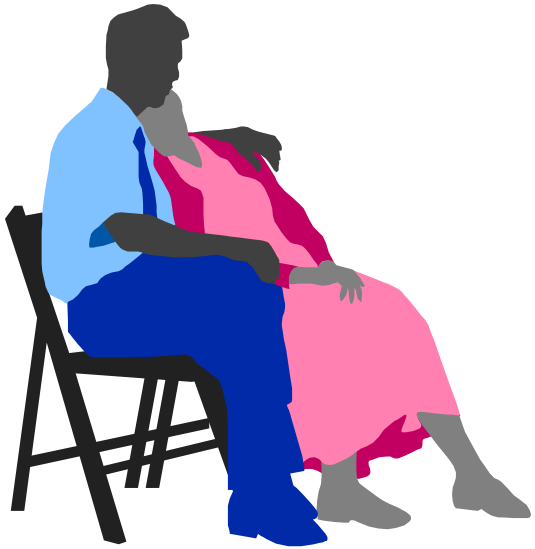
Low S/E status ; Diet poor in anti oxidants

Natural History of HPV Infections



How HPV infection can occur?

- **Through sexual intercourse, vertical transmission i.e. mother to child & fomites.**
- **It is found that in every 10 women 8 women might have HPV infection at anytime in life.***



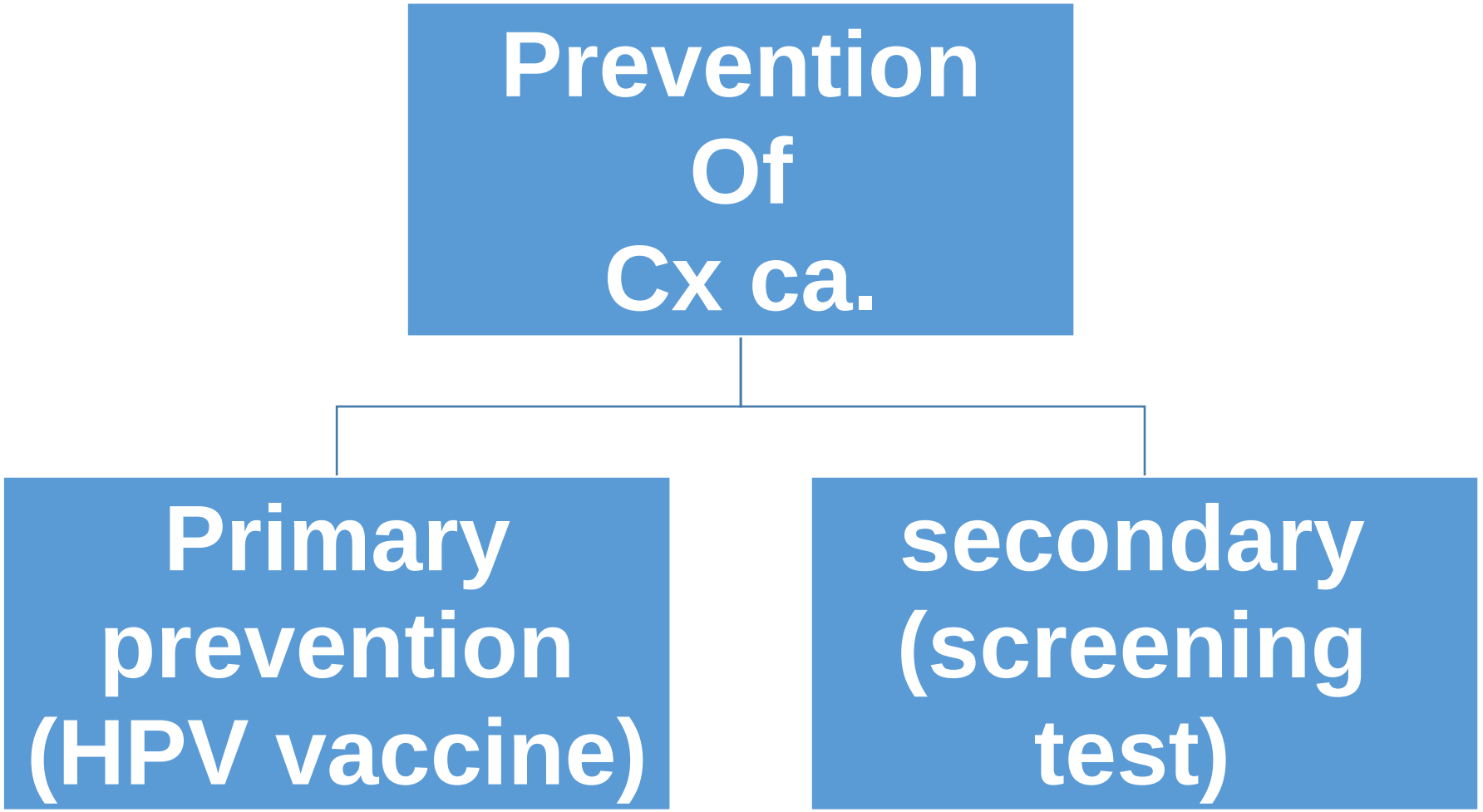
*Ref: CDC Factsheet on Genital HPV infection
www.cdc.gov/STD/healthcomm/factsheet.html

Beware of this symptoms

Consult your doctor immediately if you have

- Continuous vaginal discharge,inspite of treatment
- Foul smelling, thick discharge,
- Repeated vaginitis and UTI
- Post coital bleeding(bleeding after sex)
- Non healing or recurrent cervical erosion
- Irregular or intermenstrual bleeding specially in pre menopausal phase

Is it possible to get protection against cervical cancer?


Prevention
Of
Cx ca.
Primary prevention (HPV vaccine)
secondary (screening test)

What is the use of screening program?

- **Secondary prevention or screening program are helpful in detecting cancer at the early stage hence useful in saving lives.**

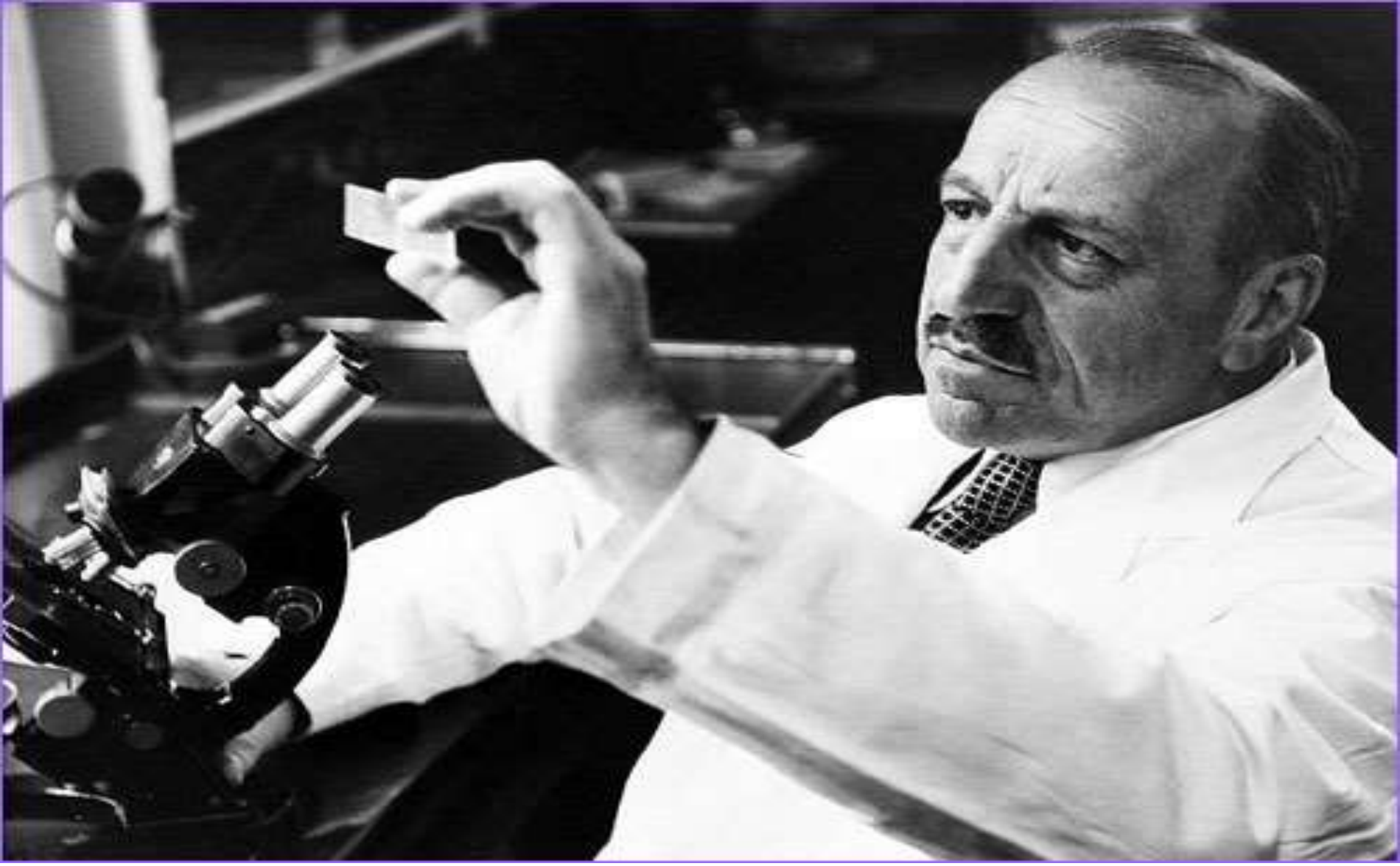
Screening for cervical cancer and its precursors

Cervical screening tests

- Conventional cervical cytology
- Liquid based cytology (LBC)
- HPV testing
- Visual inspection with 3-5% acetic acid(VIA)
- Visual inspection with Lugol's iodine(VILI)

Pap Smear

- **Single Pap false negative rate is 20%.**
- **The latency period from dysplasia to cancer of the cervix is variable.**
- **50% of women with cervical cancer have never had a Pap smear.**
- **25% of cases and 41% of deaths occur in women 65 years of age or older.**



Cytologic evaluation of cervix was first proposed by Dr.Papanicolaou in the 1940s.

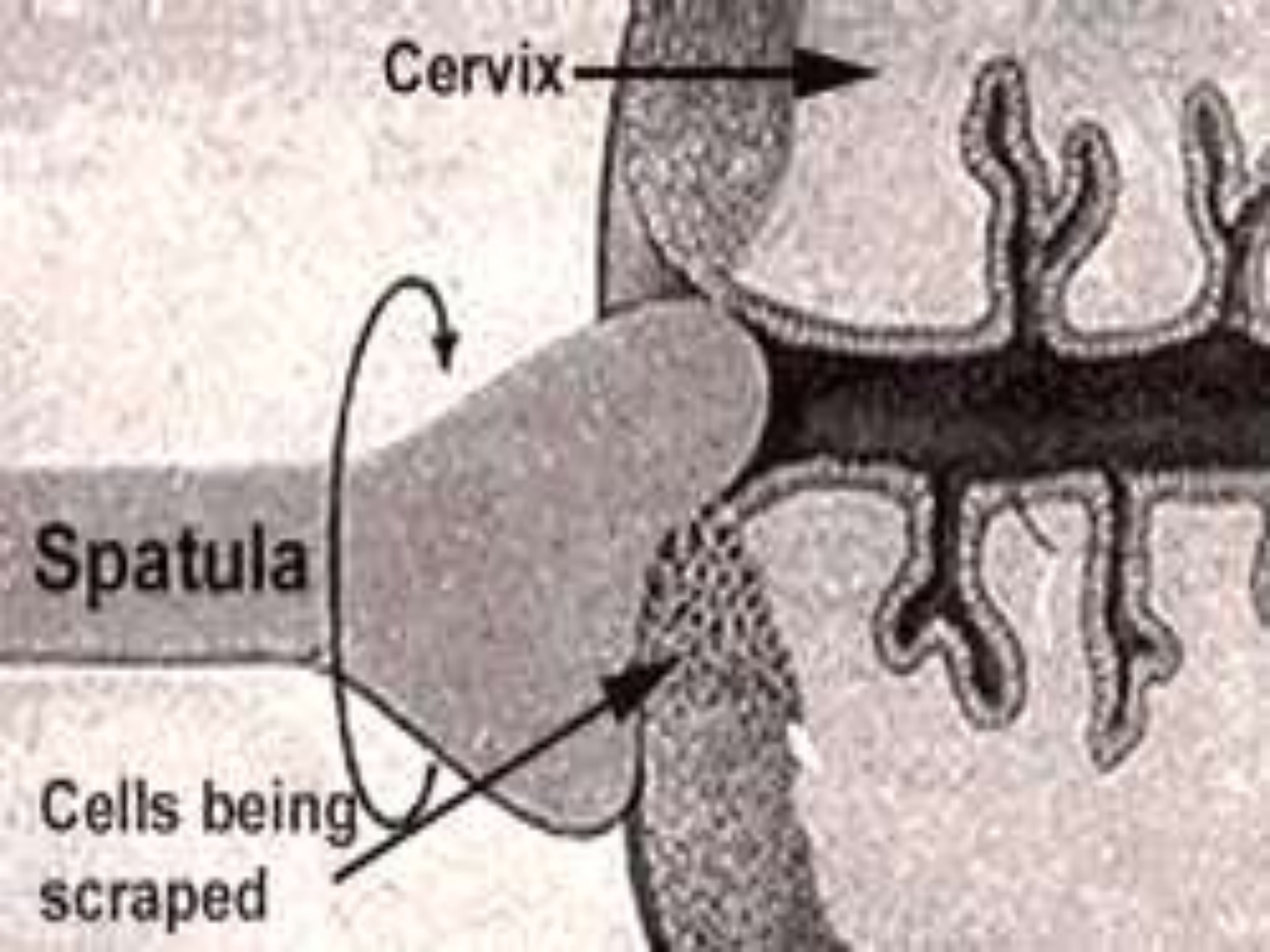
Conventional cytology

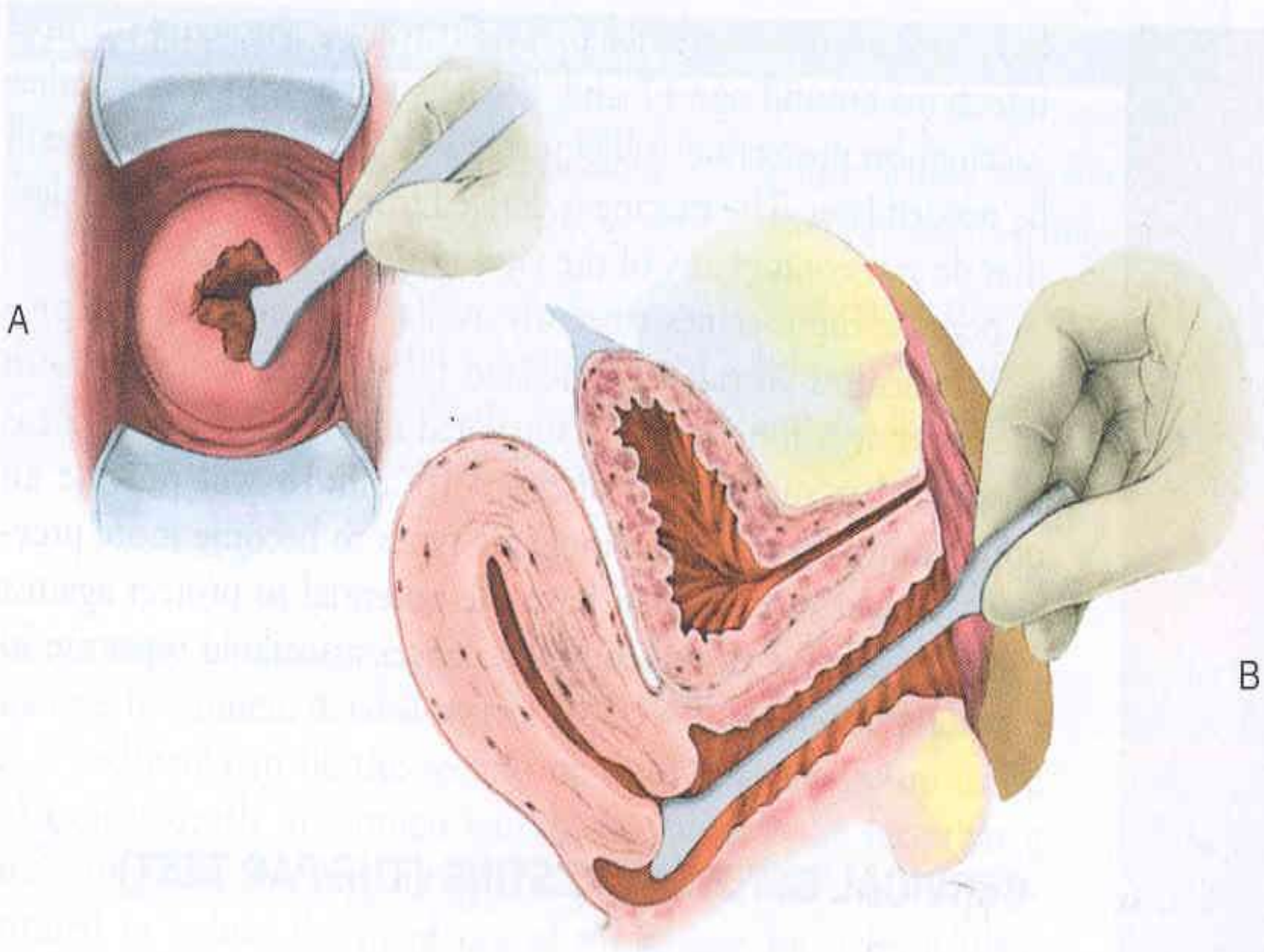
- Previously ,it had been widely believed that SN of the pap test was in the 80% range.
- In 3 recent reviews of the accuracy of cervical cytology assessment, the SN of pap test in detecting CIN2-3 ranged from 47- 62% and the SP ranged from 60-95%.
- Their SN system is from repeated testing rather than the SN of pap test, per se.
- 15-50% false negative rate in detecting HGL & invasive ca.

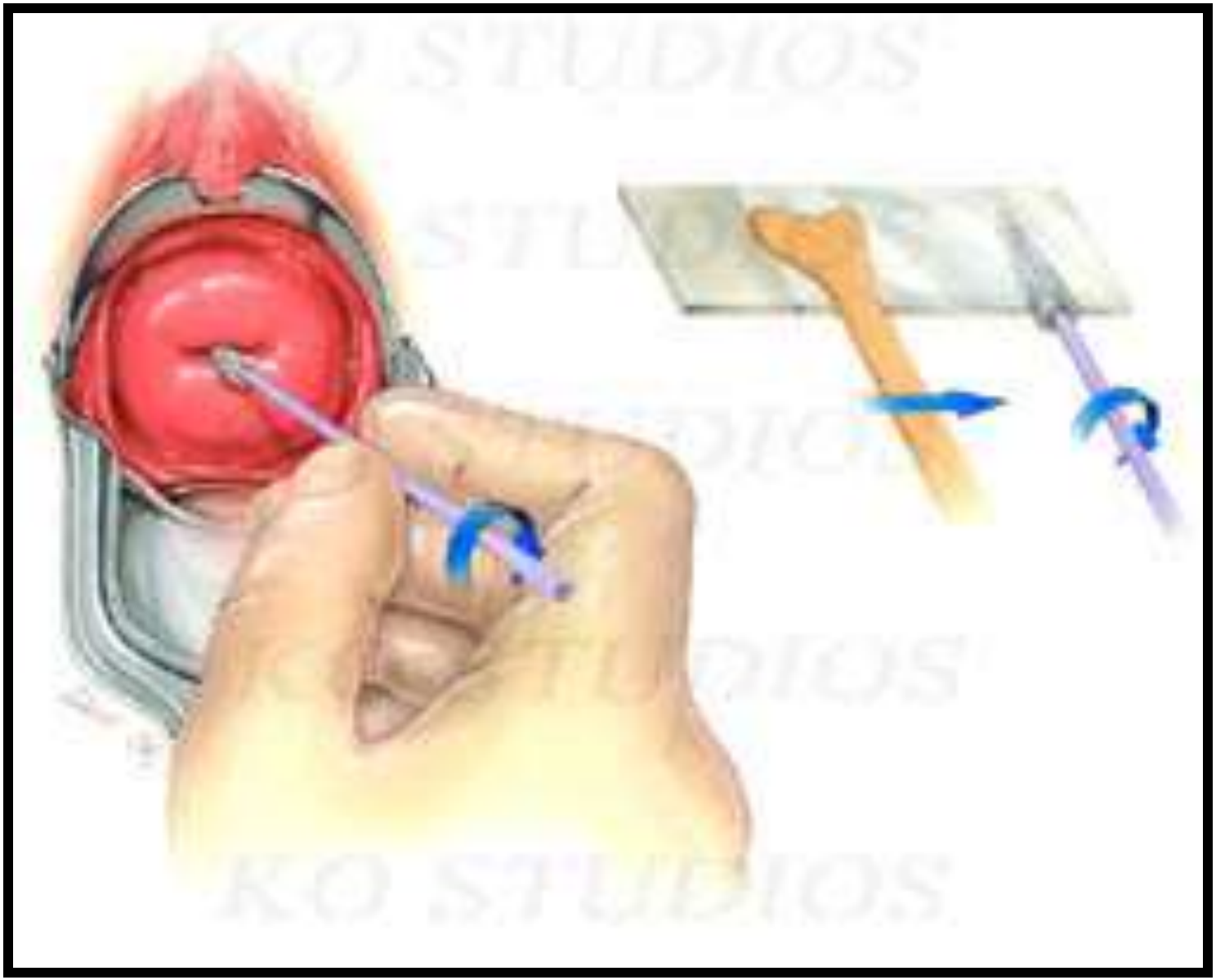
Conventional cytology

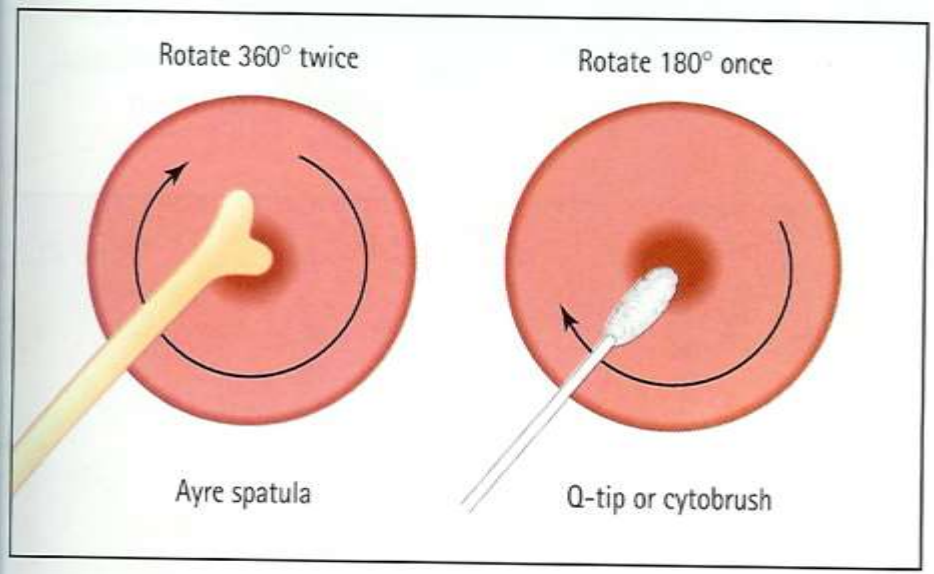
- False negative errors occur in sampling, preparation, and interpretation.

1. Sampling errors occur because a lesion is too small to exfoliate cells or the device used did not pick up the cells and transfer them to the slide.
2. Preparation errors may occur because of Poor fixation, leading to air-drying and an inability to interpret the results.
3. The slide may also be too thick, and leads to poor fixation because the fixative can not penetrate the sample.
4. Interpretive errors occur when the slide contains diagnostic cells that the screening technician did not identify.


Cervix
Spatula
Cells being scraped


A
B


KO STUDIOS



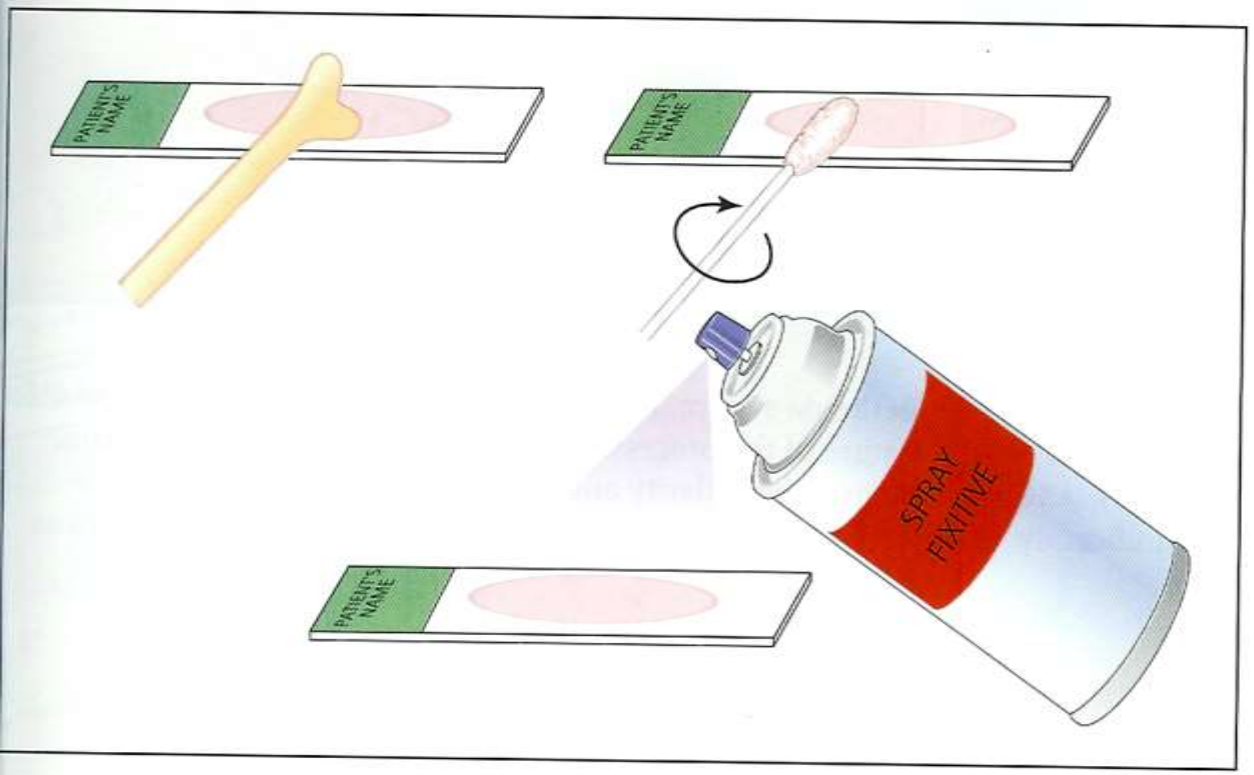


FIGURE 7–6.

Pap smear technique. **A**, The Pap smear is obtained by exposing the cervix with a speculum. A spatula or other collection device is used to scrape the ectocervix, rotating 360 degrees twice to sample the entire transformation zone. A sample is also taken from the endocervix with a cotton-tipped swab or brush by rotating it 180 degrees once. **B**, The specimen is immediately placed evenly on a glass slide with the patient's name and medical record number. To avoid drying artifact, the sample is fixed rapidly either with a spray fixative or in alcohol; it is then ready for interpretation.

The success of screening programs in developed countries seems to be duo to:

1. Repeated testing at frequent intervals(1-5Y)
2. High population coverage
3. High quality control
4. Reliable follow-up

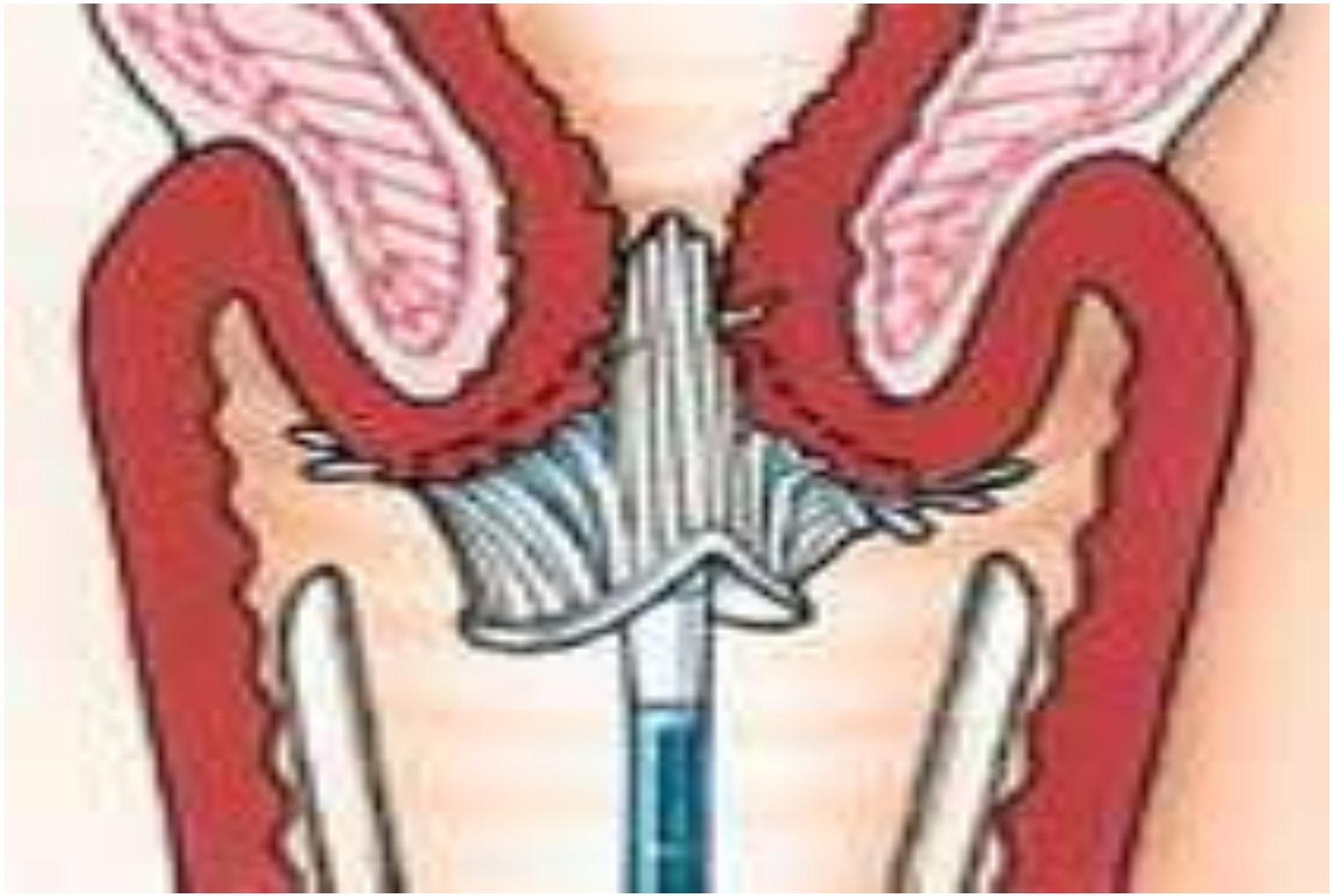
Liquid based cytology

1-completes transfer of cx cells to the slide.
2-improves readibility due to the
elimination of poor fixation ,air drying
artifact, thickness of cellular spread,
debris from blood & inflammatory cells.
3-Reduces the rate of unsatisfactory sample
4-more sensitive (80%)
5-increases screening interval
6-is suitable for additional testing procedures
such as HPV testing.(reflex HPV test)

Liquid based cytology

- Disadvantages:1-less specificity
  2-more expensive
  3-requires additional instrumentation
  4-increased colposcopic refer

The impact of LBC on ca. incidence & mortality remains to be established,as does its cost-effectiveness.



婦人科用固定液
SurePath-Preservative Fluid

Bethesda 2014 classification system for cervical cytology

Specimen type

Indicate conventional smear (Pap smear), liquid-based preparation (Pap test) versus other

Specimen adequacy

- Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, eg, partially obscuring blood, inflammation, etc)
- Unsatisfactory for evaluation (specify reason)
  - Specimen rejected/not processed (*specify reason*)
  - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

General categorization (optional)

- Negative for intraepithelial lesion or malignancy
- Other: see "Interpretation/results" (eg, endometrial cells in a woman older than 45 years)
- Epithelial cell abnormality: see "Interpretation/results" (specify "squamous" or "glandular," as appropriate)

Interpretation/results

Negative for intraepithelial lesion or malignancy

(When there is no cellular evidence of neoplasia, state this in the "General categorization" above and/or in the "Interpretation/results" section of the report—whether there are organisms or other non-neoplastic findings)

Non-neoplastic findings (optional to report)

- **Non-neoplastic cellular variations:**
  - Squamous metaplasia
  - Keratotic changes
  - Tubal metaplasia
  - Atrophy
  - Pregnancy-associated changes
- **Reactive cellular changes associated with:**
  - Inflammation (includes typical repair)
    - Lymphocytic (follicular) cervicitis
  - Radiation
  - Intrauterine contraceptive device (IUD)
- **Glandular cells status posthysterectomy**

Organisms

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* spp.
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces* spp.
- Cellular changes consistent with herpes simplex virus
- Cellular changes consistent with cytomegalovirus

Other

- Endometrial cells (in a woman older than 45 years)
  (also specify if "negative for squamous intraepithelial lesion")

Epithelial cell abnormalities

- **Squamous cell**
  - Atypical squamous cells
    - Of undetermined significance (ASC-US)
    - Cannot exclude HSIL (ASC-H)
  - Low-grade squamous intraepithelial lesion (LSIL)
    (encompassing: HPV/mild dysplasia/CIN-1)
  - High-grade squamous intraepithelial lesion (HSIL)
    (encompassing: moderate and severe dysplasia, CIS, CIN-2 and CIN-3)
    - With features suspicious for invasion (if invasion is suspected)
  - Squamous cell carcinoma
- **Glandular cell**
  - Atypical
    - Endocervical cells (NOS or *specify in comment*)
    - Endometrial cells (NOS or *specify in comment*)
    - Glandular cells (NOS or *specify in comment*)
  - Atypical
    - Endocervical cells, favor neoplastic
    - Glandular cells, favor neoplastic
  - Endocervical adenocarcinoma in situ
  - Adenocarcinoma
    - Endocervical
    - Endometrial
    - Extrauterine
    - Not otherwise specified (NOS)

Other malignant neoplasms (*specify*)

Adjunctive testing

Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician

Computer-assisted interpretation of cervical cytology

If case examined by an automated device, specify the device and result

Educational notes and comments appended to cytology reports (optional)

Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included)

From: Nayar R, Wilbur DC. The Pap Test and Bethesda 2014: "The reports of its demise have been greatly exaggerated. (after a quotation from Mark Twain)". J Low Genit Tract Dis 2015; 19:175. DOI: 10.1097/LGT.0000000000000115. *Copyright © 2015 American Society for Colposcopy and Cervical Pathology, The International Society for the Study of Vulvovaginal Disease, and The International Federation of Cervical Pathology and Colposcopy. Reproduced with permission from Lippincott Williams & Wilkins. Unauthorized reproduction of this material is prohibited.*

UpToDate

HPV – DNA testing

Advantages:

- Higher SN
- identifies the women with concurrent cervical disease and at risk for developing neoplasia within the next 3-10 years.
- Is objective and built in quality control.

USPSTF and ACS/ASCCP/ASCP Guidelines at a Glance

Population	USPSTF	ACS/ASCCP/ASCP
Younger than 21 years	Recommends against screening. Grade: D recommendation.	Women should not be screened regardless of the age of sexual initiation or other risk factors. ?
21–29 years	Recommends screening with cytology every 3 years. Grade: A recommendation.	Screening with cytology alone every 3 years is recommended.
30–65 years	Recommends screening with cytology every 3 years or for women who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 years. Grade: A recommendation.	Screening with cytology and HPV testing ("co-testing") every 5 years (preferred) or cytology alone every 3 years (acceptable) is recommended.

USPSTF and ACS/ASCCP/ASCP Guidelines at a Glance

Population	USPSTF	ACS/ASCCP/ASCP
Older than 65 years	Recommends against screening women who have had adequate prior screening and are not otherwise at high risk for cervical cancer. Grade: D recommendation.	Women with evidence of adequate negative prior screening and no history of CIN2+ within the last 20 years should not be screened. Screening should not be resumed for any reason, even if a woman reports having a new sexual partner.
After hysterectomy	Recommends against screening in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (i.e. CIN 2 or 3) or cervical cancer. Grade: D recommendation	Women of any age following a hysterectomy with removal of the cervix who have no history of CIN2+ should not be screened for vaginal cancer. Evidence of adequate negative prior screening is not required. Screening should not be resumed for any reason, including if a woman reports having a new sexual partner.
HPV vaccinated	Women who have been vaccinated should continue to be screened	Recommended screening practices should not change on the basis of HPV vaccination status.

LOW income country

- ● **Screening age and frequency**
- For patients in whom cervical cancer screening will be performed once or twice in a lifetime, we initiate screening between the ages of 30 and 39 years rather than other age ranges. Screening between these ages appears to result in the largest reduction in cervical cancer incidence and mortality.

- For patients in whom more frequent testing can be performed, we initiate screening at age 30 years and repeat testing every three to ten years (depending on test used) until age 50 years.

LOW income country

- **Screen-and-treat protocols** – Screen-and-treat protocols include a screening test
- followed in the same visit by treatment of positive results. This approach is only possible
- in settings where tests that produce immediate results (ie, rapid-result human
- papillomavirus [HPV] testing, visual inspection) are available. Such protocols eliminate
- communication difficulties involved in delivering and interpreting written results as well
- as the issue of noncompliance with follow-up

LOW income country

- **Rapid-result HPV** – For patients undergoing a screen-and-treat protocol, we prefer
- HPV testing rather than visual inspection . This is consistent with the World Health Organization (WHO) recommendations.
- Rapid-result HPV tests include

Xpert HPV (Cepheid) and careHPV (Qiagen) ; screening with these tests is repeated every five to ten years.

HIGH income country

- For patients <21 years, we do **not** screen for cervical cancer, regardless of the age of initiation of sexual activity.
- For patients ages 21 to 29, we initiate cervical cancer screening at the age of 21 with
- cervical cytology every three years. Our approach is consistent with the 2018 United
- States Preventive Services Task Force (USPSTF) guidelines. Another acceptable
- approach is to initiate screening at age 25 with primary HPV testing every five years
- (consistent with the 2020 American Cancer Society [ACS] guidelines). (See 'Age 21 to
- 29' above.)

- For patients ages 30 to 65, we continue cervical cancer screening with any of the
- following strategies :

- Primary HPV testing (with a test approved by the US Food and Drug
- Administration [FDA]) every five years; or
- -
- - Co-testing (Pap and HPV testing) every five years; or
- - Pap test alone every three years

.

HIGH income country

- For patients >65 years, the decision to **discontinue** screening depends on whether

the patient has had adequate prior screening, life expectancy, and preferences in a shared decision-making discussion.

- For patients who have had adequate prior screening with all normal results and

no cervical cancer risk factors, the optimal age to discontinue screening is uncertain. We screen through at least age 65 years. While data are limited and potential harms of screening need to be considered (eg, false positives), some UpToDate authors and editors continue to offer screening through age 74 years.

- For patients in whom screening is unknown or has not been adequate, we

perform co-testing annually for three years before spreading out the interval to every five years, and we extend screening to age 70, or beyond.

Thank you