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CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

OUTLINE OF PRESENTATION:

1. **BURDEN OF DISEASE**

2. **RELATIONSHIP OF HPV AND CERVICAL CARCINOMA**

3. **SCREENING MODALITIES**

a. **CLINICAL PROFILING OF THE PATIENT**

b. **CERVICAL SMEARS**

i. **CONVENTIONAL SMEARS**
ii. **MONOLAYER**
iii. **COMPARISON**

c. **HPV SCREENING**

5. **PRACTICE GUIDELINES OF SCREENING**

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

1. BURDEN OF DISEASE

CME February 2010 Vol.28 No.2

Cervical cancer in South Africa: An overview of current status and prevention Strategies

Cervical cancer is distressingly common in developing countries.

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Current estimates are that 493 243 women are diagnosed with cervical cancer per year and 273 505 die from the disease.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

Table 1: Numbers of cancer deaths by cause, South Africa 2000 – Revised [SAMRC]

Persons			Males			Females		
Rank	Cause of death	Deaths	Rank	Cause of death	Deaths	Rank	Cause of death	Deaths
1	Trachea/bronchi/ lung cancer	6885	1	Trachea/bronchi/ lung cancer	4669	1	Cervix cancer	3498
2	Oesophageal cancer	5579	2	Oesophageal cancer	3566	2	Breast cancer	3156
3	Cervix cancer	3498	3	Prostate cancer	2524	3	Trachea/bronchi/ lung cancer	2216
4	Breast cancer	3206	4	Liver cancer	1666	4	Oesophageal cancer	2013
5	Liver cancer	2651	5	Stomach cancer	1386	5	Colo-rectal cancer	1410
6	Colo-rectal cancer	2567	6	Colo-rectal cancer	1157	6	Liver cancer	986
7	Prostate cancer	2524	7	Mouth and oropharynx cancer	985	7	Stomach cancer	962
8	Stomach cancer	2348	8	Leukaemia	818	8	Pancreas cancer	752
9	Pancreas cancer	1541	9	Pancreas cancer	789	9	Ovary cancer	707
10	Leukaemia	1465	10	Larynx cancer	633	10	Leukaemia	647
11	Mouth and oropharynx cancer	1386	11	Lymphoma	601	11	Corpus uteri cancer	638
12	Lymphoma	1032	12	Bladder cancer	469	12	Lymphoma	431
13	Larynx cancer	746	13	Bone and connective tissue cancer	360	13	Mouth and oropharynx cancer	401
14	Bone and connective tissue cancer	707	14	Brain cancer	274	14	Bone and connective tissue cancer	331
15	Ovary cancer	691	15	Kidney cancer	251	15	Brain cancer	253
16	Bladder cancer	673	16	Melanoma	233	16	Bladder cancer	204
17	Corpus uteri cancer	638	17	Non-melanoma skin cancers	158	17	Melanoma	203
18	Brain cancer	527	18	Breast cancer	50	18	Kidney cancer	176
19	Melanoma	437	19			19	Larynx cancer	114
20	Kidney cancer	427				20	Non-melanoma skin cancers	108
	All cancers	41657		All cancers	21361		All cancers	20296

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

2. RELATIONSHIP OF HPV AND CERVICAL CARCINOMA

a. Association between certain oncogenic (high-risk) strains of HPV and cervical cancer is well established:

- **Abnormal Pap smears show cytopathic effects of HPV**
- **Over 99% of cervical cancers have HPV DNA detected within the tumor**
- **70% of cervical cancer is caused by one of two types of HPV, 16 or 18 (mainly SCC)**
- **Adenocarcinomas of the cervix are also related to HPV, but the correlation is less pronounced and is age dependent**

b. HPV recognized as the underlying cause of cervical cancer since 1996

- **NIH Consensus Conference on Cervical Cancer, 1996**
- **World Health Organization/European Research Organization on Genital Infection and Neoplasia, 1996**

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

2. RELATIONSHIP OF HPV AND CERVICAL CARCINOMA

c. Cytopathic effects of the HPV virus

• Viral particles are assembled in the nucleus, and complete virions are released as the cornified layers of the epithelium are shed. In the replication process, viral DNA becomes established throughout the entire thickness of the epithelium but intact virions are found only in the upper layers of the tissue.

• In warts or condylomata, viral replication is associated with proliferation of all epidermal layers except the basal layer. This leads to acanthosis, parakeratosis, hyperkeratosis, and deepening of rete ridges, creating the typical papillomatous cytoarchitecture seen histologically.

• Some infected cells transform into koilocytes, which are large, usually polygonal, squamous cells with a shrunken nucleus inside a cytoplasmic vacuole.

• Excessive proliferation of cells in the basal layer accompanied by large number of mitoses, some abnormal, is a feature of malignant and premalignant disease.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

2. RELATIONSHIP OF HPV AND CERVICAL CARCINOMA

d. Molecular genetics

- **HPV DNA detected in 90% of cervical cancers.**

- **The E6 and E7 gene products deregulate the host cell growth cycle by binding and inactivating tumor suppressor proteins, cell cyclins, and cyclin-dependent kinases.**

- **The function of the E6 and E7 gene products during a productive HPV infection is to subvert the cell growth-regulatory pathways .**

- **Cell growth is regulated largely by two cellular proteins, the tumor suppressor protein, p53, and the retinoblastoma gene product, pRB.**

- **Unlike in many other cancers, the p53 in cervical cancer is usually wild type**

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

a. CLINICAL PROFILING OF THE PATIENTG

b. CERVICAL SMEARS

i. CONVENTIONAL SMEARS
ii. MONOLAYER SMEARS
iii. COMPARISON

c. HPV SCREENING

c. HISTOPATHOLOGY

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

a. Clinical profiling of the patient

- sexual history [number of sex partners; sexual practices; age of first intercourse; history of STDs]
- history of previous Pap smears and results

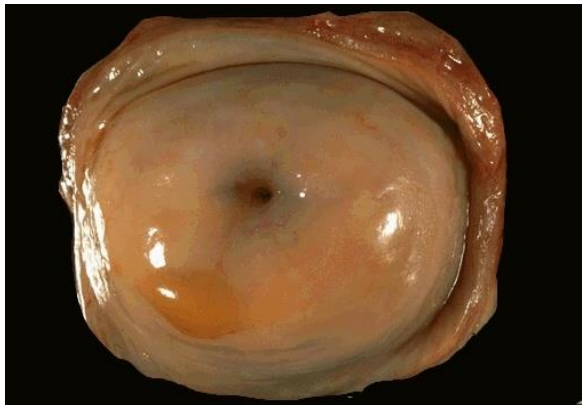
b. Visual examination [color, margin contour, vascular pattern, and iodine staining]

- identifying warts
  - visible to the naked eye, and are diagnosed based on their appearance [Condyloma acuminatum]
  - Acetowhite staining [Condyloma planum (flat warts)]
- identifying invasive lesions
  - punch biopsy

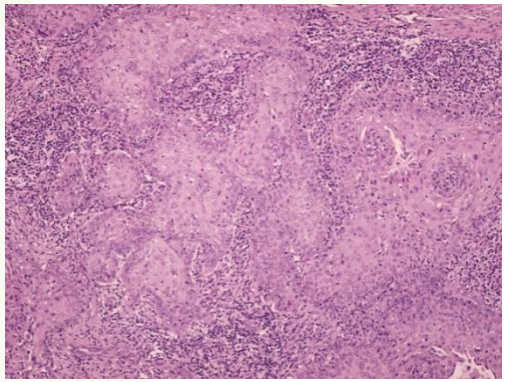
c. Colposcopy [magnify the tissue - improve diagnostic accuracy and recognition of flat warts]

CERVICAL CANCER screening – PATHOLOGIST'S PERSPECTIVE

Colposcopy



Normal cervix



H & E: Photomicrograph

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

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CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

i. CONVENTIONAL SMEARS [PAPANICOLAOU SMEAR]

- **Papanicolaou-stained (Pap) smear. [Pathologist George Papanicolaou - 1949]**

- **Pap smear has helped reduce cervical cancer incidence and mortality rates by half to two-thirds**

- **Cellular changes in cells of the transformation zone of the cervix - caused by HPV.**

- **The Pap smear reporting classification has evolved and been refined over time.**

-The current reporting system is the Bethesda System [1988, 1991 to replace the CIN System, and -updated again in 1999, 2001 and 2014]

- **The CIN System is based on tissue architecture and was introduced in 1973 [three-tired system]**

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

i. CONVENTIONAL SMEARS [PAPANICOLAOU SMEAR]

The Bethesda System - to introduce uniform descriptive diagnostic histologic terminology.

- Inclusion of a statement regarding the adequacy of the specimen as an integral part of the report

- The Bethesda System was modified in 1991 to reflect actual laboratory and clinical experience after its implementation.

- It was modified again in 2001 - taking into account:
 # increased utilization of new cervical screening technologies

 # adjunctive molecular tests

 # lessons learned from litigation

 # better understanding of the biology of cervical neoplasia

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

i. CONVENTIONAL SMEARS [PAPANICOLAOU SMEAR]

The Bethesda System 2001 classifies squamous cell abnormalities into four categories:

(i) ASC (atypical squamous cells)
(ii) LSIL (low-grade squamous intraepithelial lesions)
(iii) HSIL (high-grade squamous intraepithelial lesions),
(iv) squamous cell carcinoma

-The ASC category was termed "atypical cells of undetermined significance (ASCUS)" in the previous version of the Bethesda System and is considered to be a category for reporting borderline or equivocal results.

- In the previous version of the Bethesda System, pathologists were encouraged to qualify ASCUS with respect to whether a reactive process or SIL was favored.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

i. CONVENTIONAL SMEARS [PAPANICOLAOU SMEAR]

- The Pap smear procedure has some limitations:
Inadequate samples constitute about 8% of specimens received.
False-negative rates as high as 20 to 30% have been reported:

[clumping of cells when the cells are not spread evenly and uniformly on the microscope slide]
[Sometimes, other contents of the cervical specimen such as blood, bacteria, or yeast contaminate the sample and prevent the detection of abnormal cells]
[If exposed to air too long before being fixed on the slide, cervical cells can become distorted]
[Human error is probably the primary threat to accurate interpretation][overworked readers]

N.B: In 1988, the Clinical Laboratory Improvement Act (CLIA) established national guidelines that restricted technologists/technicians from reading more than 100 slides per day. Some experts think that this number is still too large. Also, CLIA mandated a manual rescreening of 10% of negative satisfactory smears to reduce the number of false-negative results.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

i. CONVENTIONAL SMEARS [PAPANICOLAOU SMEAR]

- Many laboratories appended comments such as "favor SIL," "favor repair," "favor a high-grade lesion," "favor a low-grade lesion," and "ASCUS, not otherwise specified." This reporting was confusing to clinic

- In attempt to provide clearer terminology, the "ASC-US favor repair" comment has been eliminated in the Bethesda System 2001, and these cases are now called "negative."

-The new ASC category contains two subcategories: the "atypical squamous cells of undetermined significance (ASC-US)" subcategory includes lesions that have cellular abnormalities suggestive of SIL, and the "atypical squamous cells, cannot exclude HSIL (ASC-H)" subcategory was separated out because it was felt that most of these cases would be referred to colposcopy.

-The LSIL and HSIL categories present in the previous version of the Bethesda System were retained.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

i. CONVENTIONAL SMEARS [PAPANICOLAOU SMEAR]

- can detect abnormal cells before they become cancerous

- Keratinizing [LSIL; HSIL]
- None-keratinizing [small cell HSIL; ASC-H; ASC-US]
- Hormone-related changes [atrophy; crowded atrophy; reserve cell hyperplasia]
- Atypical glandular cells [AGS]
- Adenocarcinoma/SCC

- Can detect infections [Trichomonas; Herpes Simplex; chlamydia, etc.

- Disadvantages of conventional smears
- Haemorrhagic smears (bloody smears)
- Inflammatory smears (reparative changes)
- Sampling adequacy

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

ii. MONOLAYER SMEARS [LIQUID-BASED CYTOLOGY]

- developed to improve the diagnostic reliability of Papanicolaou (Pap) smears.
- rinses cervical cells in preservatives (blood and other potentially obscuring material can be separated)
- allows for additional testing of the sample, such as for human papillomavirus (HPV).

- Conventional Pap smears can have false-negative and false-positive results
  - because of inadequate sampling and slide preparation
  - errors in laboratory detection and interpretation.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

ii. MONOLAYER SMEARS [LIQUID-BASED CYTOLOGY]

-To reduce the number of false-negative results by half [specimen is collected in a preservative solution rather than being spread directly on the microscope slide by hand.

- Cellular structure is better preserved because the cells are immediately fixed. In addition, a cervical brush is used to collect the specimen, which provides almost twice as many epithelial cells as do other collection devices.

- Slides are prepared under the control of the Cytology Laboratory, avoiding uneven manual smearing.

-The uniform monolayer created by these methods is easier to read. The process prevents drying artifacts and removes most contaminating mucus, protein, red blood cells, bacteria, and yeast.

-There are currently two Food and Drug Administration (FDA)-approved liquid-based monolayer cytology -methods: [PrepStain system and the ThinPrep Pap Smear method]

-Results showed statistically significant improvement in the diagnostic sensitivity of monolayer cytology, -with increased detection of epithelial cell abnormalities from 4 to 17%.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

iii. COMPARISON

Conventional Pap Smear vs. Liquid-Based Cytology

***Am Fam Physician.* 2010 Feb 15;81(4):542-549.**

Background: Liquid-based cervical cytology was developed to improve the diagnostic reliability of Papanicolaou (Pap) smears. Conventional Pap smears can have false-negative and false-positive results because of inadequate sampling and slide preparation, and errors in laboratory detection and interpretation. However, liquid-based cytology rinses cervical cells in preservatives so that blood and other potentially obscuring material can be separated. It also allows for additional testing of the sample, such as for human papillomavirus (HPV). The comparative accuracy of each technique has been studied extensively and has yielded conflicting results; recent systematic reviews reported that there is no convincing evidence to recommend one technique over the other. Siebers and colleagues designed this prospective study to compare the histologic detection rates and positive predictive values of conventiona Pap smears and liquid-based cervical cytology.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

iii. COMPARISON

Conventional Pap Smear vs. Liquid-Based Cytology

Am Fam Physician. **2010 Feb 15;81(4):542-549.**

Results: Approximately 84,000 women were evaluated from 246 family practices participating in the trial. In this intention-to-treat analysis, 45,818 liquid-based cytology tests and 38,504 conventional Pap smears were reviewed. Several of the large, urban practices were assigned to the liquid-based cytology group, which accounted for the difference in sample sizes. Among 2,474 persons with abnormal results, 1,918 (77.5 percent) had low-grade lesions and 556 (22.5 percent) had high-grade SIL or above. Abnormalities were detected at statistically similar rates between the two screening tests at all levels.

Conclusion: The authors conclude that conventional Pap smears and liquid-based cytology screening tests have equivalent detection ratios and positive and negative predictive values for detecting CIN or cervical cancer.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

iii. COMPARISON

Indian J Pathol Microbiol. 2015 Jan-Mar;58(1):17-21.

Liquid-based cytology versus conventional cytology for evaluation of cervical Pap smears: experience from the first 1000 split samples.

Singh VB, Gupta N[1], Nijhawan R, Srinivasan R, Suri V, Rajwanshi A.
Author information

[1]Department of Cytology and Gynecological Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Abstract
Screening programs using conventional cytology conventional Pap smear (CPS) have successfully reduced cervical cancer, but newer tests like liquid-based cytology (LBC) and human papillomavirus testing might enhance screening. The main aim of the present study was to assess the diagnostic accuracy of LBC versus CPS using "split samples."

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

iii. COMPARISON

Indian J Pathol Microbiol. 2015 Jan-Mar;58(1):17-21.

RESULTS:
There were 4.3% unsatisfactory (U/S) cases in CPS and 1.7% in LBC; the main cause is insufficient cells, and excess of blood in CPS. About 25/100 (2.5%) split samples had epithelial abnormalities both in CPS and LBC (1.2%-atypical squamous cells of undetermined significance; 0.4%-low grade squamous intraepithelial lesion; 0.2%-high grade squamous intraepithelial lesion; 0.5%-squamous cell carcinoma; 0.1%-atypical glandular cells favouring neoplasia; 0.2%-adenocarcinoma). Inflammatory organisms were almost equally identified in both techniques but were better seen in LBC samples.

CONCLUSIONS:
LBC technique leads to significant reduction of U/S rate. LBC samples offered better clarity, uniform spread of smears, less time for screening and better handling of hemorrhagic and inflammatory samples. LBC had equivalent sensitivity and specificity to CPS.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

b. CERVICAL SMEARS

iii. COMPARISON

LIQUID BASED CYTOLOGY- IS IT A GOOD ALTERNATIVE?

Sonti Sulochana, Divya Gopalan, Chitra Srinivasan.

Abstract

The objectives of the study were to evaluate Liquid Based Cytology (LBC) over conventional Pap smear with respect to adequacy of smear, preservation of morphological features, clarity of background, detection of infective organisms and dysplastic cells.

Results: There was not much difference in the sensitivity between the conventional Pap smear and LBC in detecting infective organisms. However dysplastic changes were detected in two smears using LBC whereas this was not possible using the conventional smear.

Conclusion: Using LBC it was possible to detect infective organisms even when their load was low. Since the cells are in a monolayer, and the smear is uniformly prepared, the quality of the smear is improved thereby decreasing the screening time and easier to read. Therefore LBC can be considered superior to conventional smear with respect to adequacy of smear, preservation of morphological feature clarity of background, detection of infective organisms like bacterial vaginosis, trichomonas vaginalis, Candida etc and dysplastic cells.

HPV SCREENING IN CERVICAL CANCER - PATHOLOGIST PERSPECTIVE

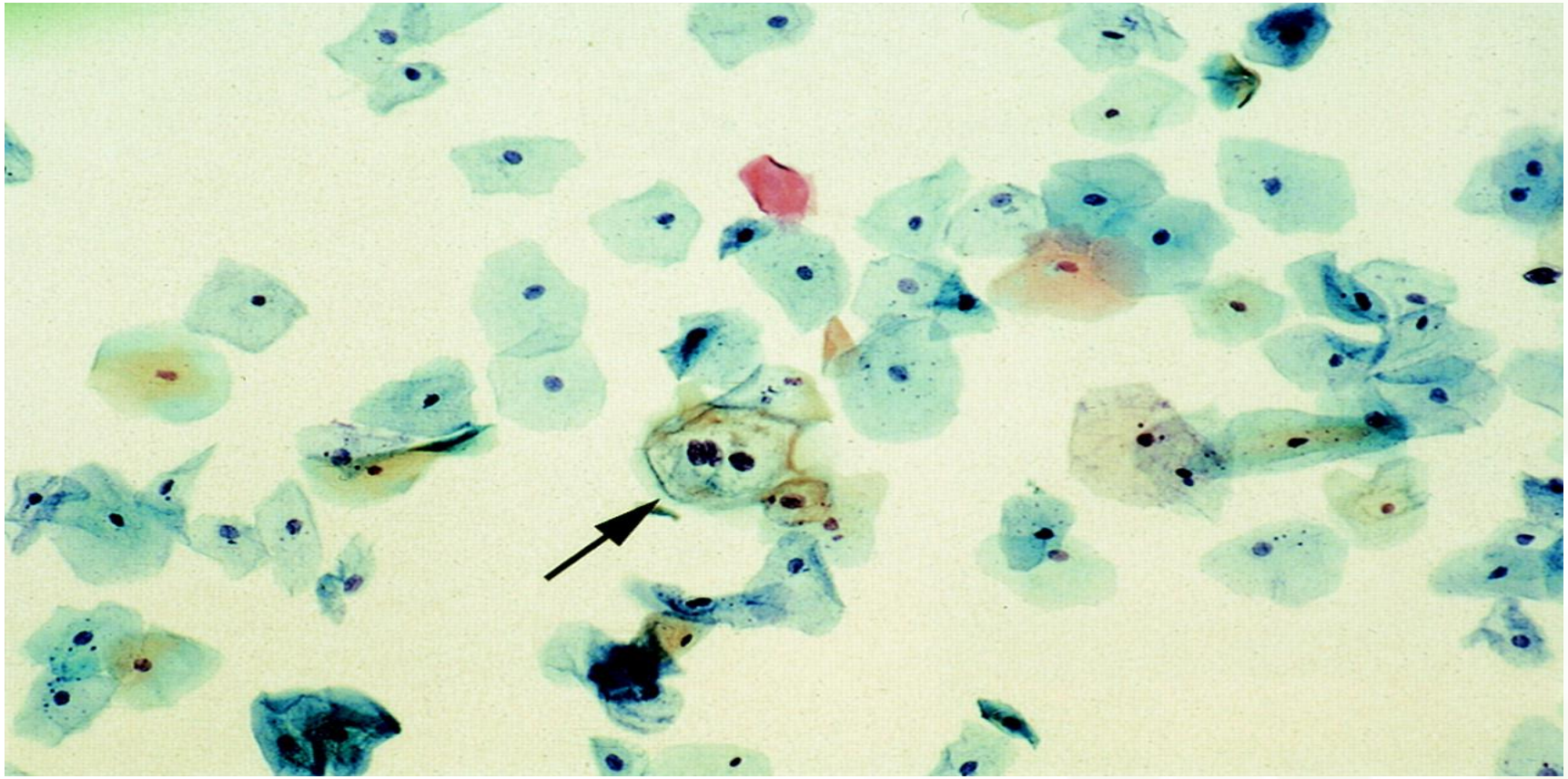


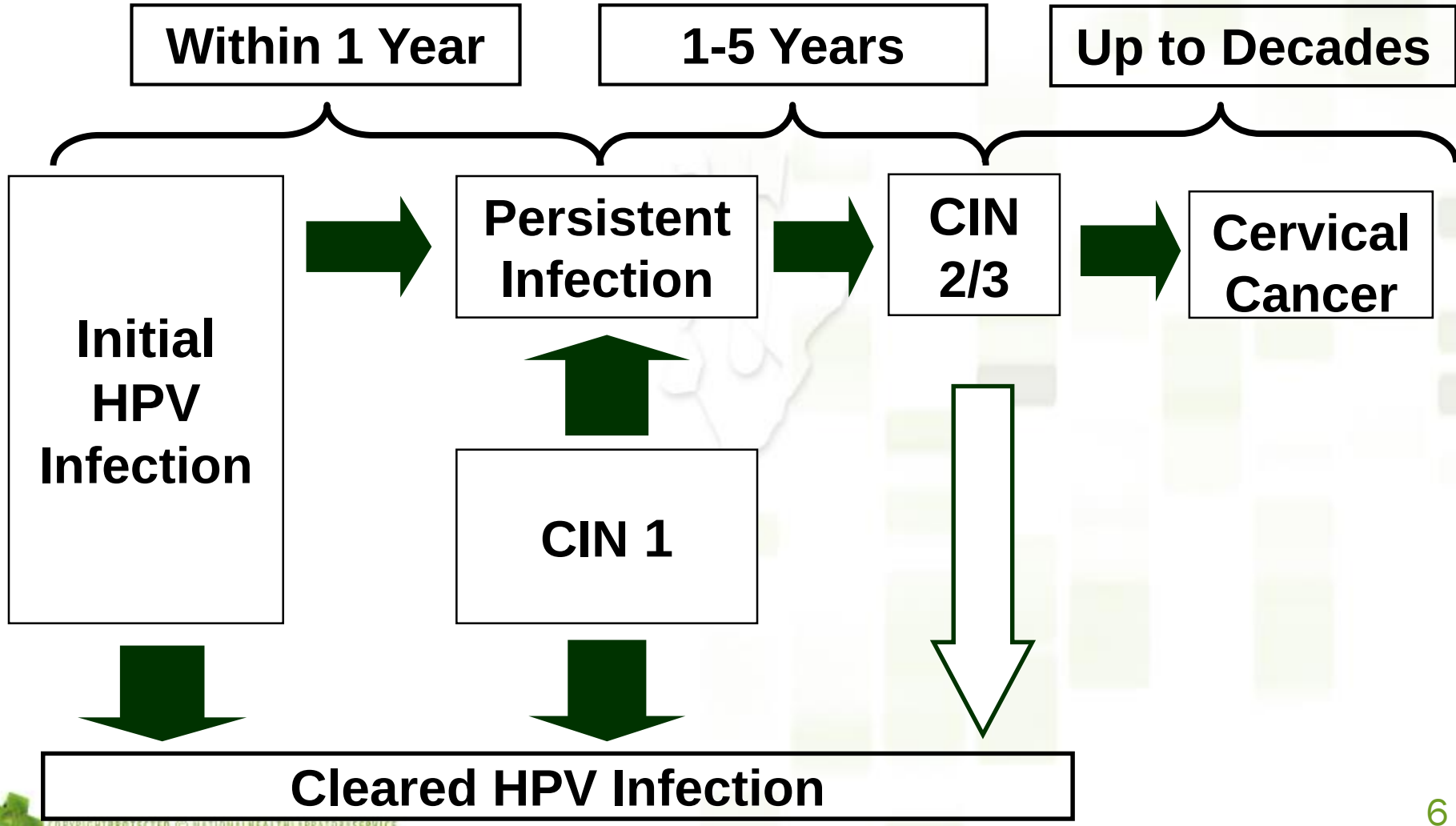
Fig 1: ThinPrep Pap Smear showing abnormal squamous cells with HPV cytopathic effect (arrow), consistent with LSIL.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

c. HPV SCREENING

NATURAL HISTORY OF HPV INFECTION



CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

c. HPV SCREENING

i. Molecular methods to detect HPV DNA sequences in clinical specimens.

• Type-specific PCR
- Based on the sequence variations present in the E6 and E7 genes of HPV subtypes.
- Internal control primers are included to detect inhibitory substances.
- The analytical sensitivity of these assays is between 10 and 200 HPV copies per sample.

• General primer PCR
- Consensus primers to amplify a broad spectrum of HPV types in a single PCR amplification.
- These primers target conserved regions of the HPV genome such as the L1 capsid gene.
- Less specific [failed to detect HPV DNA in 7% of cervical cancers in one study

ii. Detection methods:

-Sequence analysis
- Restriction fragment length polymorphism
-Hybridization with type-specific probes.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

c. HPV SCREENING

iii. Low-risk versus high-risk HPV types

• High-risk HPV types interferes with the function of cell proteins and also with the expression of cellular gene products. The genes that are down-regulated are primarily those involved in regulation of cell growth, some keratinocyte-specific genes, and interferon (IFN)-responsive genes.

• High-risk HPV types can be distinguished from other HPV types largely by the structure and function of the E6 and E7 gene products.

[In benign lesions caused by HPV, viral DNA is located extrachromosomally in the nucleus. In high-grade intraepithelial neoplasias and cancers, HPV DNA is generally integrated into the host genome]

[In some cases, episomal and integrated HPV DNAs are carried simultaneously in the host cell. Integration of HPV DNA specifically disrupts or deletes the E2 ORF, which results in loss of its expression This interferes with the function of E2, which normally down-regulates the transcription of the E6 and E7 genes and leads to an increased expression of E6 and E7]

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

c. HPV SCREENING

iii. Low-risk versus high-risk HPV types

- In high-risk HPV types, the E6 and E7 proteins have a high affinity for p53 and pRB. Binding disrupts the normal function of these cellular proteins and can give rise to an increased proliferation rate and genomic instability.

- As a consequence, the host cell accumulates more and more damaged DNA that cannot be repaired.

- Efficient immortalization of keratinocytes requires the cooperation of the E6 and E7 gene proteins; however, the E7 gene product alone at high levels can immortalize host cells.

- Eventually, mutations accumulate that lead to fully transformed cancerous cells.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

c. HPV SCREENING

iii. Low-risk versus high-risk HPV types

- In addition to the effects of activated oncogenes and chromosome instability, potential mechanisms contributing to transformation include:

- Methylation of viral and cellular DNA

- Telomerase activation

- Hormonal

- Immunogenetic factors.

N.B: Progression to cancer generally takes place over a period of 10 to 20 years. Some lesions become cancerous more rapidly, sometimes within a year or two.

COMMON HPV TYPES AND THEIR EFFECTS

HPV Types	Lead to:
Low-Risk: HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81	Benign cervical changes Genital warts
High-Risk: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82	Precancer cervical changes Cervical cancer Anal and other cancers

1. Cox. *Baillière's Clin Obstet Gynaecol.* 1995;9:1.
2. Munoz et al. *N Engl J Med*. 2003;348:518.

HPV SCREENING IN CERVICAL CANCER - PATHOLOGIST PERSPECTIVE

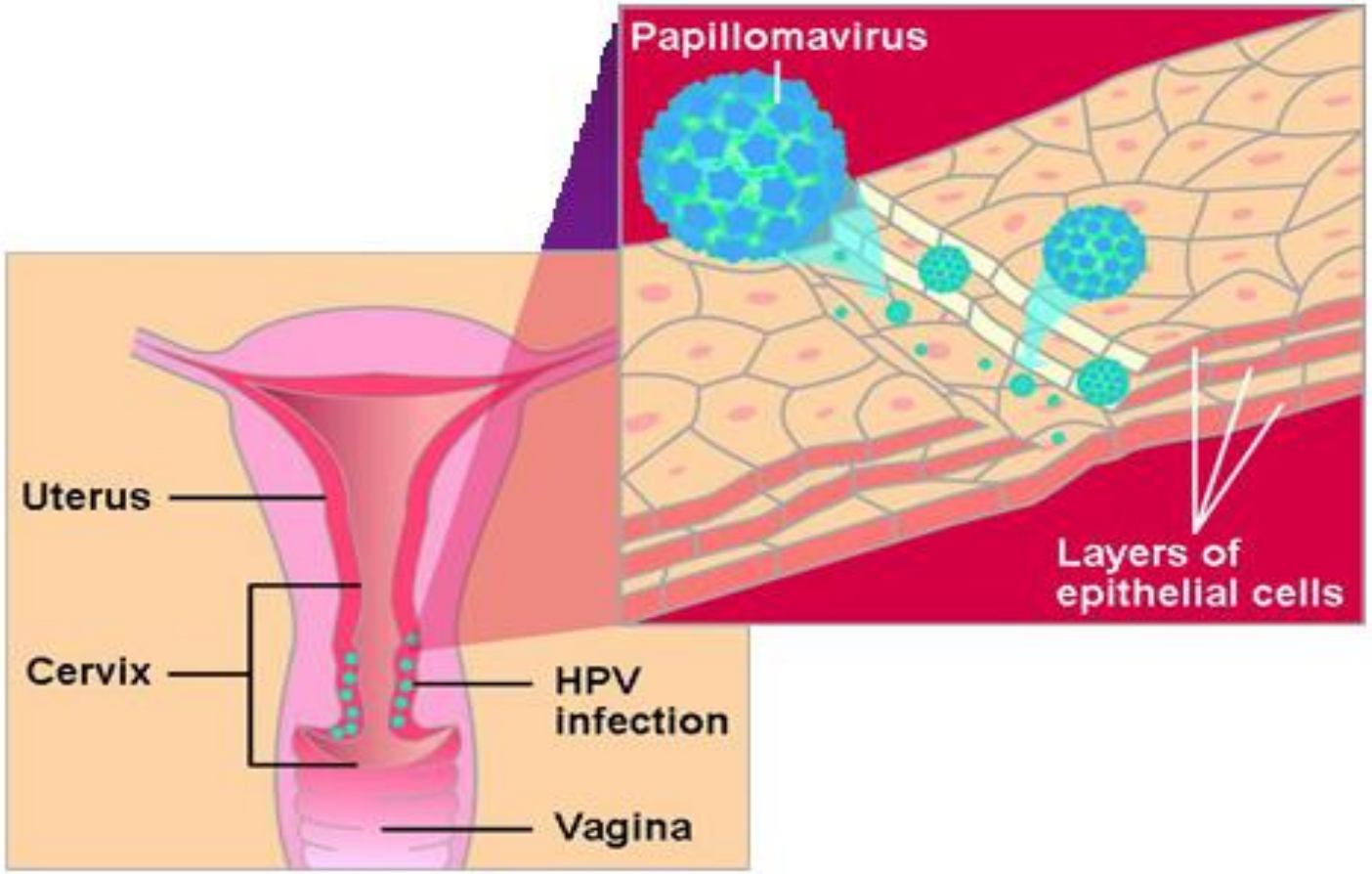
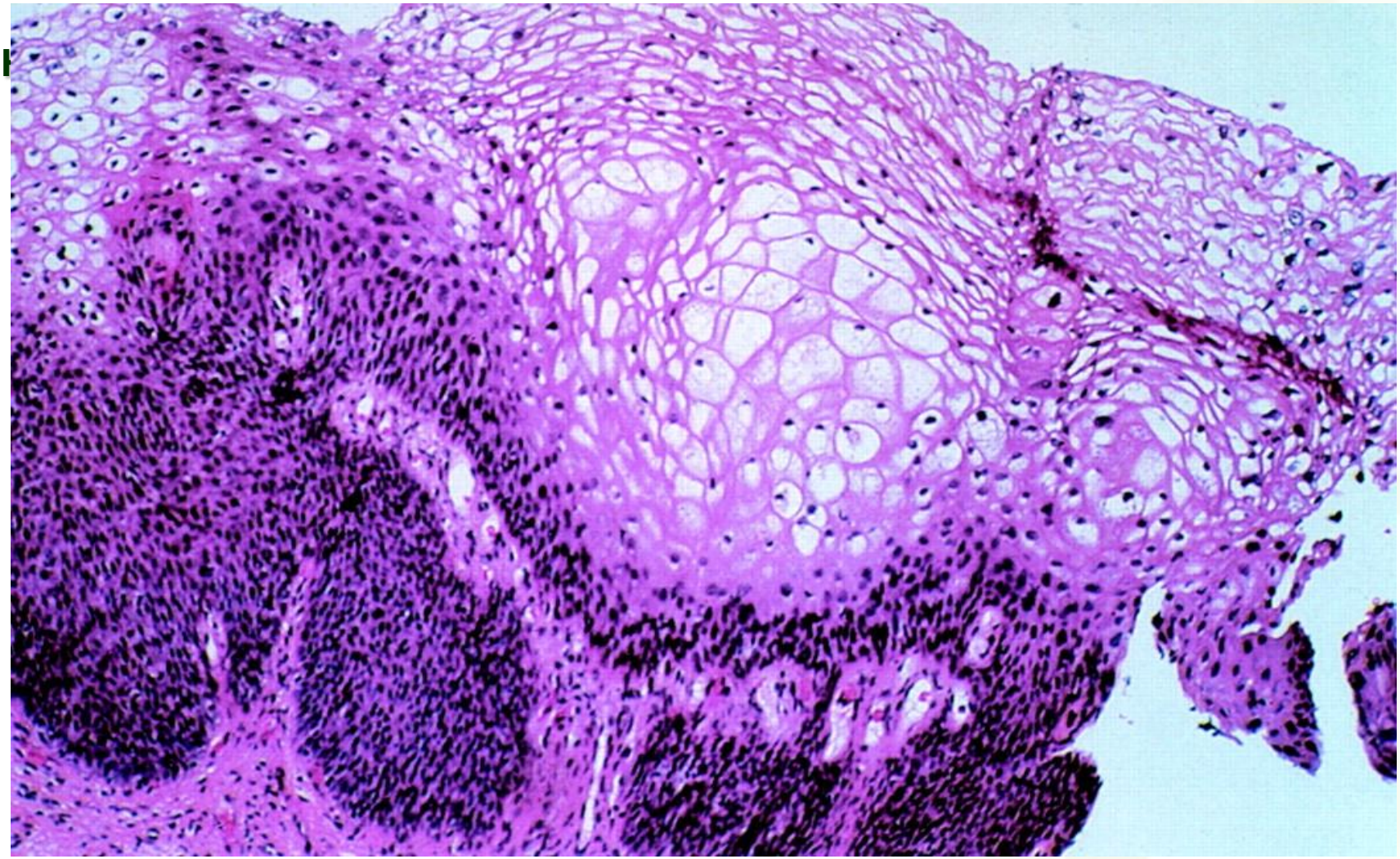


Figure 1: Target cells in the uterine cervix



Cervical condyloma showing proliferation of the suprabasal epithelial layers and koilocytic atypia, consisting of nuclear pyknosis and a well-defined perinuclear cavity associated with peripherally thickened cytoplasm.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

d. HISTOPATHOLOGY

*Abnormal Pap smear findings who do not have a gross cervical lesion are usually evaluated by colposcopy and colposcopy-directed biopsy.

• Following application of a 3% acetic acid solution, the cervix is examined with a bright filtered light under 10- to 15-fold magnification. [Acetowhitening and the vascular patterns characteristic of dysplasia or carcinoma can be seen]

• Colposcopy can detect low-grade and high-grade dysplasia but does not detect micro-invasive disease.

• If no abnormalities are found or if the entire squamocolumnar junction cannot be visualized, a cervical cone biopsy is done.

• Biopsy can be used to confirm most diagnoses by observing characteristic pathologic features of HPV infection such as epithelial hyperplasia (acanthosis) and degenerative cytoplasmic vacuolization

• (koilocytosis) in terminally differentiated keratinocytes with atypical nuclei.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

3. SCREENING MODALITIES

d. HISTOPATHOLOGY

• In addition, stains can be used which detect HPV antigens or HPV nucleic acids. Monoclonal and polyclonal antibodies are available that detect HPV common antigen, which is broadly expressed among the different HPV subtypes using immunocytohemistry.

• HPV DNA or RNA can be demonstrated in biopsy tissues by in situ hybridization with probes labeled with either radioisotopes or chemically reactive ligands which are detected by autoradiography, fluorescence, or a detection of color reaction.

• In situ methods can be nonamplified, target amplification by PCR, or signal amplified.

• Characteristics of the signal (confluent versus punctate) may reflect either the episomal or integrated form of the viral target DNA.

• Intensity of the signal may reflect copy number. Target-amplified or signal-amplified in situ techniques have been developed to immunoenzymatically detect a small number of HPV nucleic acid sequences with high sensitivity by using bright-field microscopy.

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

4. PRACTICE GUIDELINES OF SCREENING

- **Patient profile**
- **Age of patient**
- **Risk factors [sexual history; immune status (e.g. RVD)**

- **Previous screening results**
- **Smear results [CPS/LBC] : LSIL/HSIL**
- **HPV DNA [LR-HPV /HR-HPV]**

- **Repeat screening tests**
- **6 months/ 1year/2 years/5years**

CERVICAL CANCER SCREENING – PATHOLOGIST'S PERSPECTIVE

4. PRACTICE GUIDELINES OF SCREENING

a. First screen 3 years after first intercourse or by age 21

b. Screen annually with regular Paps or every 2 years with liquid-based tests

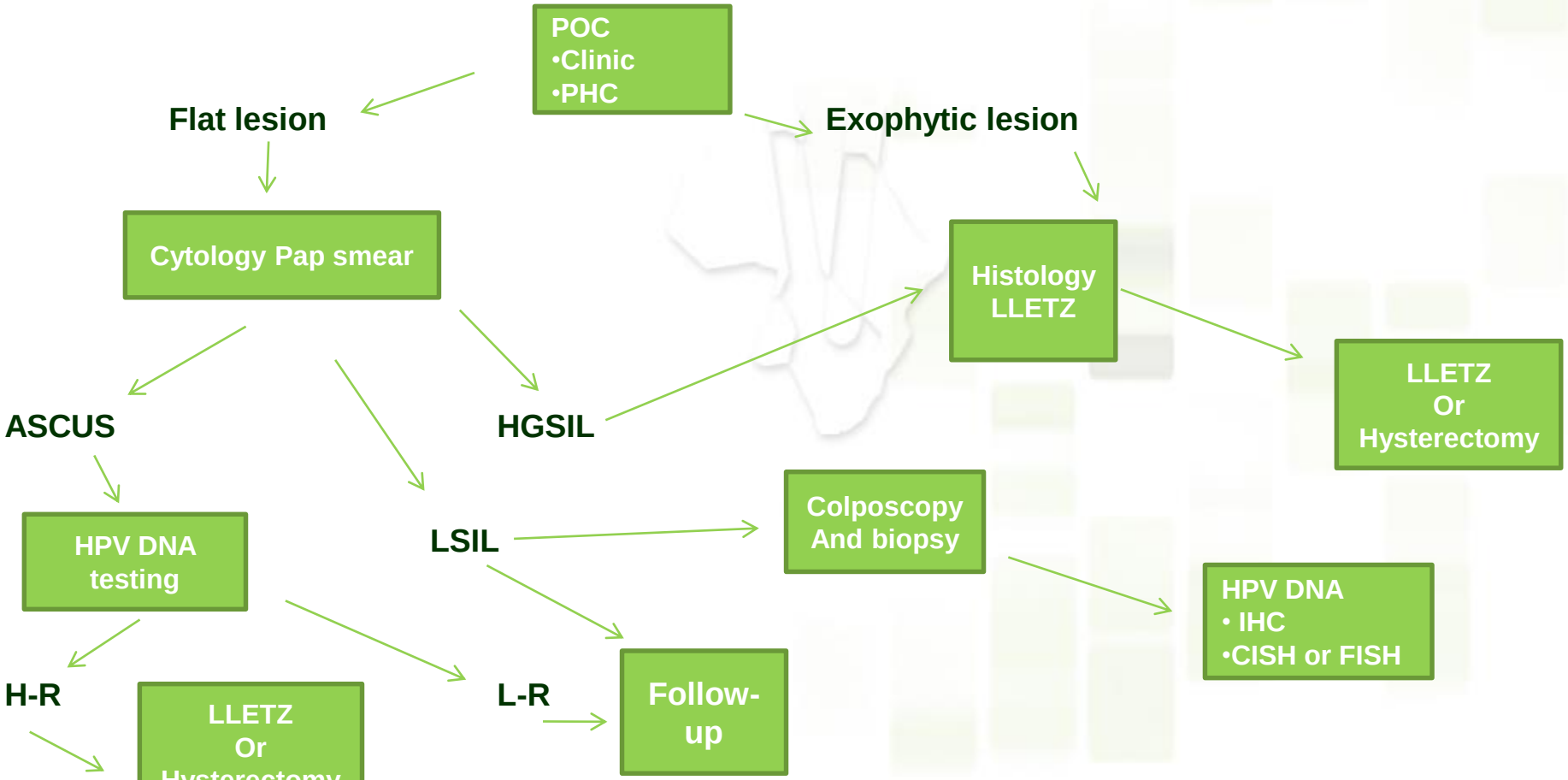
c. After three normal tests, can go to every three years

d. Stop at 65-70 years with history of negative tests

e. Still need annual check-ups

HPV SCREENING IN CERVICAL CANCER - PATHOLOGIST PERSPECTIVE

5. MULTIMODALITY LEVELS OF SCREENING - ALGORYTHMIC APPROACH



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ANATOMICAL PATHOLOGY

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Any questions?

HPV SCREENING IN CERVICAL CANCER - PATHOLOGIST PERSPECTIVE

HPV AND CERVICAL CANCER