HPV and cervical cancer screening

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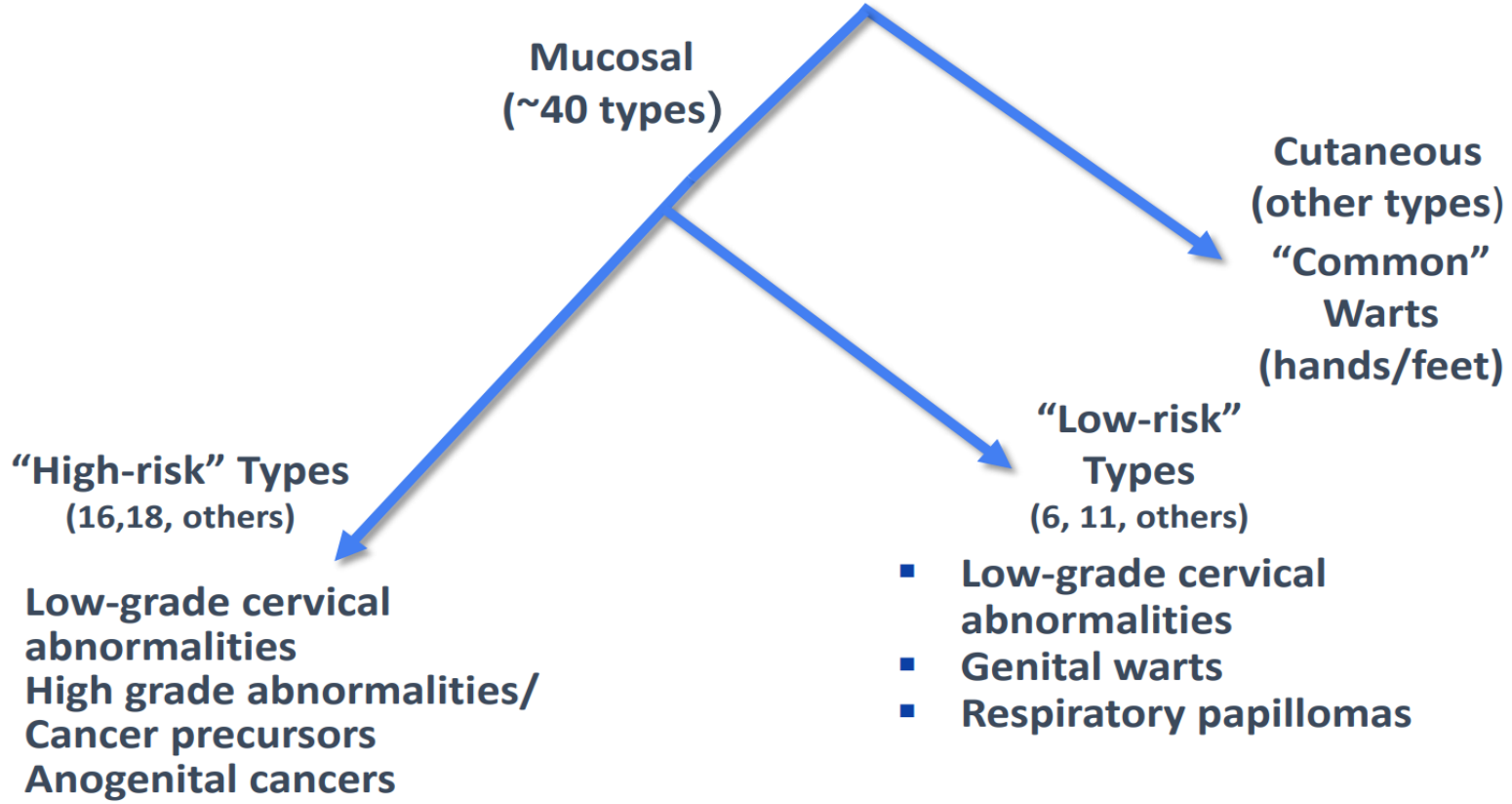
آزمایشگاه راز

پاتوبیولوژی و مولکولار

- Human Papillomavirus (HPV) Disease
- Most common sexually transmitted infection in the U.S.
- Small DNA virus
- More than 150 types

Human Papillomavirus Type and Disease Association



HPV

Two categories of genital HPV infection

- **High-risk** or oncogenic (cancer causing)
  - Cervical dysplasia (“abnormal cells”) and cervical cancer
  - Other types of cancer: penile, anal, vaginal, vulvar, oral,

- **Low-risk** or non-oncogenic (not cancer causing)
  - Condylomata Acuminata **(**Genital warts)
  - HPV types **6, 11**

High risk HPV

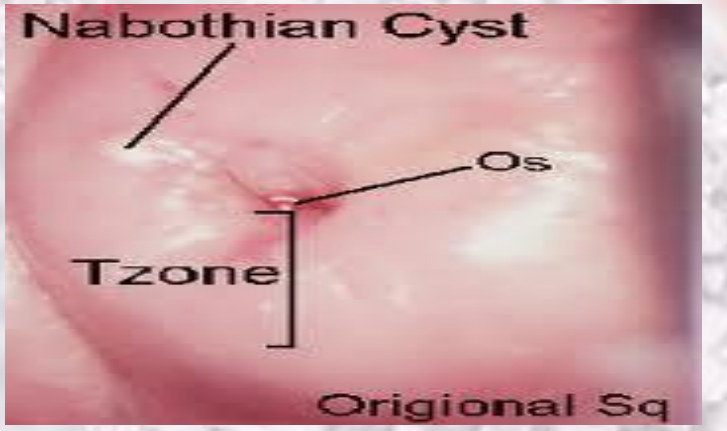
- **Twelve** HPVs (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) are defined by the World Health Organization (WHO) as being high-risk cancer causing types
-
- Additional types (**68, 73**)being recognized as ‘possiblly’ cancer-causing
- several other HPV types also belong to the high-risk clade based on evolutionary similarity to the known cancer-causing types

Cervix

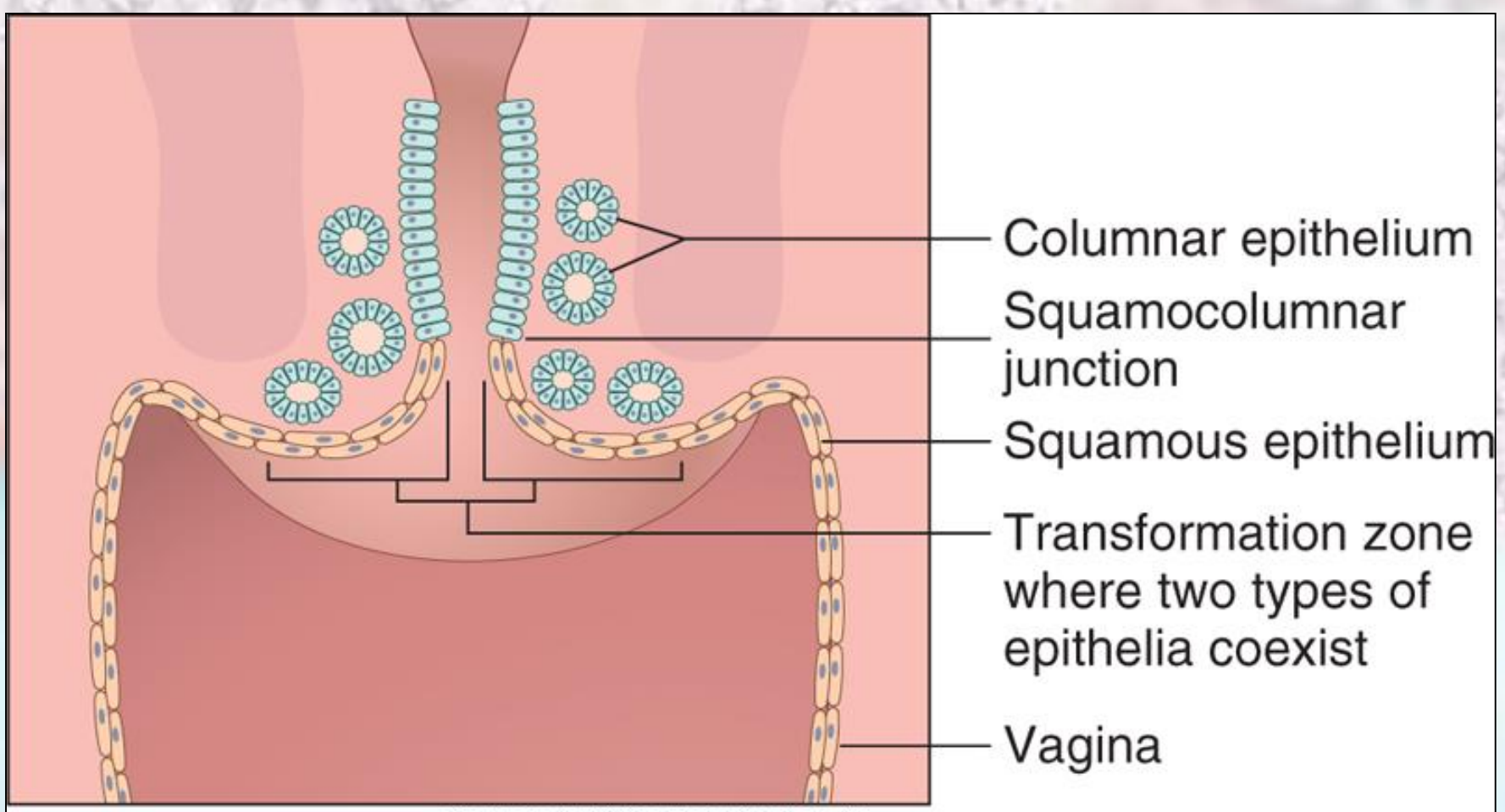
- The cervix is a tubular structure.
- It is composed of stromal tissue which is lined by sequamous epithelium in the vagina (ectocervix) and columnar epithelium within the cervical canal (endocervix).
- The meeting of the two types of the epithelium is called squamocolumnar junction SCJ and this is usually at the ectocervix.

Transformation zone:

- Is an important area on the cervix which is defined as the area where the original SCJ was to the current SCJ and it includes areas of metaplasia.
- The transformation zone TZ is the site where pre-malignancy and malignancy develop.



Cervical Transformation Zone



Kumar et al: Robbins Basic Pathology, 9e.
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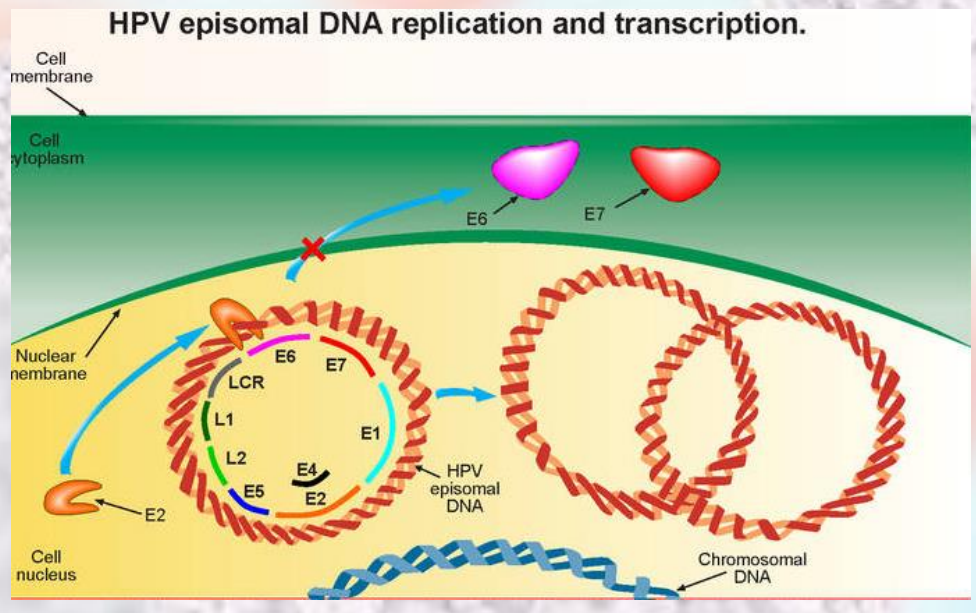
Neoplasm of The Cervix

- **Most tumors : Epithelial origin**
- **Caused by oncogenic strains of HPV**

Human papillomavirus interacts with squamous epithelium in 2 basic way:

- In the first, the squamous epithelium supports virion production but lesions are transient (low risk HPV)
- Grade 1 Intra- Epithelial Neoplasia
- Condyloma



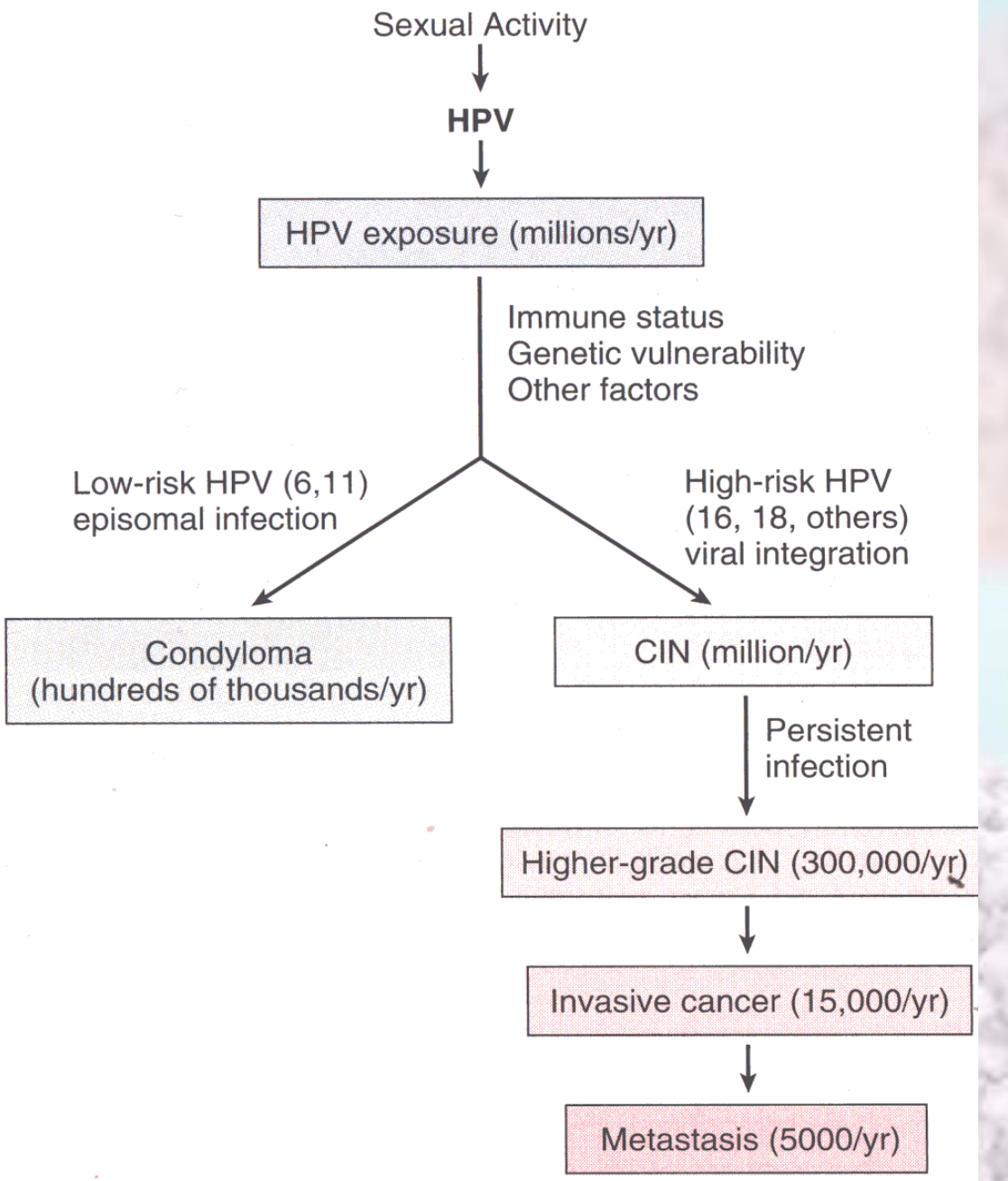
Human papillomavirus interacts with squamous epithelium in 2 basic way:

- The second **lesions** → precancerous (high risk HPV)

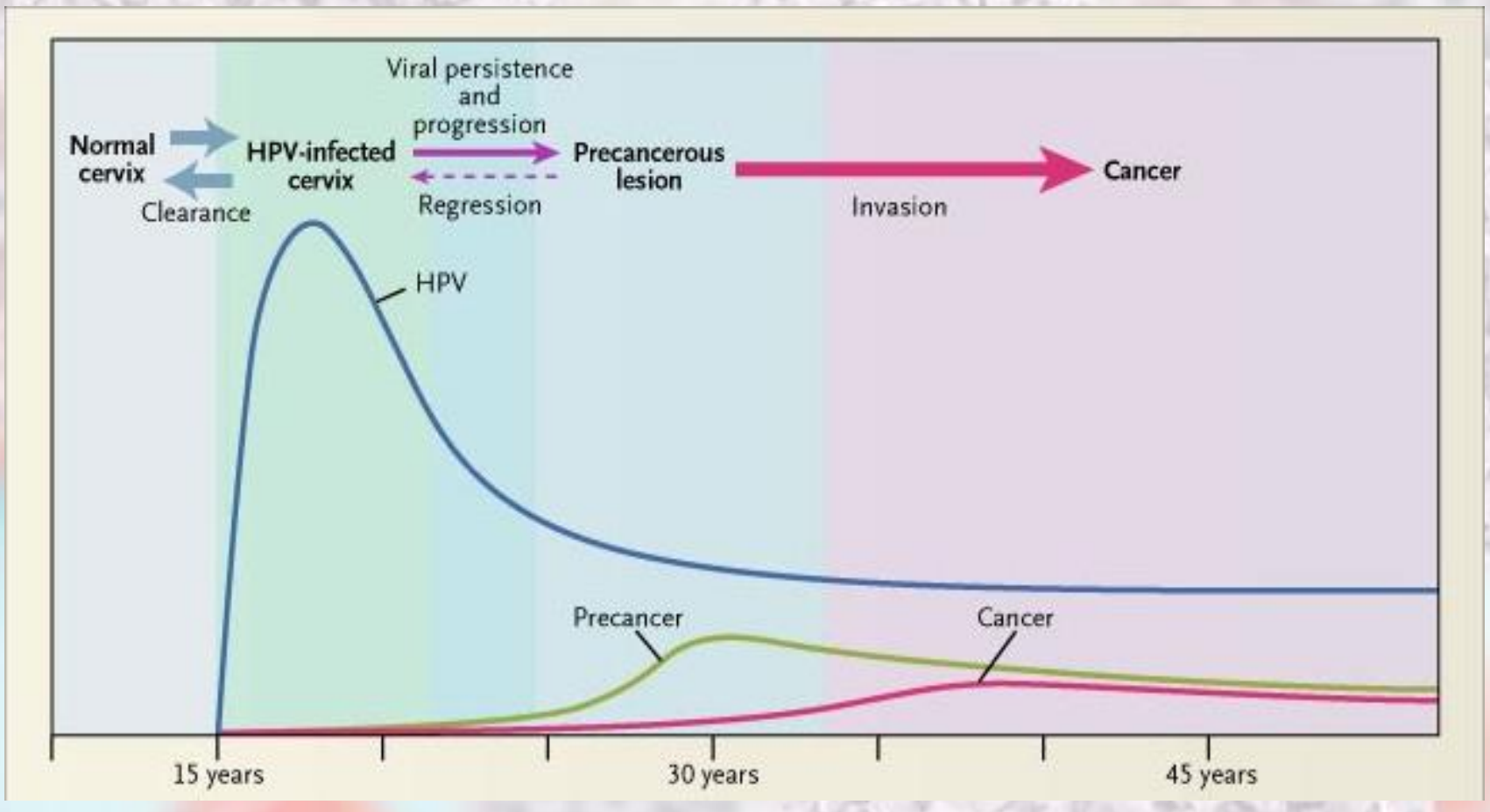
Viral DNA Integrate into the host genome which the coordinate control between viral gene expression and epithelial differentiation is broken and over time , a substantial risk of malignant transformation.

Pathogenesis

- Many women harbor these viruses, only a few develop cancer, suggesting other influences on cancer risk.
- **Well-defined risk factors:**
  - Cigarette smoking
  - Exogenous or endogenous immunodeficiency
    - HIV positive women
  - Somatically acquired mutations in the tumor suppressor gene *LKB I (liver kinase B1*)

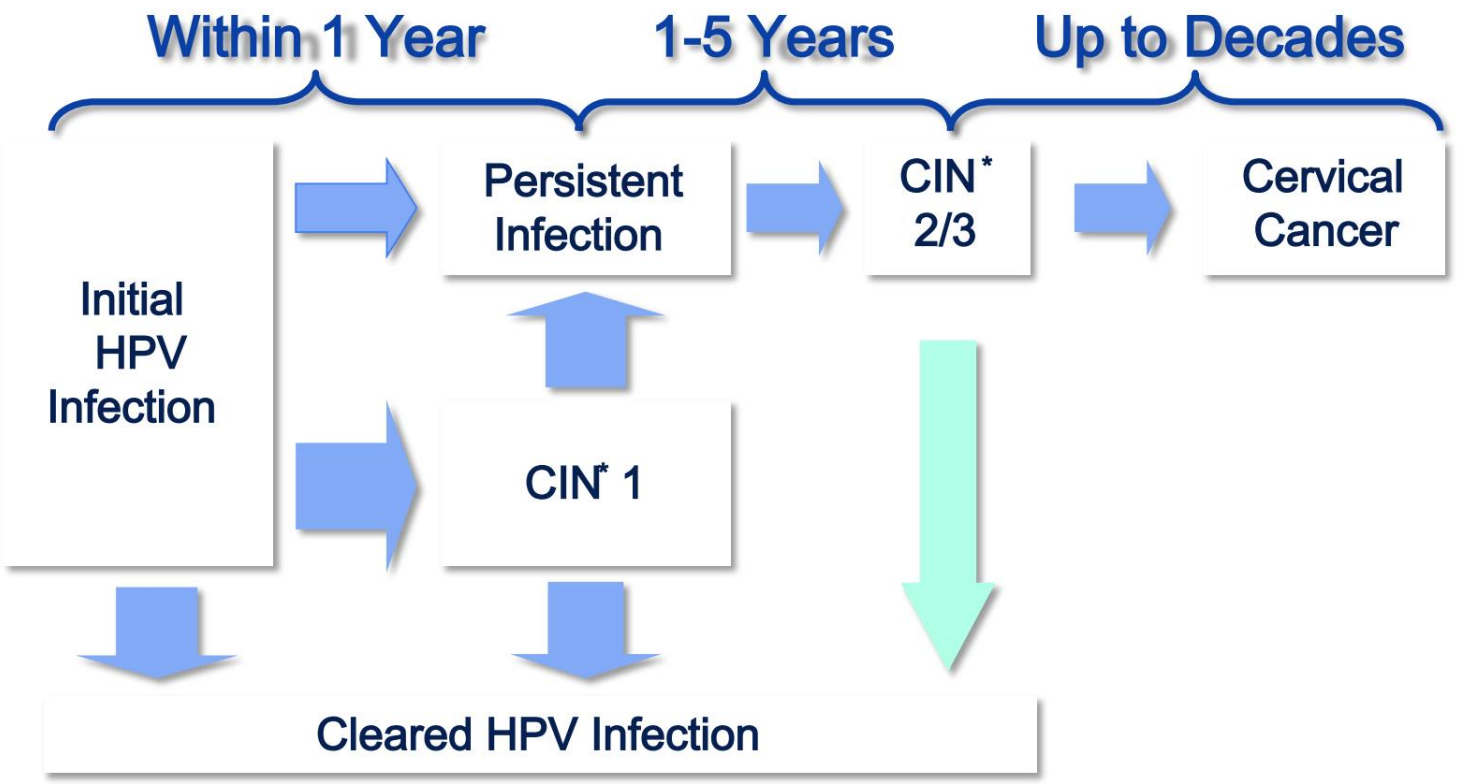

Sexual Activity
HPV
HPV exposure (millions/yr)
Immune status
Genetic vulnerability
Other factors
Low-risk HPV (6,11)
episomal infection
High-risk HPV
(16, 18, others)
viral integration
Condyloma
(hundreds of thousands/yr)
CIN (million/yr)
Persistent
infection
Higher-grade CIN (300,000/yr)
Invasive cancer (15,000/yr)
Metastasis (5000/yr)

Natural history of HPV infection



Schiffman M, Castle P. N Engl J Med 2005, 353:2101-2104

Natural History of HPV Infection



*CIN = cervical intraepithelial neoplasia

Cervical Intraepithelial Neoplasia And Squamous Cell Carcinoma

- **Most (perhaps all) invasive cervical squamous cell carcinomas arise from precursor epithelial changes referred to as CIN**
- **Not all cases of CIN progress to invasive cancer**

Cervical Intraepithelial Neoplasia

- **The incidence of precursor cervical intraepithelial neoplasia (CIN) has increased, attributable to better case finding.**

Cervical Intraepithelial Neoplasia

The grading of CIN is based on expansion of the atypical cells from basal layer

- **Graded as follows:**
  - **CIN I :mild dysplasia**
  - **CIN II :moderate dysplasia**
  - **CIN III :severe dysplasia and carcinoma in situ**

Classification of CIN

A revised classification has been introduced:

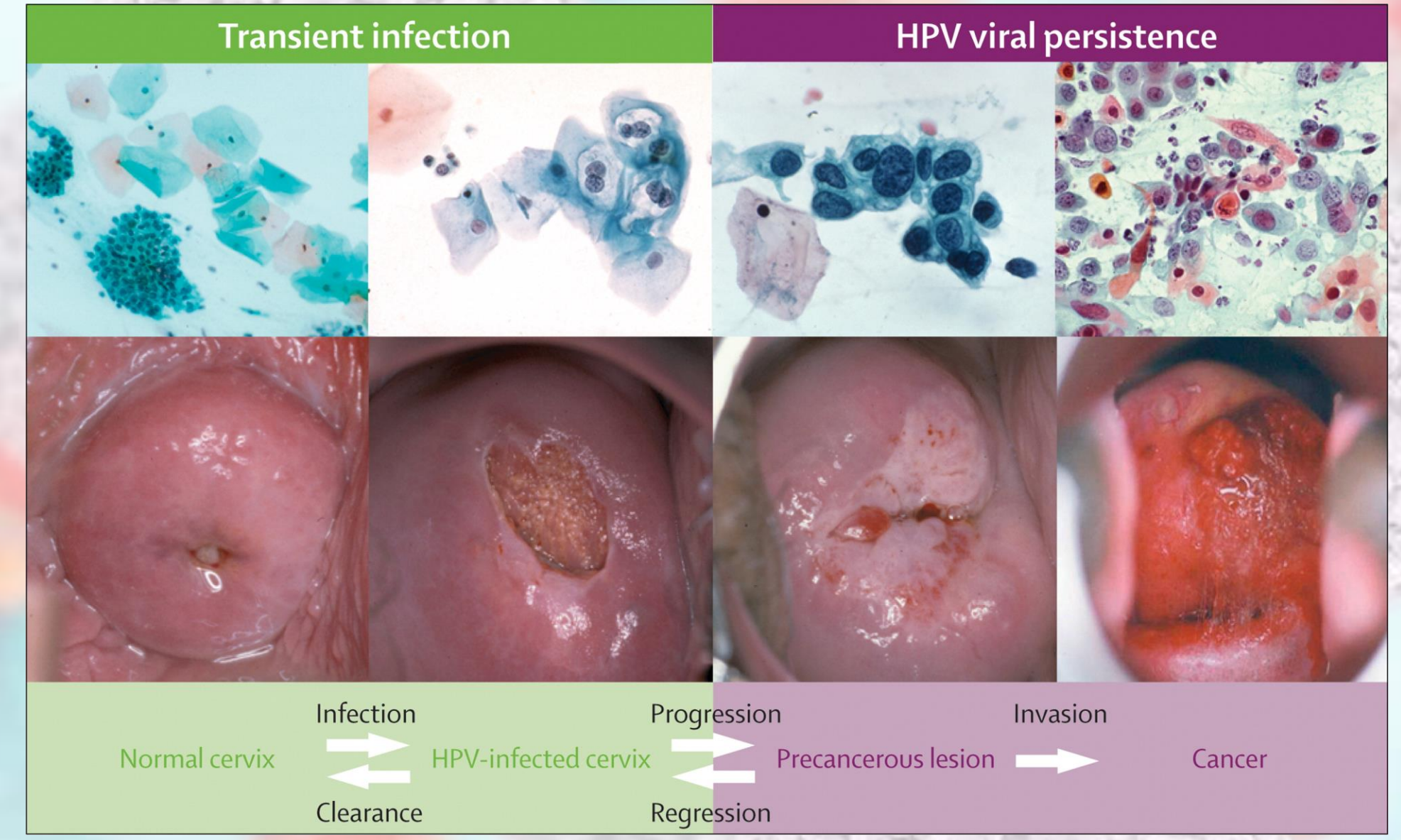
- **Low – grade squamous intraepithelial lesion :** CIN I and HPV associated changes with unknown but a likely low progressive potential.
- **High-grade squamous intraepithelial lesion :** CIN II and CIN III that is likely to behave as cancer precursors.

Simpler classification is according to Bethesda divided to:

- Low grade squamous intraepithelial lesion (LSIL) = CIN I.
- High grade squamous intraepithelial lesion (HSIL) = CIN II and CIN III

Current Options for Cervical Cancer Screening

- A: Cytology-only
- B: HPV-based screening
- C: HPV and cytology co-testing


Transient infection
HPV viral persistence
Infection
Progression
Invasion
Normal cervix
HPV-infected cervix
Precancerous lesion
Cancer
Clearance
Regression

Applications of *hr* HPV Testing

Applications of High-Risk Human Papillomavirus Testing (hrHPV)

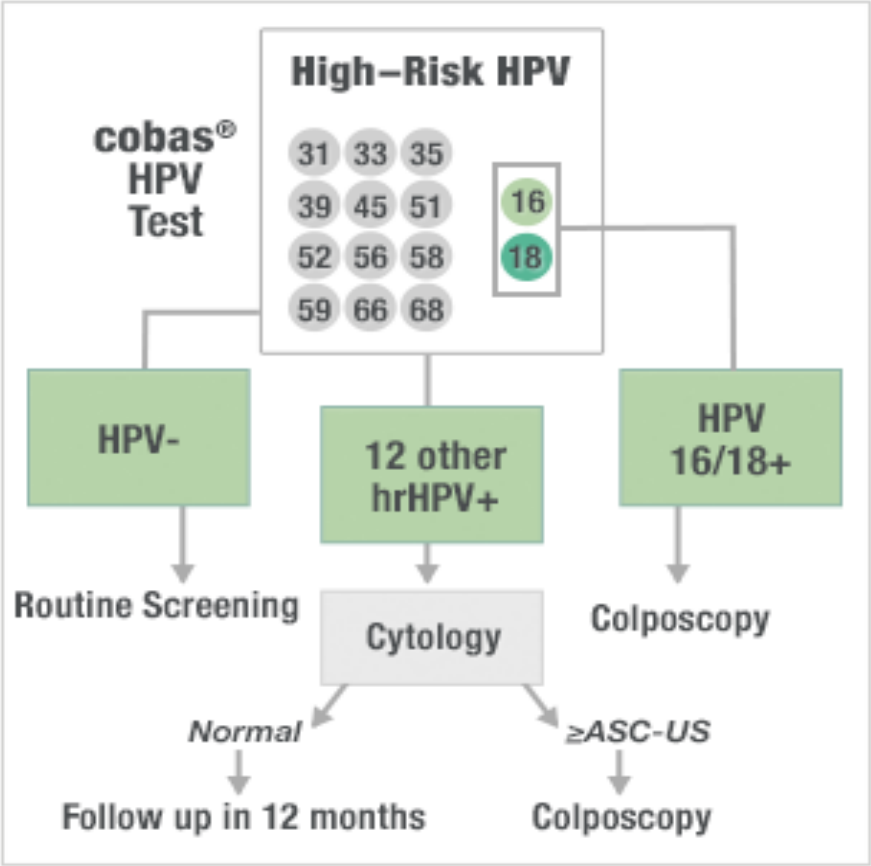
- ***Primary HPV screening*** refers to screening with an HPV test and performing cytology only as part of the triage of a positive result.

Applications of High-Risk Human Papillomavirus Testing (hrHPV)

- ***Cotesting*** refers to the performance of ***both*** *an HPV test and a cervical cytology at the time of screening.*
- Thus, combinations of HPV and cytology test results lead to algorithmic referral to colposcopy, with short-term follow-up or routine long interval screening being based on the risk of precancer or cancer.

Applications of High-Risk Human Papillomavirus Testing (hrHPV)

- ***Triage*** of an **abnormal cytology** result by a hrHPV test effectively improves the balance of sensitivity vs. specificity for colposcopic referral and prevalent disease detection.
- **ASC-US is the largest TBS category** in which this utility is established
- **ASCH**
- **LSIL in older patients**
- **AGC**



Now recommended by medical societies as an option for cervical cancer screening

Applications of High-Risk Human Papillomavirus Testing (hrHPV)

- ***HPV genotyping*** refers to the selective reporting of individual HPV types in conjunction with a positive pooled high-risk test.
- The concept is driven by the idea that the **presence of selected types at clinically valid cutoffs (e.g., HPV 16 and 18) is so highly associated with an increased risk of precancer** that such patients should be referred to colposcopy rather than followed over the short term.

	ACS 2020	ACS 2012	USPSTF 2018
21 تا 24 سال	بدون غربالگری	تست پاپ در هر سه سال	تست پاپ در هر سه سال
25 تا 29 سال	تست HPV در هر 5 سال (ترجیحی) کوتست HPV/Pap در هر 5 سال (قابلقبول) تست پاپ در هر 3 سال (قابلقبول)	تست پاپ در هر سه سال	تست پاپ در هر سه سال
30 تا 65 سال	تست HPV در هر 5 سال (ترجیحی) کوتست HPV/Pap در هر 5 سال (قابلقبول) تست پاپ در هر 3 سال (قابلقبول)	کوتست HPV/Pap در هر 3 سال (ترجیحی) تست پاپ در هر 3 سال (قابلقبول)	تست پاپ در هر سه سال، تست HPV در هر 5 سال و یا کوتست HPV/Pap در هر 5 سال
65 سال و بیشتر	در صورتی که سری آزمایشهای اولیه نرمال باشند نیازی به غربالگری نیست	در صورتی که سری آزمایشهای اولیه نرمال باشند نیازی به غربالگری نیست	در صورتی که سری آزمایشهای اولیه نرمال باشند و با ریسک بالای سرطان دهانه رحم همراه نباشد نیازی به غربالگری نیست

دلیل ارجحیت HPV به تست پاپ

- اگرچه آزمایش پاپ به کاهش چشمگیر میزان سرطان دهانه رحم و مرگ ناشی از بیماری منجر شده است، محدودیت‌هایی دارد.

- تست پاپ در مقایسه با آزمایش **HPV** حساسیت کمتری دارد
- بنابر این، ممکن است برخی مراحل پیش سرطانی را شناسایی نکرده و باید به طور مرتب تکرار شود.
- آنها همچنین طیف وسیعی از تغییرات غیرطبیعی سلول، از جمله برخی تغییرات جزئی را که با **HPV** ارتباط ندارند، تشخیص می‌دهند. بنابراین، بسیاری از افرادی که نتیجه آزمایش غیر طبیعی پاپ را دریافت می‌کنند، در واقع احتمال بسیار اندکی برای ابتلا به سرطان دهانه رحم دارند

▪ چرا در دستورالعمل جدید، آزمایش HPV بیش از کوتست HPV / Pap توصیه شده است؟

هر سه آزمایش می‌توانند در شناسایی و تشخیص سرطان دهانه رحم پیش از سرطانی شدن کمک نمایند. اما پژوهش‌ها نشان داده است که آزمایش‌های **HPV** دقیق‌تر و قابل اعتمادتر از آزمایش پاپ است.

- همچنین، با آزمایش **HPV** می‌توان به‌خوبی از ابتلا به این بیماری پیشگیری نمود تا نیازی به تکرار آنها نباشد.

کوتست *HPV / Pap* کمی حساس‌تر از آزمایش **HPV** است اما کارآیی کمتری دارد؛ زیرا به دو آزمایش نیاز دارد و بسیاری از تغییرات جزئی را تشخیص می‌دهد که خطر تبدیل شدن آنها به سرطان بسیار اندک است و در عمل این امر مستلزم تلاش و هزینه اضافی است.

غربالگری فقط با آزمایش **HPV** در سال 2012 توسط **ACS** توصیه نشده است؛ زیرا این روش هنوز توسط **FDA** تأیید نشده بود.

دستورالعمل **USPSTF** 2018 شامل آزمایش **HPV** به تنهایی، کوتست و تست پاپ به‌عنوان گزینه‌های برابر بود.

تفاوت در دستورالعمل‌های جدید **ACS** در این است که آزمایش **HPV** به تنهایی نسبت به دو آزمایش دیگر اهمیت بیشتری دارد.

▪چرا در دستورالعمل جدید غربالگری به جای 21 سالگی از 25 سالگی توصیه می‌شود؟

- این یک تغییر مهم است که مربوط به واکسن‌های HPV است.
- نخستین گروه از زنانی که واکسن HPV را در جوانی دریافت کردند اکنون 20 ساله و واجد شرایط برای غربالگری سرطان دهانه رحم هستند. واکسن‌های HPV در پیشگیری از عفونت‌های HPV، به ویژه عفونت با HPV نوع 16 و 18، انواعی که موجب ابتلا به سرطان‌های دهانه رحم می‌شوند، بسیار موثر هستند. بنابراین، واکسن‌ها به کاهش عفونت‌های HPV و پیش سرطان دهانه رحم در این گروه سنی منجر شده‌اند.
- همچنین، در زنان جوان، بیشتر عفونت‌های HPV به خودی خود از بین می‌روند. غربالگری افراد در این گروه سنی اغلب به درمان غیرضروری منجر می‌شود که می‌تواند عوارضی به همراه داشته باشد. به همین دلیل ACS توصیه می‌کند از 25 سالگی غربالگری را آغاز گردد.
-

▪ آیا افرادی که واکسن HPV دریافت کرده‌اند باز هم نیاز به غربالگری سرطان دهانه رحم دارند؟

بله، در دستورالعمل جدید غربالگری برای افرادی که واکسن HPV دریافت نموده‌اند، انجام غربالگری سرطان دهانه رحم توصیه شده است.

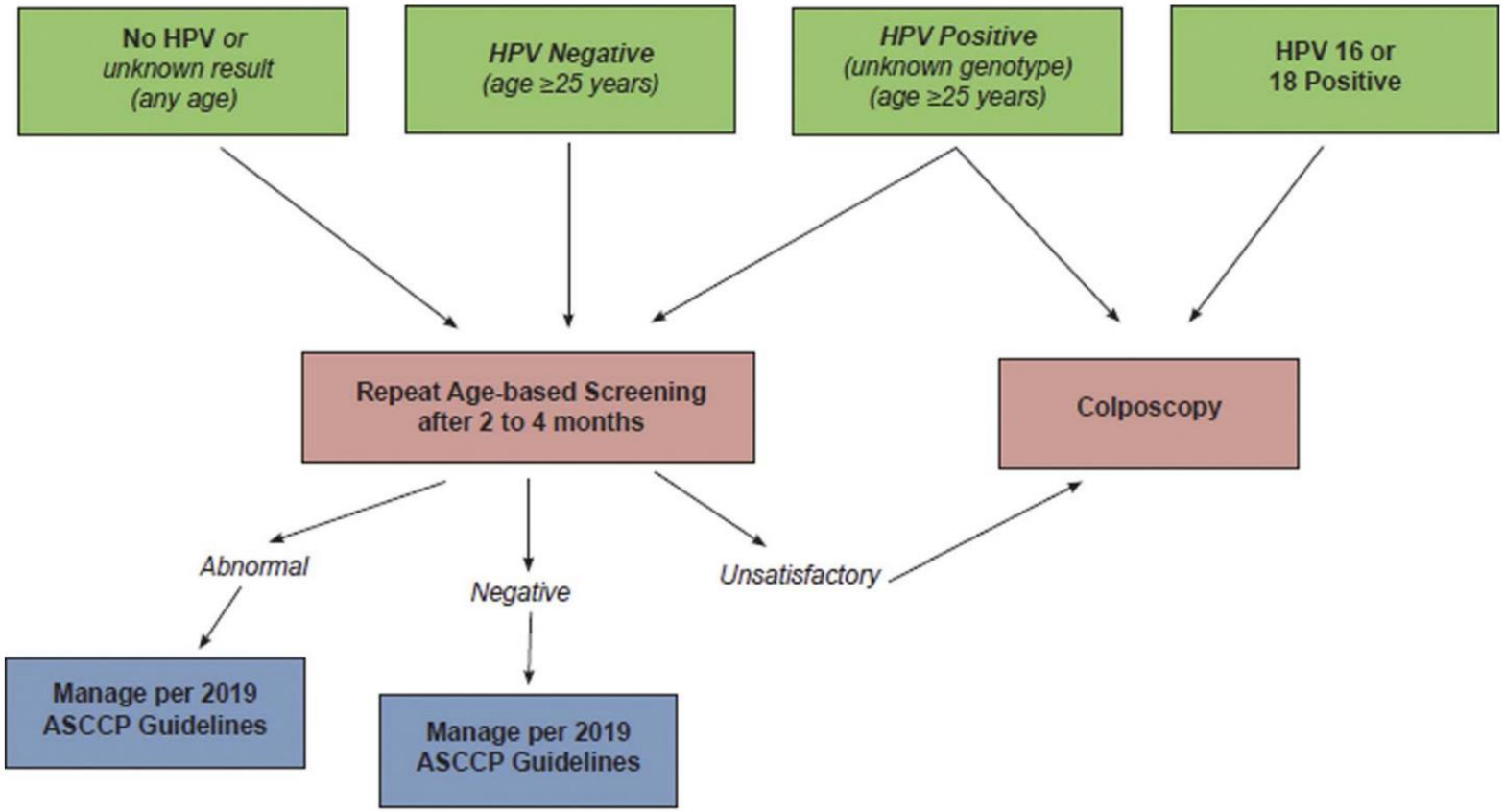
دریافت واکسن HPV با انجام غربالگری هیچ ارتباطی ندارد.
اما با گذشت زمان و با افزایش میزان واکسیناسیون HPV در میان افرادی که واجد شرایط غربالگری سرطان دهانه رحم هستند، ممکن است شاهد تغییرات بیشتری در توصیه‌های غربالگری باشیم.

•

Recommended guidelines based on pap smear and HPV results

Bethesda Classification of Cervical Cytology*

Category	Specifics	Comments
Specimen type	Conventional (Papanicolaou [Pap]), liquid-based preparation, or another	Type of test is noted.
Adequacy of the specimen	Satisfactory for evaluation	Any quality indicators (eg, presence or absence of endocervical or transformation zone component, partially obscuring blood, inflammation) are described.
	Unsatisfactory for evaluation (rejected and not processed)	Reason is specified.
	Unsatisfactory for evaluation but processed and evaluated	Reason is specified.
General categorization (optional)	Negative for intraepithelial lesion or cancer Epithelial cell abnormalities Other findings	Findings are stated or described under Interpretation, below.



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	Unsatisfactory for evaluation but processed and evaluated	Reason is specified.
General categorization (optional)	Negative for intraepithelial lesion or cancer Epithelial cell abnormalities Other findings	Findings are stated or described under Interpretation, below.

Interpretation of negative (nonmalignant) abnormalities†	Organisms	Possible findings include the following: • *Trichomonas vaginalis* • Fungi morphologically consistent with *Candida* species • Shift in vaginal flora suggesting bacterial vaginosis • Bacteria morphologically consistent with *Actinomyces* species • Cellular changes consistent with herpes simplex virus • Cellular changes consistent with cytomegalovirus
	Nonneoplastic findings (reporting is optional)	Possible findings include the following: • Nonneoplastic cellular variations (squamous metaplasia, keratotic changes, tubal metaplasia, atrophy, or pregnancy-associated changes) • Reactive cellular changes associated with inflammation (lymphocytic cervicitis), radiation, or IUD use • Glandular cell status after hysterectomy

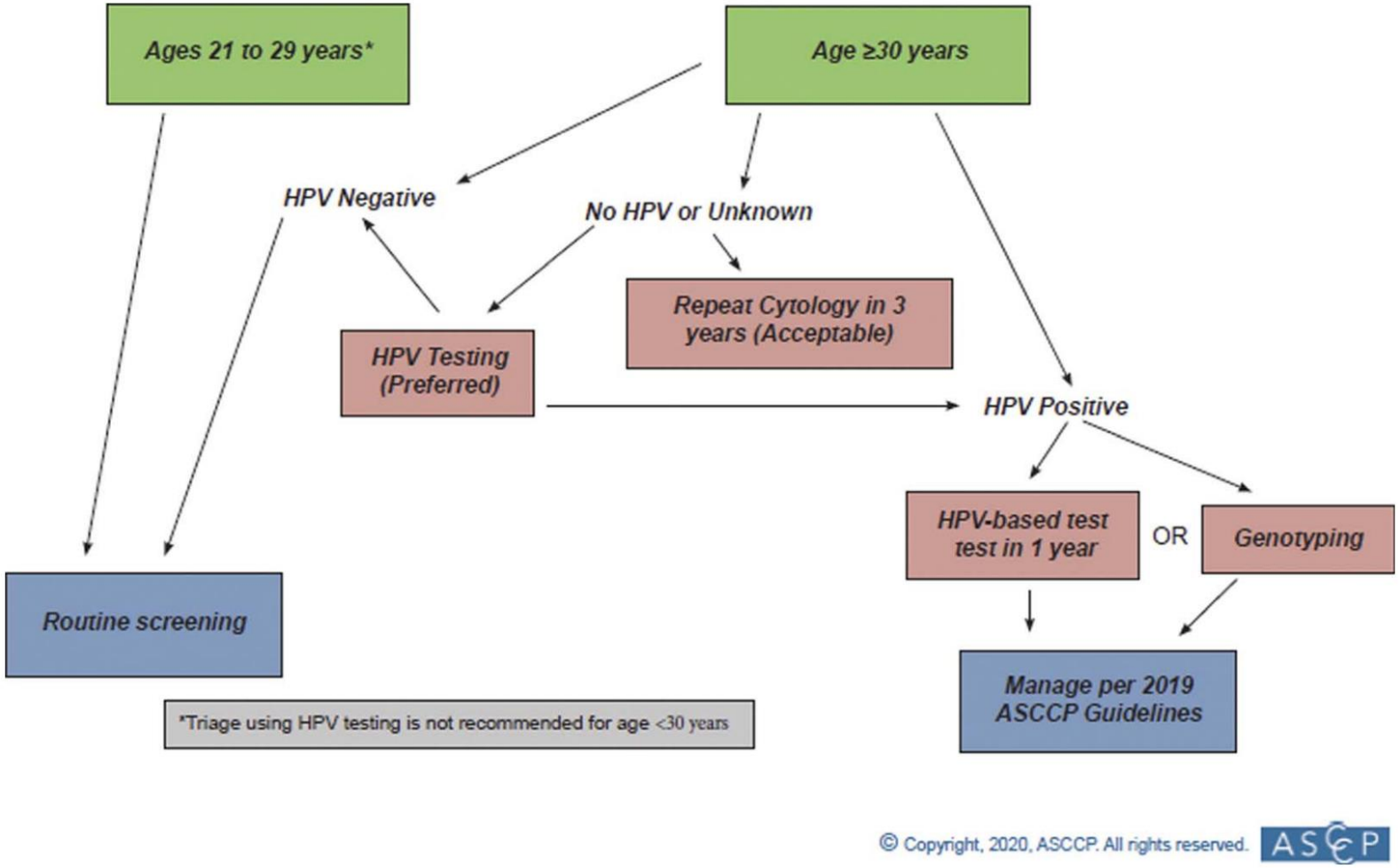

FIGURE 6. **This figure describes the steps involved in clinical management of cytology that is negative for intraepithelia lesion or malignancy, but with absent transformation zone or endocervical cells.**

Interpretation of epithelial cell abnormalities	Squamous cell	Possible findings include the following: • Atypical squamous cells of undetermined significance (ASC-US) • Atypical squamous cells for which a high-grade lesion cannot be excluded (ASC-H) • Low-grade squamous intraepithelial lesion encompassing HPV‡ infection or mild dysplasia (CIN 1) • High-grade squamous intraepithelial lesion encompassing moderate (CIN 2) and severe dysplasia (CIN 3/CIS), noting whether the lesion has features suggesting invasion • Squamous cell carcinoma
	Glandular cell	Possible findings include the following: • Atypical cells: Endocervical, endometrial, or glandular • Atypical cells likely to be cancerous: Endocervical or glandular • Adenocarcinoma in situ: Endocervical • Adenocarcinoma: Endocervical, endometrial, extrauterine, or NOS
Interpretation of other abnormalities	Endometrial cells (in a woman ≥ 45)*	Whether sample is negative for squamous intraepithelial lesion is specified.
Other cancers	—	Type is specified.

Squamous Intraepithelial Lesions (SIL)

-TBS Sub-classifying SIL Into **Two Grade**:

Low Grade

High Grade

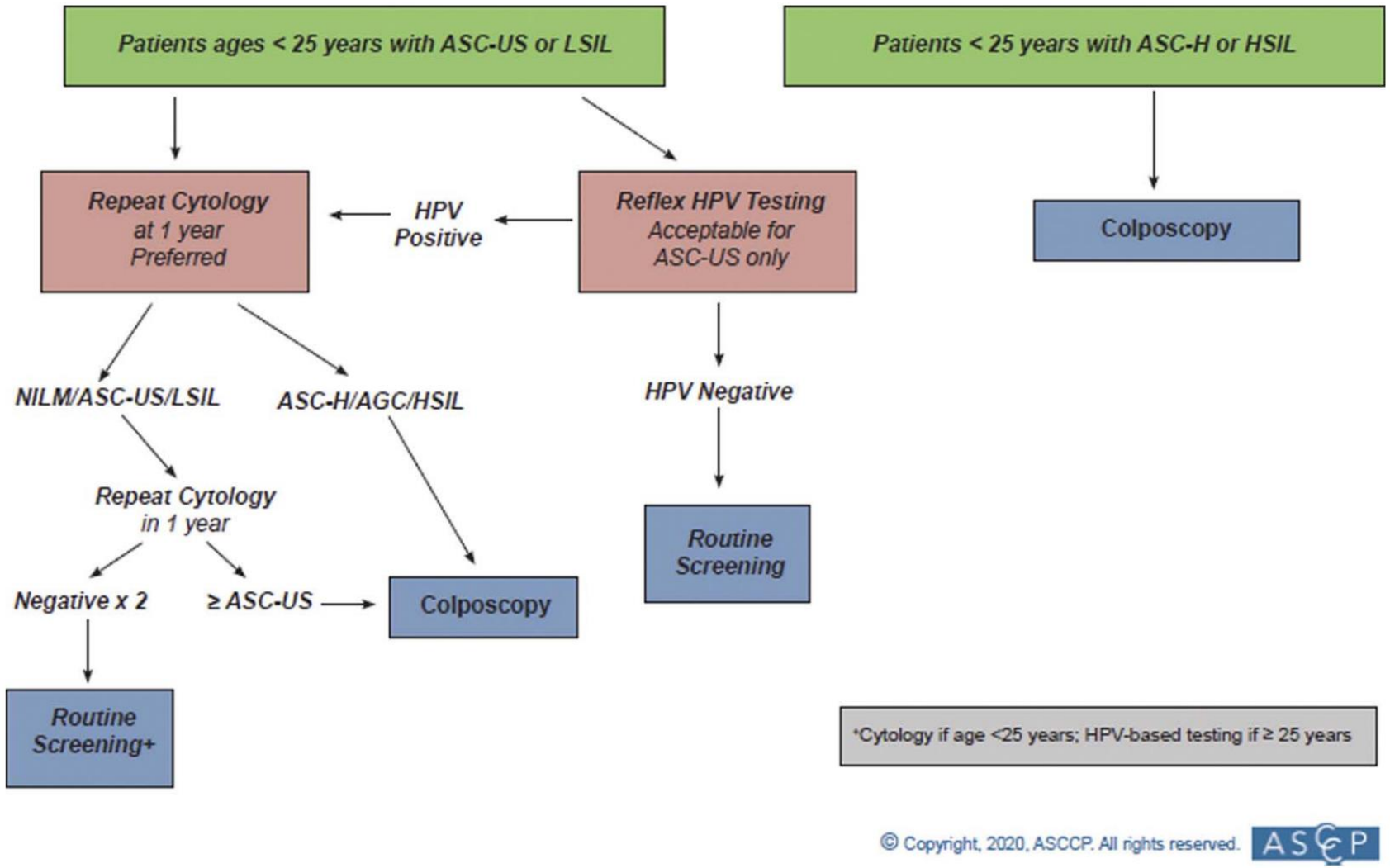

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FIGURE 12. **This figure describes management of cytologic abnormalities in patients younger than 25 years.**

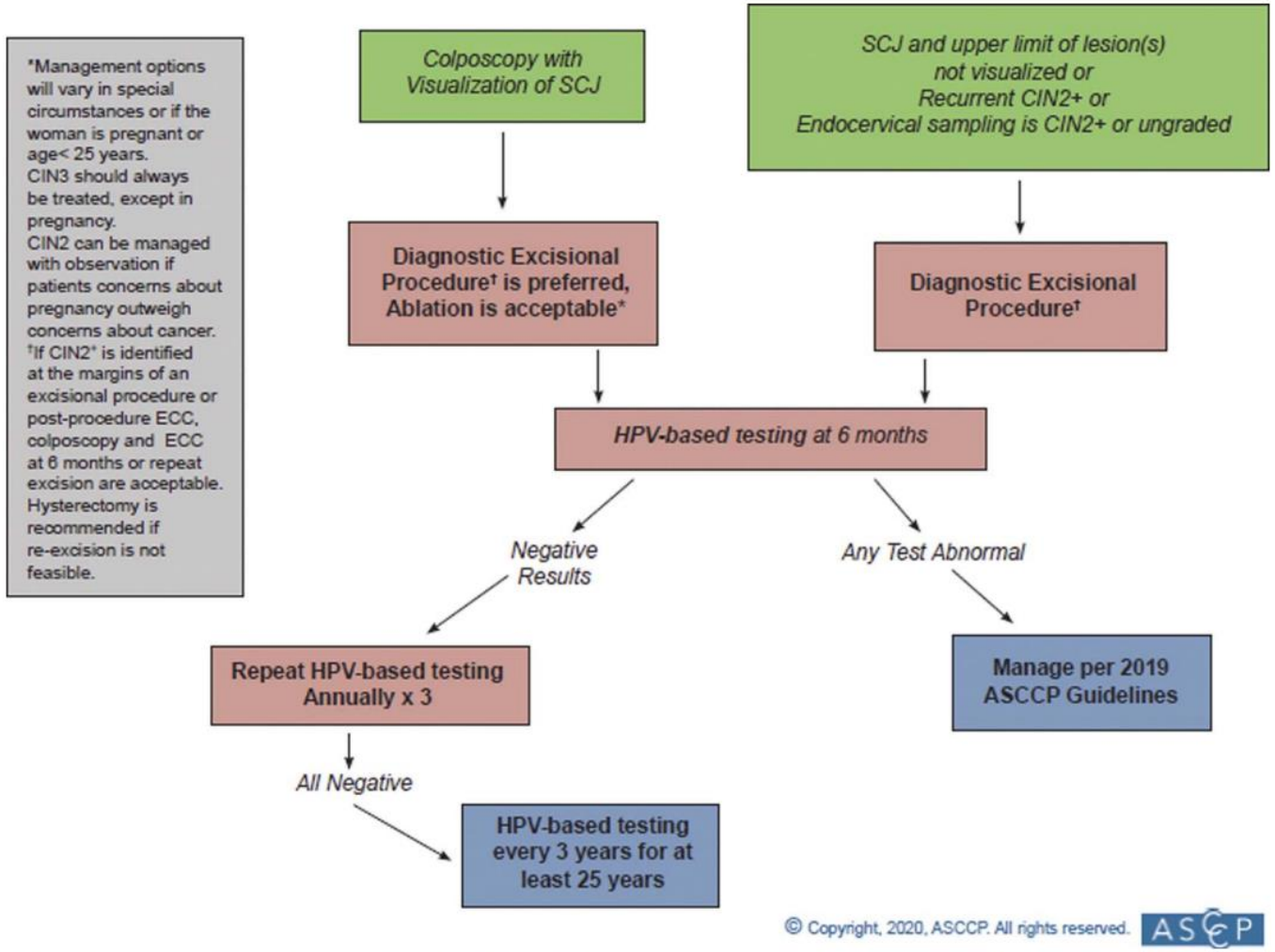

FIGURE 7. **This figure describes the steps involved in clinical management of histologic HSIL.**

TABLE 2. Comparison of Current and Previous American Cancer Society (ACS) Guidelines for Cervical Cancer Screening

	RECOMMENDATIONS FOR CERVICAL CANCER SCREENING	
POPULATION	**ACS 2020[a]**	**ACS 2012[b]**
Aged <25 y	No screening	Cytology alone every 3 y starting at age 21 y
Aged 25-65 y	Starting at age 25 y, primary HPV test alone every 5 y (preferred)	Cytology alone every 3 y until age 29 y
	Use an FDA-approved HPV test for primary screening	Aged 30-65 y, switch to cotesting (preferred), cytology alone every 3 y (acceptable)[a]
	Cotesting every 5 y or cytology alone every 3 y are acceptable options[b]	*Screening by primary HPV testing alone not recommended for most clinical settings*
	Cotesting or cytology testing alone are acceptable where access to primary HPV testing is limited or not available; as the United States makes the transition to primary HPV testing, the use of cotesting or cytology alone for cervical cancer screening will not be included in future guidelines[b]	
	For management of positive results and subsequent surveillance, refer to ASCCP 2020 Risk-Based Management Consensus Guideline (Perkins, 2020[21])	
Aged >65 y	Discontinue screening if adequate negative prior screening	No screening after adequate negative prior screening
	Individuals aged >65 y without documentation of prior screening should continue screening until criteria for cessation are met	
	Adequate negative prior screening is currently defined as 2 consecutive, negative primary HPV tests, or 2 negative cotests, or 3 negative cytology tests within the past 10 y, with the most recent test occurring within the past 3-5 y, depending on the test used	
After hysterectomy	Individuals without a cervix and without a history of CIN2 or a more severe diagnosis in the past 25 y or cervical cancer ever should not be screened	No screening after hysterectomy (with removal of the cervix) for reasons not related to cervical cancer and no history of cervical cancer or serious precancer
HPV vaccinated	Follow age-specific screening recommendations (same as unvaccinated individuals)	Follow age-specific screening recommendations