CLINICAL APPLICATIONS OF HPV TESTING

A PRACTICAL LECTURE OUTLINE BASED ON ASCCP AND UPTODATE

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MAJOR CLINICAL ROLES

High-risk human papillomavirus (hrHPV) testing has evolved from a screening adjunct into a central tool for cervical cancer prevention.

Its **major clinical roles** include

1. primary screening,
2. triage,
3. risk stratification,
4. determination of the need for colposcopy,
5. post-colposcopy surveillance,
6. and post-treatment surveillance

WHY IS HPV TESTING CLINICALLY IMPORTANT?

. **Persistent infection** with oncogenic or high-risk HPV is the central causal factor in the development of the great majority of cervical cancers. HPV testing detects viral infection before or alongside the morphologic abnormalities identified by cytology.

A useful conceptual sequence is:

HPV infection → persistence → cervical precancer (CIN2/CIN3) → invasive cervical cancer

However, **HPV positivity is not equivalent to cervical precancer** or cervical cancer. Most HPV infections, particularly in younger individuals, are transient.

The principal clinical value of HPV testing is therefore **risk stratification**: identifying individuals at sufficiently increased risk of CIN3+ to require additional evaluation or surveillance.

WHAT DOES AN HPV TEST DETECT?

. In cervical cancer prevention, HPV testing refers to **testing for high-risk (oncogenic)** HPV types rather than low-risk types associated primarily with genital warts.

Clinically important oncogenic types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

These types do not carry identical risks. **HPV16** has the strongest association with cervical precancer and cancer, while **HPV18** is particularly important because of its association with cervical cancer, including glandular disease.

Modern HPV assays may provide partial or extended genotyping, allowing more precise risk stratification than a simple positive/negative result.

PRIMARY HPV SCREENING

High-risk HPV testing can be used as the primary cervical cancer screening test. In primary HPV screening, HPV testing is performed first rather than using cytology as the initial screening test.

A negative validated hrHPV test is highly reassuring and is associated with a very low short-term risk of CIN3+.

A **positive result does not diagnose cancer**; instead, it triggers appropriate triage based on genotype, cytology, other validated biomarkers when applicable, and the patient's previous history.

CO-TESTING

Co-testing refers to performing **hrHPV testing and cervical cytology together**. The combination provides information about both the presence of oncogenic HPV and cytologic abnormalities.

For example, **HPV-negative/NILM represents a very low-risk situation,** whereas HPV positivity combined with abnormal cytology may substantially increase the estimated risk of CIN3+.

Current management should not be based on one isolated result alone when prior screening, colposcopy, histology, or treatment history is available.

REFLEX HPV TESTING FOR ASC-US

One of the classic clinical applications of HPV testing is triage of ASC-US cytology. **Reflex hrHPV testing helps distinguish individuals with ASC-US who have a higher likelihood of clinically significant cervical disease** from those at sufficiently low risk to avoid immediate colposcopy.

Management after ASC-US is determined by the HPV result together with age and relevant screening history, according to the applicable risk-based guideline.

TRIAGE OF A POSITIVE PRIMARY HPV TEST

A positive primary HPV test requires further risk assessment rather than automatic treatment.

Depending on the assay and clinical setting, triage may include HPV genotyping, reflex cytology, and selected validated biomarkers such as p16/Ki-67 dual-stain testing.

The clinical question is not simply, “Is HPV present?” but rather,

“What is this patient's current risk of CIN3+, and what action is appropriate for that risk?”

HPV GENOTYPING

HPV genotyping improves risk stratification because oncogenic HPV types do not confer equal risk.

Traditional **partial genotyping commonly distinguishes HPV16 and HPV18** from other high-risk types. Newer assays can provide extended genotyping.

Extended genotyping can further separate high-risk HPV types or groups according to their **different associations with CIN3+** and can therefore refine decisions regarding triage, surveillance, and colposcopy

HPV TESTING IN RISK-BASED MANAGEMENT

A central concept of the ASCCP framework is **risk-based** rather than purely result-based management. The same current HPV result may lead to different management in two patients because their previous histories differ.

Risk estimation may incorporate:

- **Current HPV result and genotype**
- **Current cytology**
- **Previous HPV and cytology results**
- **Previous colposcopy and biopsy findings**
- **Previous treatment for cervical precancer**

Management is then selected according to the estimated risk of CIN3+ and the relevant clinical action threshold

DETERMINING THE NEED FOR COLPOSCOPY

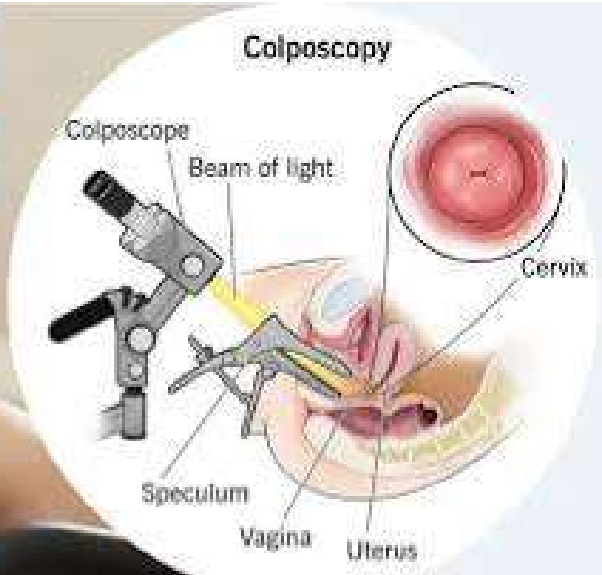
HPV testing is an important determinant of whether a patient can

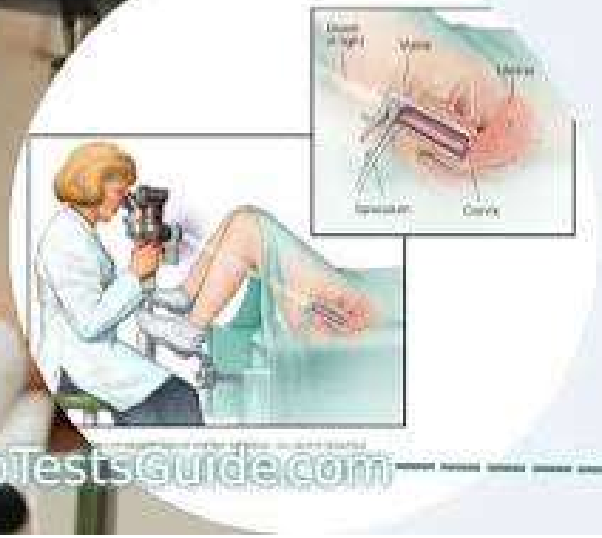
- return to screening,
- requires repeat HPV-based testing,
- should undergo colposcopy, or
- in selected very high-risk circumstances—may qualify for **expedited treatment.**

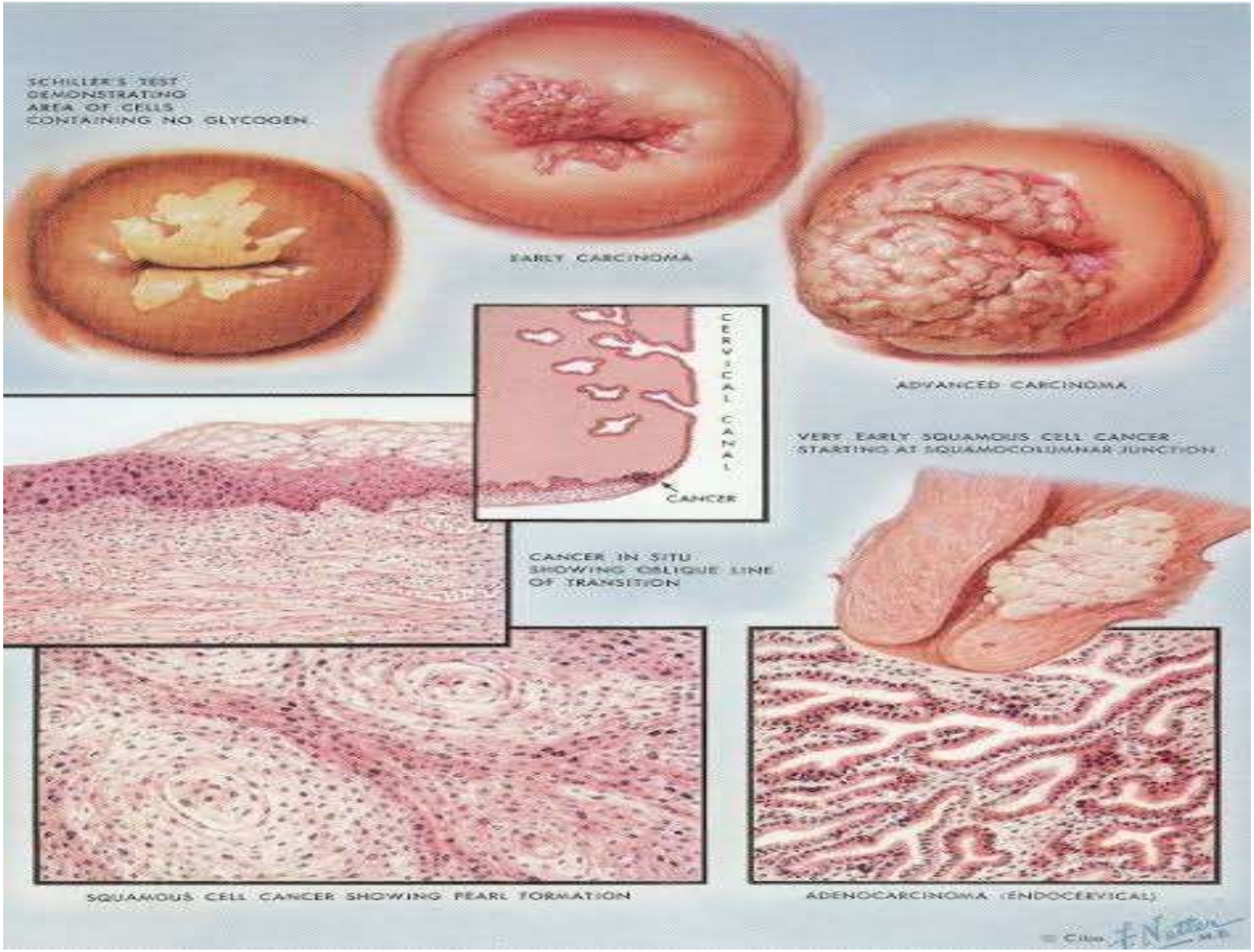
Thus, **HPV testing should be understood as a powerful risk-stratification tool** rather than a diagnostic test for cervical cancer.

Colposcopy

Conditions: Causes, Diagnosis, Treatment, and Support



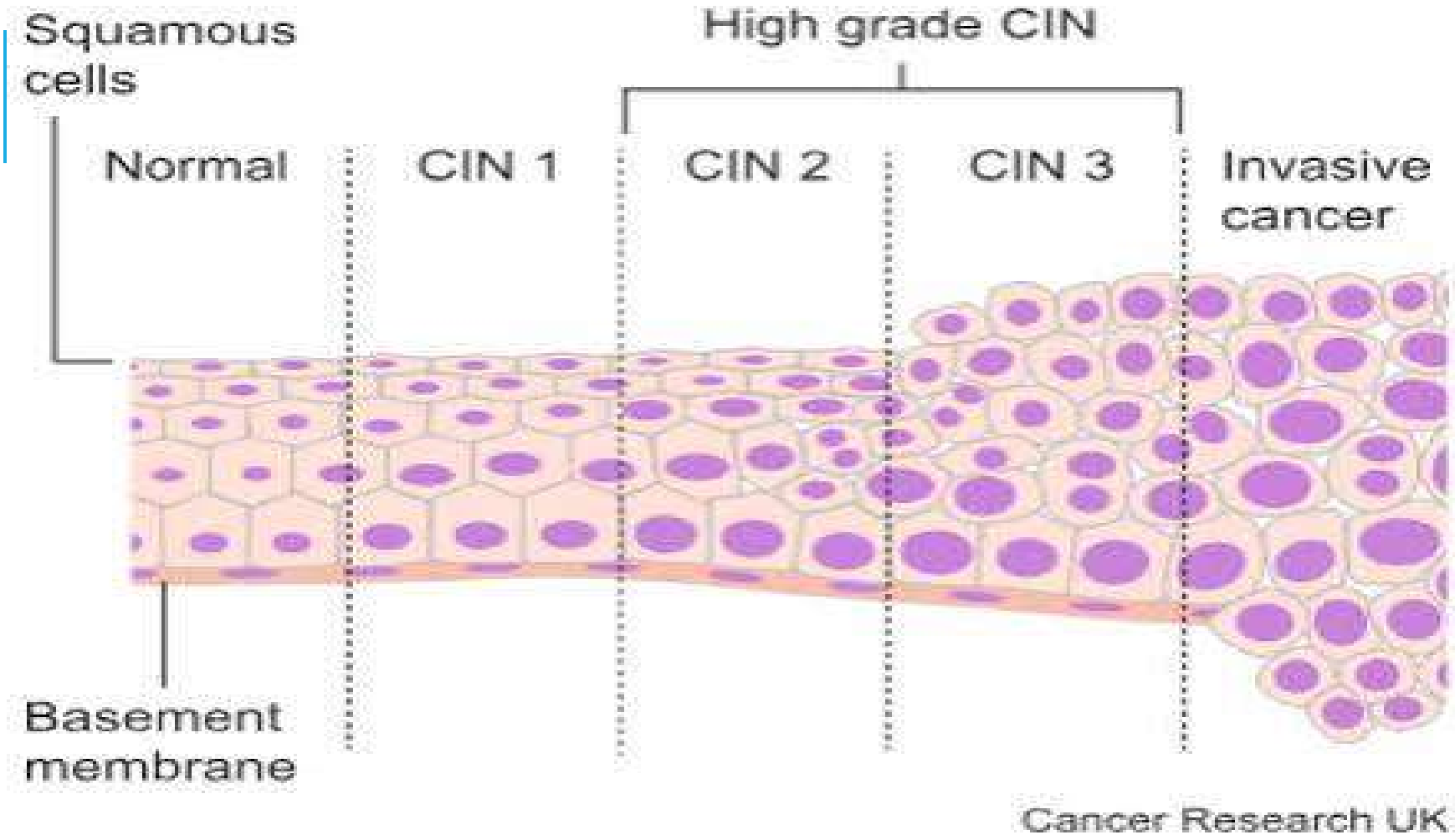



SCHILLER'S TEST DEMONSTRATING AREA OF CELLS CONTAINING NO GLYCOGEN
EARLY CARCINOMA
ADVANCED CARCINOMA
CERVICAL CANAL
CANCER
VERY EARLY SQUAMOUS CELL CANCER STARTING AT SQUAMOCOLUMNAR JUNCTION
CANCER IN SITU SHOWING OBLIQUE LINE OF TRANSITION
SQUAMOUS CELL CANCER SHOWING PEARL FORMATION
ADENOCARCINOMA (ENDOCERVICAL)

POST-COLPOSCOPY SURVEILLANCE

HPV testing remains clinically important after colposcopy. For example, when a patient undergoes colposcopy after an abnormal screening result and histology shows less than CIN2, subsequent HPV-based testing helps determine whether risk has fallen sufficiently to extend the surveillance interval or whether repeat evaluation is required.

This is one reason that a patient's prior colposcopy and histology must be considered when interpreting a new HPV result.


Squamous cells
High grade CIN
Normal
CIN 1
CIN 2
CIN 3
Invasive cancer
Basement membrane
Cancer Research UK

CHA UNIVERSITY
FERTILITY CENTER GANGNAM

BeautyTrip

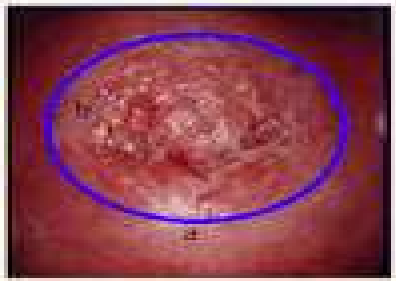
CIN IS CLASSIFIED INTO THREE LEVELS

CIN 1

Mild abnormal cells, which may resolve on their own without treatment

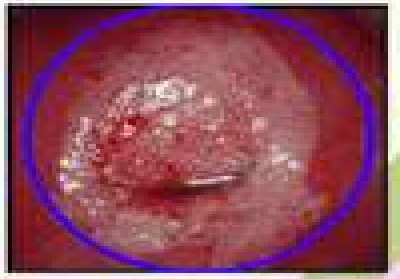
CIN 2

Moderate abnormal cells, which may require treatment



CIN 3

Severe abnormal cells, which can progress to cervical cancer if not treated



Hotline/ whatsapp : 010 5073 1606

POST-TREATMENT SURVEILLANCE OF CERVICAL PRECANCER

HPV-based testing is a key component of surveillance after treatment of histologic HSIL (CIN2/CIN3). Persistent hrHPV after treatment is associated with an increased risk of residual or recurrent high-grade disease, while a negative HPV-based test is strongly reassuring.

Therefore, HPV testing has an important role not only in screening but also in assessing risk after excisional or ablative treatment

Long-Term Surveillance After CIN2/CIN3 or AIS

. Patients treated for high-grade cervical precancer remain at increased risk for many years.

ASCCP recommends prolonged HPV-based surveillance after treatment of histologic HSIL (CIN2/CIN3) or AIS.

Long-term **surveillance continues for at least 25 years after treatment,** even if this extends beyond the age at which routine screening would otherwise stop.

Treatment of CIN3 does not immediately return a patient to the same risk level as the general screening population.

HPV TESTING AFTER HYSTERECTOMY

. Routine vaginal HPV testing is generally not recommended after total hysterectomy performed for benign disease in an individual without a relevant history of high-grade cervical precancer or cervical cancer.

In contrast**, patients with a history of cervical precancer may still require prolonged surveillance after hysterectomy** according to their treatment history and guideline-defined surveillance pathway.

HPV Testing Is Not a General STI Test

A positive HPV test should **not** be interpreted as a forensic marker of sexual transmission. HPV testing cannot reliably determine:

- **When** the infection was acquired
- **Which** partner transmitted the infection
- Whether the infection represents a **recent** sexual exposure
- The **exact source** of infection
- The individual's **current degree of infectiousness**

A positive cervical hrHPV test is primarily a marker used for **cervical cancer risk** assessment.

HPV TESTING IN MEN

Routine HPV testing of **asymptomatic male partners** of HPV-positive women is **not** recommended.

There is no routine, validated HPV screening program for asymptomatic men analogous to cervical HPV screening.

Therefore, **a positive HPV result in a woman does not, by itself, create an indication for HPV testing of her male partner**.

HPV Testing for Genital Warts

Genital warts (condyloma acuminata) are usually **diagnosed clinically.**

Routine HPV testing is **not recommended** to confirm the diagnosis of typical anogenital warts.

Furthermore, cervical hrHPV assays are designed for oncogenic HPV detection and cervical cancer risk assessment, **not for diagnosing the low-risk HPV types** responsible for most genital warts.

. SELF-COLLECTED HPV TESTING

Self-collected vaginal specimens for HPV testing are an important recent development in cervical cancer screening.

In appropriate settings and with validated assays, self-collection can increase access to screening, particularly for individuals who are underscreened or who face barriers to clinician-collected cervical sampling.

Management of a positive self-collected HPV result depends on the assay, genotype, and the subsequent triage pathway recommended by current guidance

HPV16/18 VERSUS OTHER HIGH-RISK HPV TYPES

An HPV-positive result is not a homogeneous risk category. HPV16 carries particularly high risk, and HPV18 also has special clinical importance. Other oncogenic HPV types confer variable levels of risk.

This biological and epidemiologic heterogeneity is the rationale for partial and extended HPV genotyping and for genotype-informed risk stratification.

Persistence Is More Important Than a Single Positive Test

. Transient HPV infection is common. Persistent infection with a high-risk HPV type is much more clinically important because persistence is a major prerequisite for the development of cervical precancer and cancer.

Therefore, interpretation of HPV testing should consider persistence, genotype, cytology, and previous screening or histologic history rather than treating every isolated positive result as equivalent

. Do We Need to Test for Low-Risk HPV Types?

No. Routine testing for low-risk HPV types is not recommended for cervical cancer screening, triage, or surveillance.

Low-risk types such as HPV6 and HPV11 cause the majority of anogenital warts but are not the oncogenic HPV types targeted by cervical cancer screening programs. Identifying these low-risk types generally does not alter cervical cancer prevention management.

Typical genital warts are primarily a clinical diagnosis, and HPV testing is not recommended simply to confirm that a lesion is caused by HPV6 or HPV11.

Importantly, HPV genotyping in cervical cancer prevention should not be confused with low-risk HPV testing. When guidelines discuss partial or extended genotyping, the purpose is to distinguish clinically relevant high-risk HPV genotypes for risk stratification—not to screen for HPV6/11.

Key message: Low-risk HPV testing has no role in routine cervical cancer screening, triage, or surveillance

Summary: Major Clinical Applications

. The major clinical applications of HPV testing are:

1. Primary cervical cancer screening
2. Co-testing with cervical cytology
3. Triage of ASC-US cytology
4. Triage of a positive primary HPV test
5. Partial or extended high-risk HPV genotyping
6. Risk stratification for CIN3+
7. Determining the need for colposcopy
8. Post-colposcopy surveillance
9. Post-treatment surveillance after CIN2/CIN3 or AIS
10. Long-term surveillance after treatment
11. Selected use of validated self-collected HPV testing

Low-risk HPV testing is not part of routine cervical cancer screening.

TAKE-HOME MESSAGES

- HPV testing has evolved from a simple screening test into a central tool for risk stratification throughout the continuum of cervical cancer prevention—from primary screening to post-treatment surveillance.
- A positive HPV test does not mean that the patient has cervical cancer or even cervical precancer.
- Persistent high-risk HPV infection is more clinically important than a single transient positive result.
- Genotype matters: HPV16, HPV18, and other oncogenic genotypes do not carry identical risks.
- The key principle of modern management is:
- “We do not treat an HPV test result; we manage the patient's risk of CIN3+.”
- Routine testing for low-risk HPV types such as HPV6 and HPV11 is not recommended for cervical cancer screening, triage, or surveillance.