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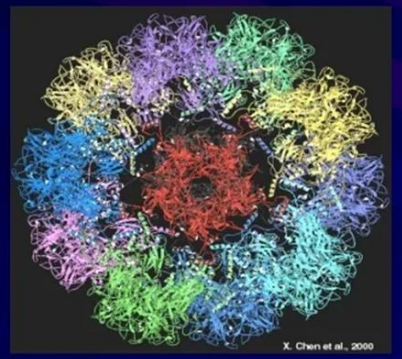
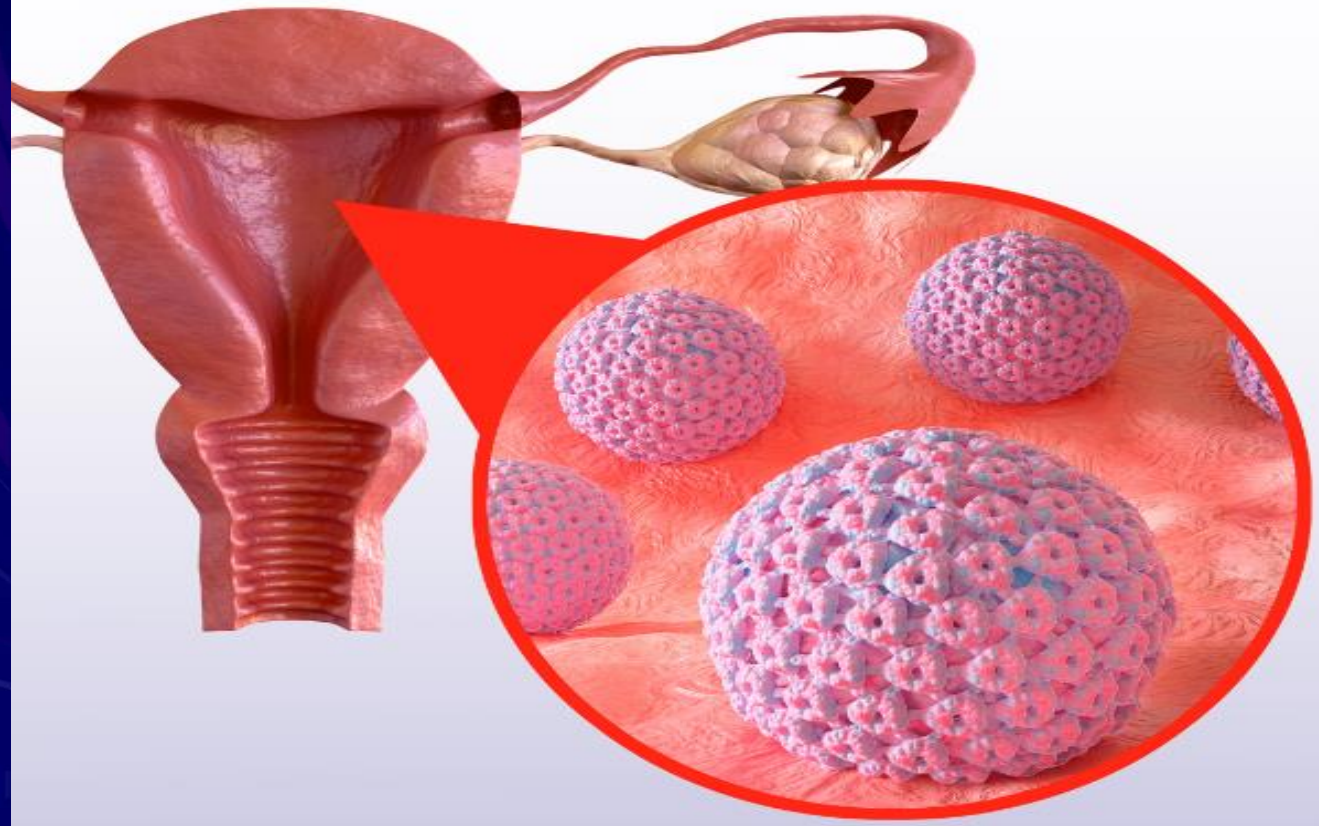
HPV AND CERVICAL CANCER

Human Papillomavirus



Cervical Cancer



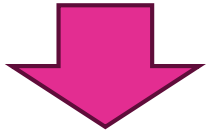
CERVICAL CANCER

- Cervical cancer remains the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death in women globally

- Cervical cancer has lower incidence and mortality rates than uterine corpus and ovarian cancer, as well as many other cancer sites.

- However, in countries that do not have access to cervical cancer screening and prevention programs, cervical cancer remains a significant cause of cancer morbidity and mortality.

- By some estimates, if vaccine rates of 70 percent worldwide are achieved



- we would expect to see a decrease of 344,520 new cases of cervical cancer annually

- avoid 178,182 cervical cancer-related deaths

- However, due to the latency period of 10 to 15 years between HPV exposure and cervical cancer development, there are not likely to be significant decreases in cervical dysplasia or cancer for many years after the implementation of vaccination programs

HPV PREVALENCE AND HIGH-RISK TYPES

- **The prevalence of hrHPV varies**:

  - geographically
  - Reflecting population immunity
  - sexual behavior
  - co-factors

International Journal of Molecular Sciences

MDPI

Review

Cervical Cancer in the Era of HPV: Translating Molecular Mechanisms into Preventive Public Health Action

Lidia Boldeanu [1,†], Mohamed-Zakaria Assani [2,3,†], Mihail Virgil Boldeanu [2,*], Isabela Siloși [2,*], Maria-Magdalena Manolea [4], Constantin-Cristian Văduva [4], Alexandru-Dan Assani [3]

AGE-SPECIFIC AND HISTOLOGY PATTERNS

- **HPV prevalence exhibits a U-shaped age curve**:

➢ peaking in younger women (<25 years)

➢ declining in mid-adulthood,

➢ and occasionally rising again post-menopause

- likely due to persistent infection or cohort effects. Conversely, the incidence of cervical cancer peaks between **ages 35 and 44**, with a median age at diagnosis near 50

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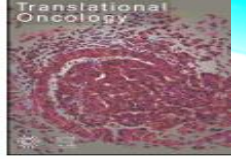


Long noncoding RNAs and HPV-related cervical cancer: Uncovering molecular mechanisms and clinical applications

Mina Alimohammadi [a], Abbas Ali Imani Fooladi [b], Alireza Mafi [c,d], Seyedeh Mana Alavioun [e], William C. Cho [f], Russel J Reiter [g], Fateme Zare Khormizi [h], Tooba Yousefi [i], Najma Farahani [j,*], Seyedeh Mahdieh Khoshnazar [k,*], Kiavash Hushmandi [l,*]

- Cervical cancer (CC) poses a significant threat to global health, being the fourth most common malignancy diagnosed in women worldwide
- Approximately 85 % of CC fatalities occur in low- and middle-income countries, with the death rate being 18 times higher than developed nations.
- About 75 % of CCs are attributed to squamous cell carcinoma (SCC), which typically originates in the transformation zone of the ectocervix,
- and adenocarcinoma accounts for around 25 %, developing in the glandular columnar layer of the endocervix

RISK FACTORS BEYOND HPV

- The two major histologic types of cervical cancer, adenocarcinoma and squamous cell carcinoma, and the preinvasive disease that corresponds with these histologies share many of the same risk factors

❑HPV-related

- In almost all cases, cervical cancer is due to human papillomavirus (HPV) infection.
- **Risk factors that are associated with HPV related cancers include**:

➢A high-risk sexual partner

(eg, a partner with multiple sexual partners or known HPV infection).

➢History of sexually transmitted infections

(eg, Chlamydia trachomatis, genital herpes).

- Immunosuppression (eg, HIV infection).

- Early onset of sexual activity

Compared with age at first intercourse of 21 years or older, the risk is approximately 1.5-fold for 18 to 20 years and twofold for younger than 18 years

- Multiple sexual partners

Compared with one partner, the risk is approximately twofold with two partners and threefold with six or more partners .

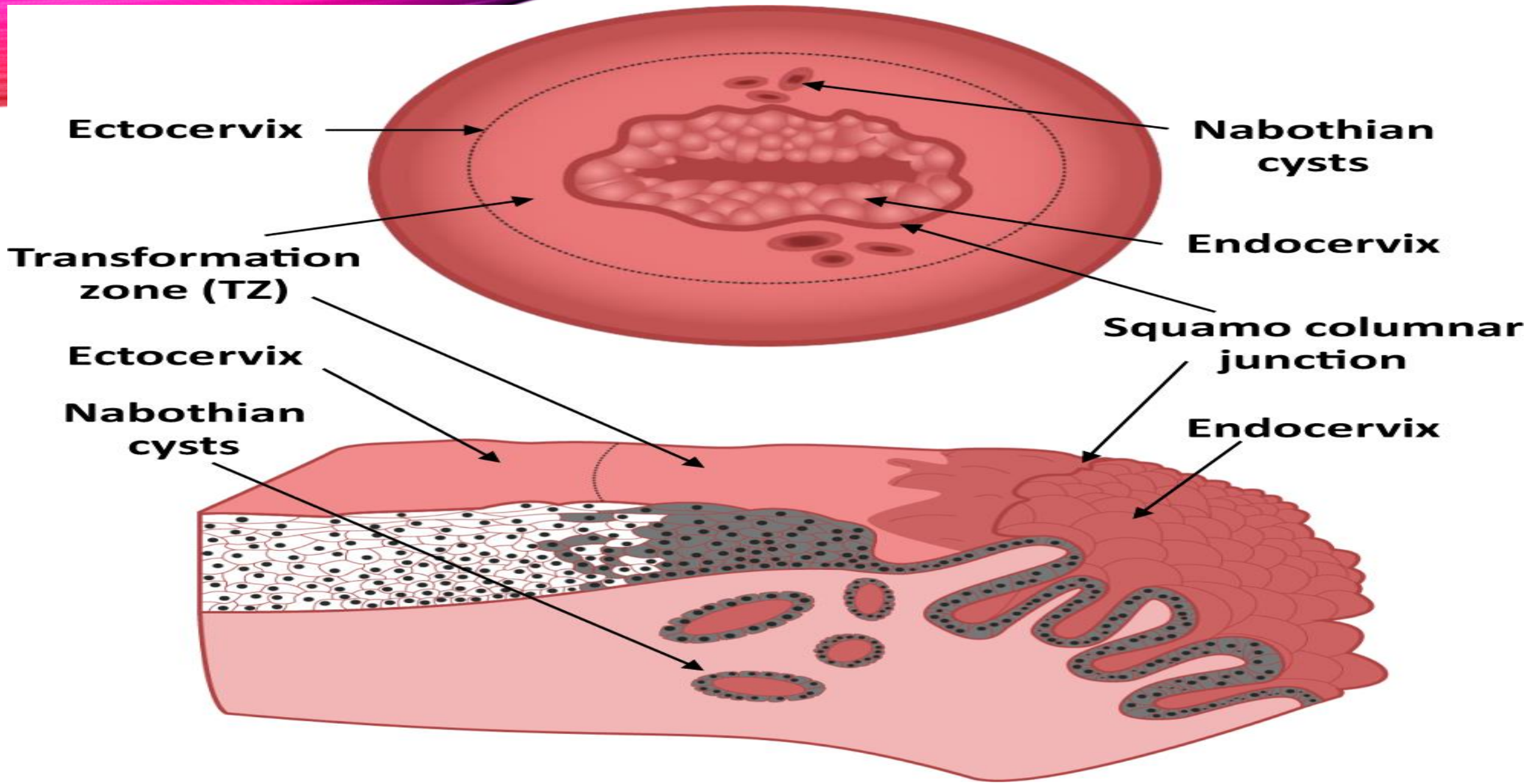
- Lower levels of vitamins **A, C, E, and folate** have been associated with a higher risk of cervical dysplasia and cancer, highlighting the **role of antioxidant defenses in modifying HPV-related progression**

- **Non-HPV-related** 
  - Low socioeconomic status
  - Nonwhite race
  - Oral contraceptive use
  - Cigarette smoking
  - Genetics
  - Cervical cancer is less common in patients whose sexual partners are circumcised males

- **There are four major steps in cervical cancer development**

1. Oncogenic HPV infection of the metaplastic epithelium at the cervical transformation zone (the junction between the squamous epithelium of the ectocervix and the glandular epithelium of the endocervical canal)

2. Persistence of the HPV infection.
3. Progression of a clone of epithelial cells from persistent viral infection to precancer.
4. Development of carcinoma and invasion through the basement membrane.


Ectocervix
Nabothian cysts
Endocervix
Transformation zone (TZ)
Squamo columnar junction
Ectocervix
Nabothian cysts
Endocervix

HISTOPATHOLOGY

- Squamous cell carcinoma – 70 to 75 percent.

- Adenocarcinoma (including adenosquamous) – 25 percent; the incidence of invasive cervical adenocarcinoma and its variants has increased dramatically over the past few decades, particularly in younger patients

- Other histologies – Rare.

- The human papillomavirus (HPV) subtypes associated with squamous cell carcinoma are different from those associated with adenocarcinoma.
- In an international study of over 30,000 cervical cancers, the distribution of HPV subtypes was :

- **Squamous cell carcinoma**

  - HPV 16 (59 percent of cases)
  - 18 (13 percent)
  - 58 (5 percent)
  - 33 (5 percent)
  - 45 (4 percent)

- **Adenocarcinoma**

  - HPV 16 (36 percent)
  - 18 (37 percent)
  - 45 (5 percent)
  - 31 (2 percent)
  - 33 (2 percent)

- Adeno squamous tumors exhibit both glandular and squamous differentiation.

- They may be associated with a poorer outcome than squamous cell cancers or adenocarcinomas

- Neuroendocrine or small cell carcinomas can originate in the cervix in patients but are infrequent

- Rhabdomyosarcoma of the cervix is rare; it typically occurs in young patients

- Primary cervical lymphoma and cervical sarcoma are also rare

Article 11 February 2025

Human Papillomavirus Infection in Partners of Women Attending Cervical Cancer Screening: A Pilot Study on Prevalence, Distribution, and Potential Use of Vaccines

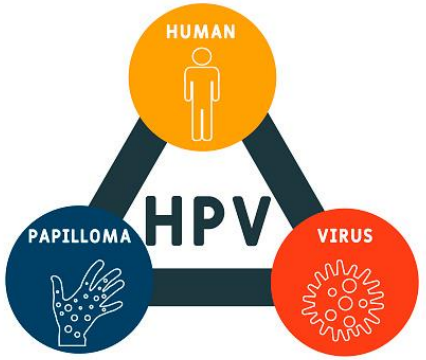
Arianna Sucato[1,†], Nicola Serra[2,†], Michela Buttà[1], Leonardo Di Gregorio[3], Daniela Pistoia[4] and Giuseppina Capra[1,4,*]

HPV

- Human papillomavirus (HPV) is one of the most widespread sexually transmitted infections (STIs) worldwide, with similar global prevalence rates in men and women, ranging from 3.5–45% and 2–44%, respectively.

- Almost 80% of sexually active men and women can become infected at least once in their lifetime, as infection can occur not only through sexual intercourse but also through rubbing or touching the skin surfaces and mucous membranes

- In this framework, the likelihood of contracting a sexually transmitted infection such as HPV has increased owing to a lower age of first sexual intercourse and a higher number of sexual partners recorded in recent decades

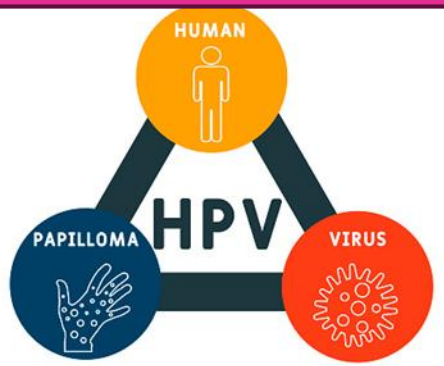


- To date, more than 200 different HPV genotypes have been described, classified as **high-risk (hrHPV**) based on their association with the onset of cervical, vaginal, vulvar, anal, head and neck, and penile cancers,
- and **low-risk (lrHPV)** associated with genital warts or condyloma acuminata .

- More often, infections are completely cleared by the immune system over 12–24 months with no clinical complications.

- However, if the immune system fails to clear the virus, a persistent infection is established, laying the foundation for the development of neoplastic hyperproliferative lesions

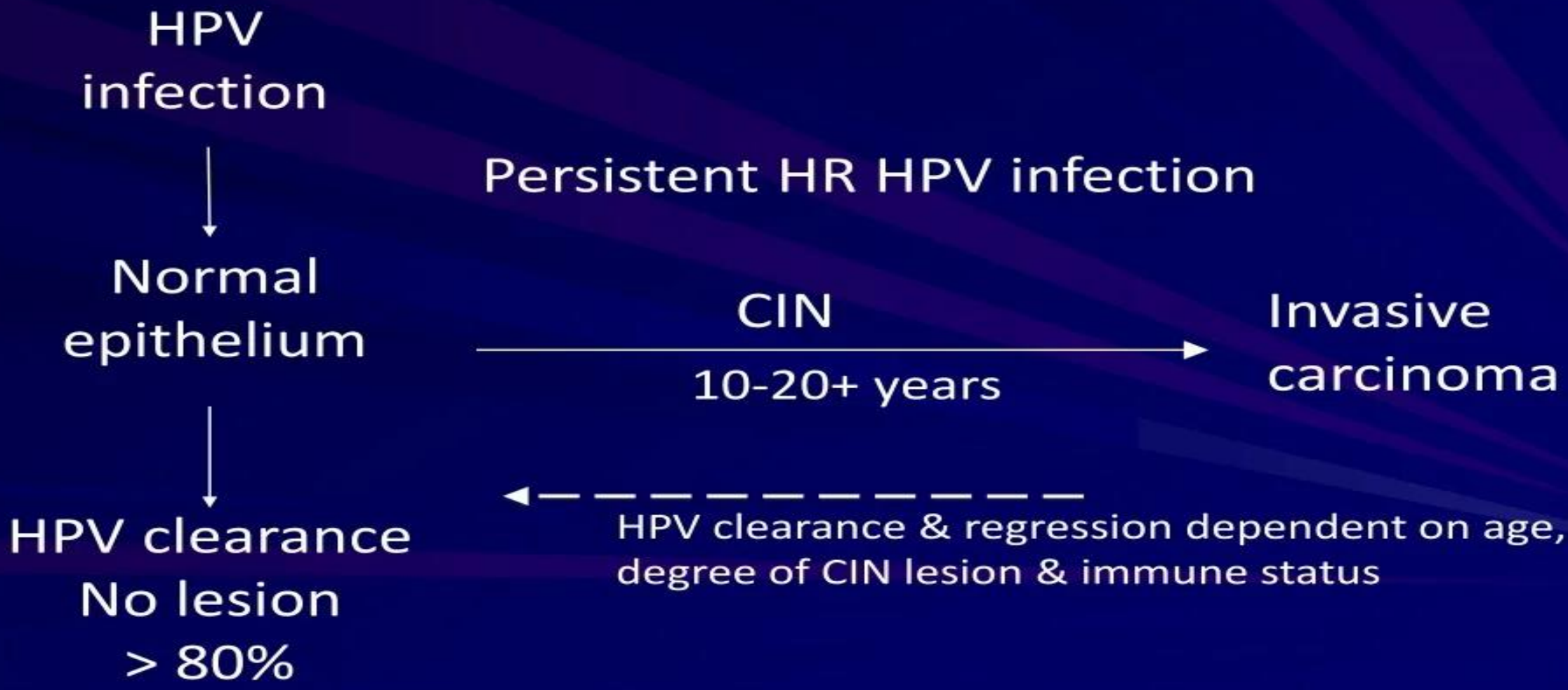
Human papillomavirus (HPV) is central to the development of cervical neoplasia and can be detected in 99.7 percent of cervical cancers



HPV TYPING

HPV Group	HPV Types	Clinical Association
Low Risk	6, 11, 42, 43, 44	Genital warts or benign lesions, not cervical cancer.
High Risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	All types isolated in cervical cancer.

How does HPV cause cancer?



DIAGNOSIS METHODS

- Cervical Cytologic Screening Test
- Human Papillomavirus Testing in Screening
- Colposcopic Diagnosis

CERVICAL INTRAEPITHELIAL NEOPLASIA

- **CIN** represents histopathological steps in cervical carcinogenesis:

❑ • **CIN1** (low-grade dysplasia):

Often transient and usually regresses spontaneously.

❑ • **CIN2/3** (high-grade dysplasia):

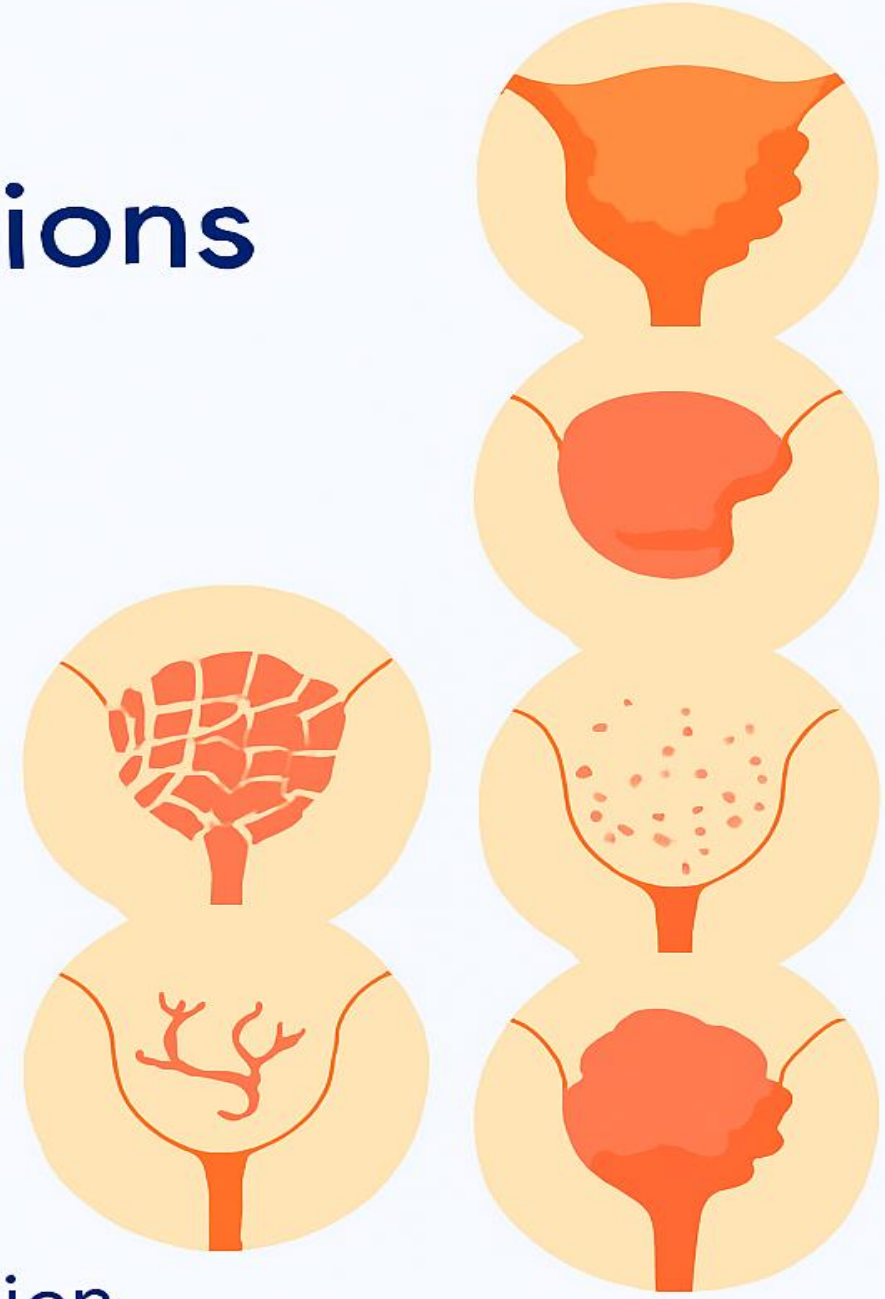
❖ A risk of progression to invasive carcinoma

❖ Natural history data emphasize close monitoring of CIN2 in young women due to frequent regression,

❖ while CIN3 is generally treated promptly due to a higher progression risk.

Colposcopic Findings of Pre-cancerous Cervical Lesions

- Irregular margin
- Erosion (fiery red patches)
- Dense acetowhite epithelium
- Mosaic pattern
- Punctuation
- Frankly initible vessels
- Irregular vascular patterns
- Irregular surface, enlargemannt of the lesion



KEY COLPOSCOPIC FINDINGS IN PRECANCEROUS CERVICAL LESIONS

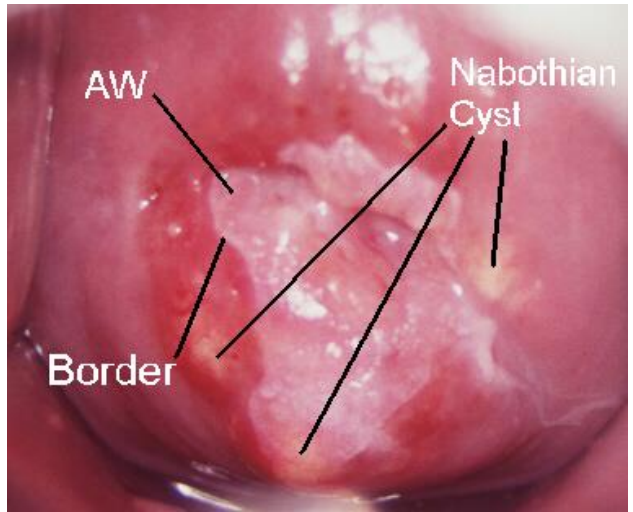
- **the classic colposcopic findings of precancerous cervical lesions include:**

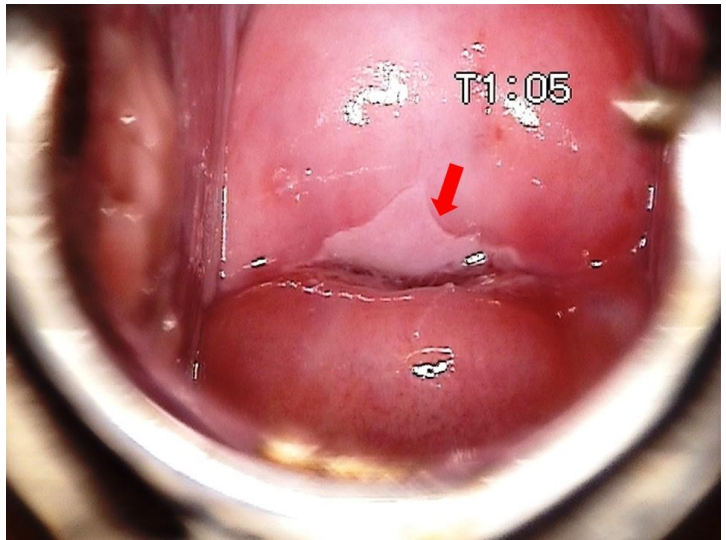
- **acetowhite epithelium**
- **punctation,**
- **mosaic patterns**
- **atypical vessels,**
- **and sharp borders of abnormal areas**

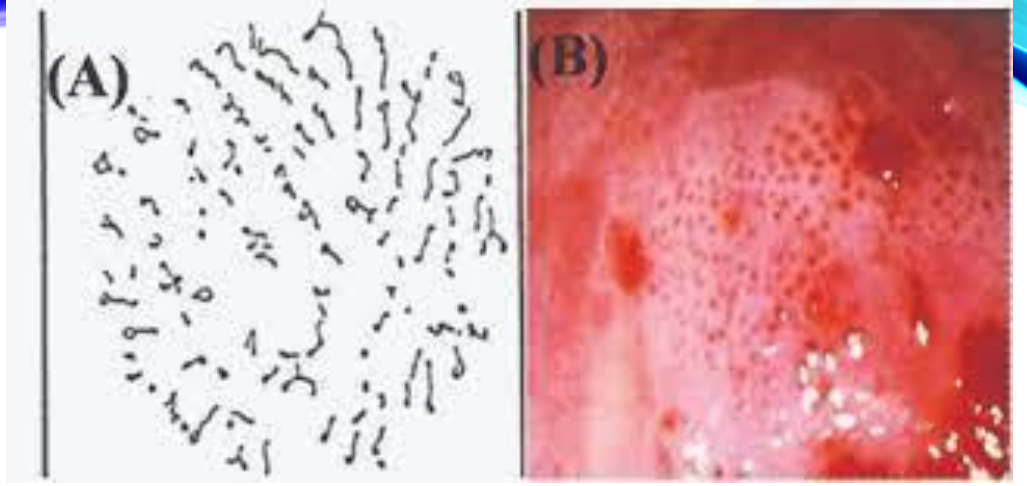
- These features help distinguish low-grade from high-grade intraepithelial lesions.

❑ Acetowhite Epithelium:

- ➢ Appears after application of 3-5 % acetic acid.
- ➢ Lesions turn white due to coagulation of nuclear proteins in dysplastic cells.
- ➢ High-grade lesions show *dense, opaque, and rapidly appearing*.egnahc etihwoteca







❑Punctation:

- ➢Fine or coarse red dots representing dilated capillary loops perpendicular to the surface.
- ➢**Fine punctation** → often associated with low-grade lesions.
- ➢**Coarse punctation** → more typical of high-grade lesions (CIN 2/3)

❑Mosaic Pattern

•Network of vessels surrounding small blocks of epithelium, resembling a tiled floor.

➢**Fine mosaic** .segnahc edarg-wol →

➢**Coarse mosaic**.snoisel suorecnacerp edarg-hgih →

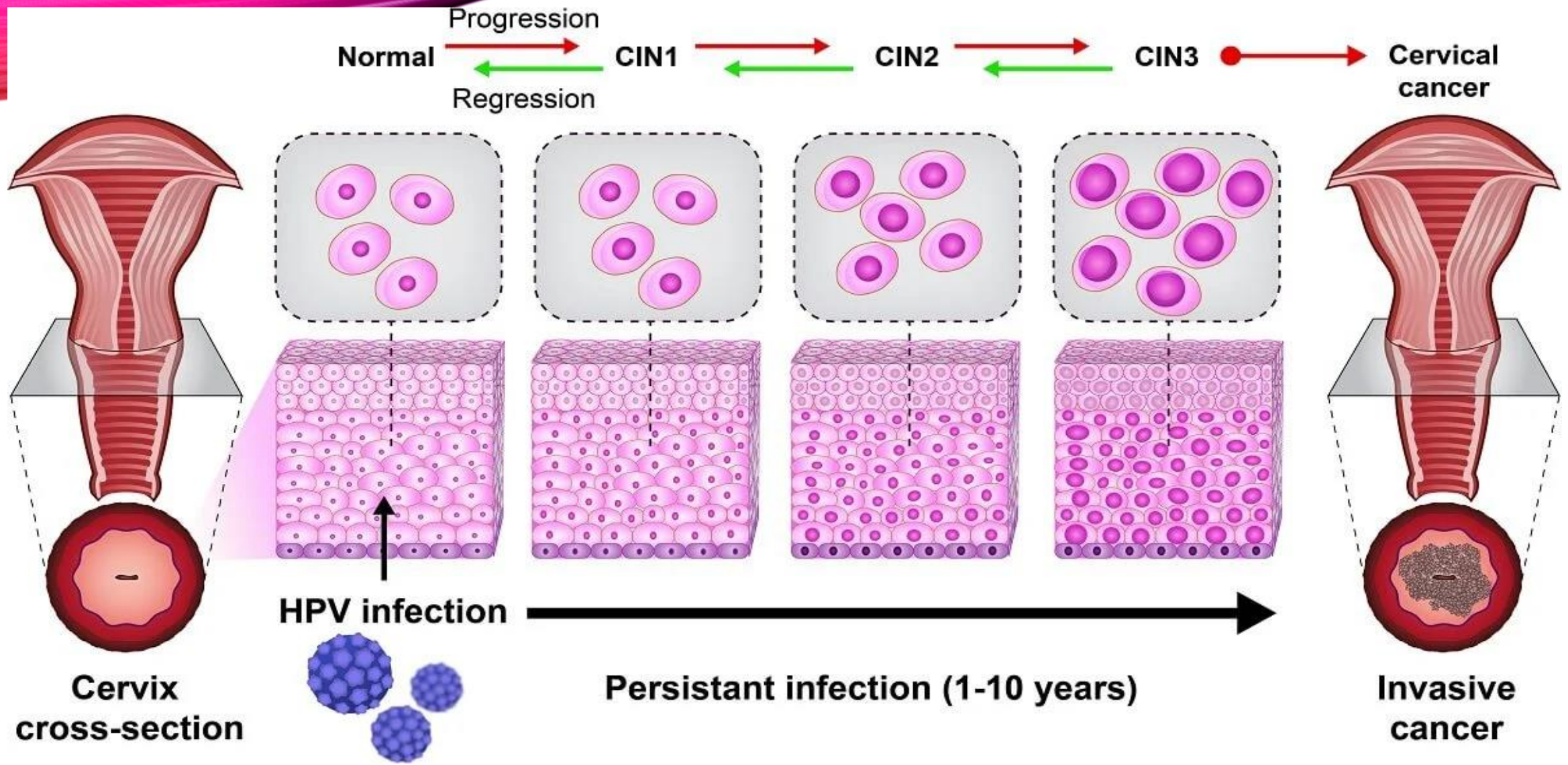
❑Atypical Vessels:

➢Irregular, bizarre vascular patterns not conforming to normal branching.

➢Strongly suggestive of high-grade CIN or invasive carcinoma.

ATIPICAL VESSEL

MOSAICISM

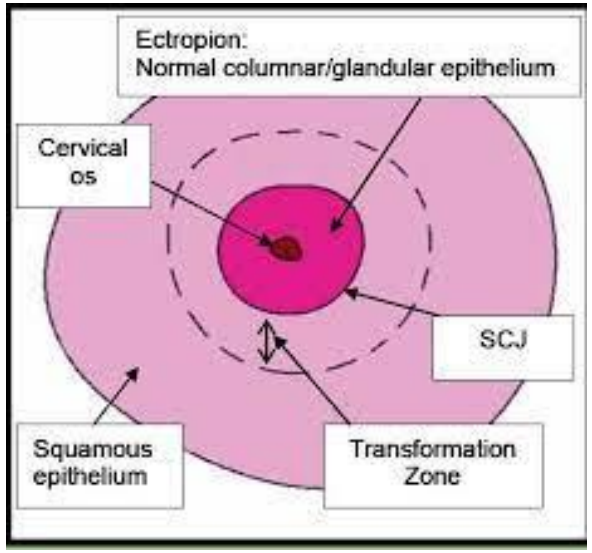

Progression
Normal
CIN1
CIN2
CIN3
Cervical cancer
Regression
HPV infection
Cervix cross-section
Persistant infection (1-10 years)
Invasive cancer

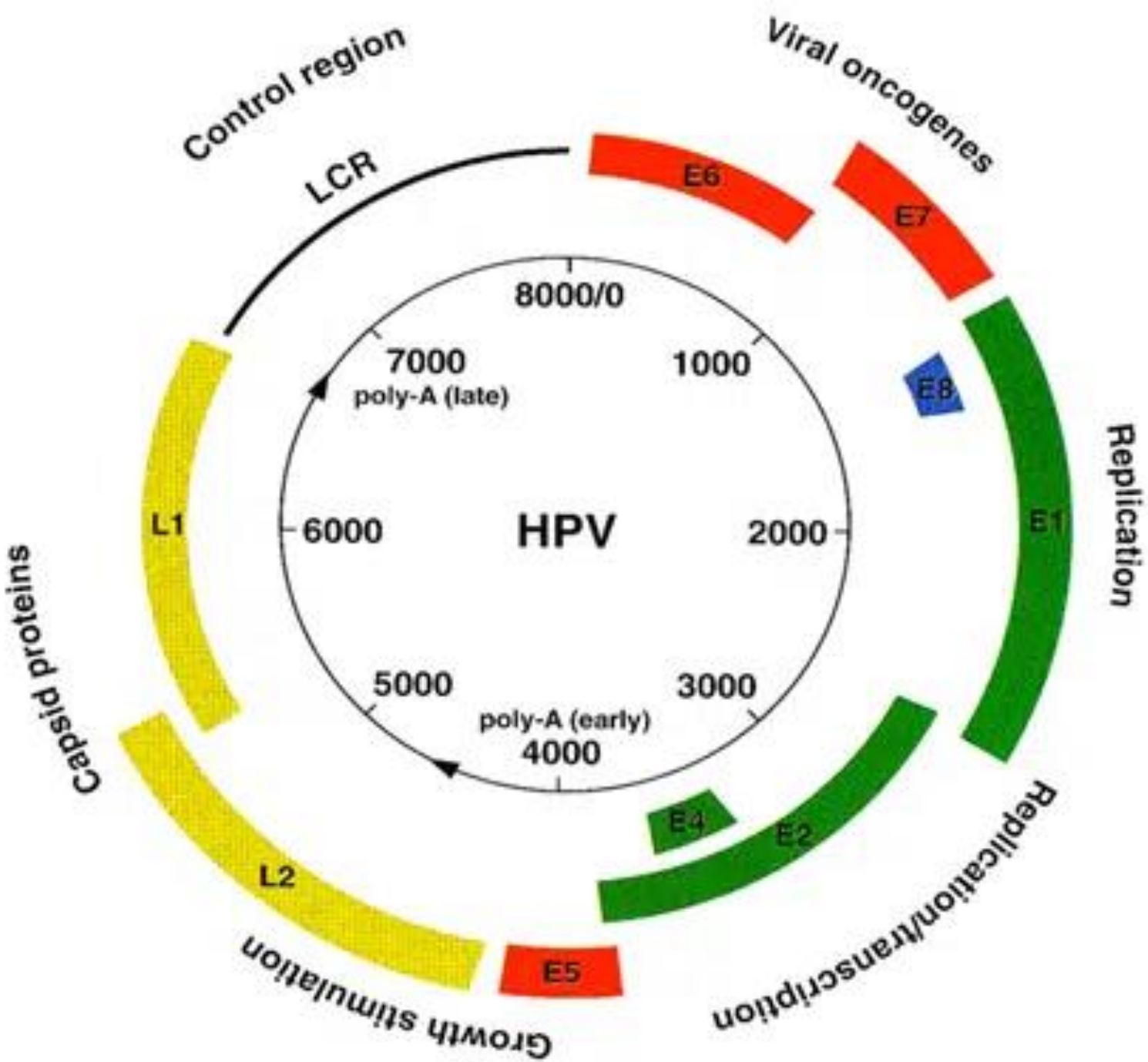
How is HPV spread?

- Any kind of sexual activity involving skin to skin genital contact with an infected person — intercourse isn't necessary.
- People with HPV may not show any signs or symptoms, so they can pass the virus on without knowing it.

- HPV is an epitheliotropic virus that enters the basal epithelial cells through micro-wounds or micro-abrasions.

- The infection occurs in the transformation zone (TZ), a dynamic area where metaplasia takes place and where the ectocervix and endocervix meet




Control region
LCR
Viral oncogenes
E6
E7
8000/0
7000
poly-A (late)
1000
E8
Replication
E1
L1
6000
HPV
2000
Capsid proteins
5000
3000
poly-A (early)
4000
E4
E2
L2
Replication/transcription
E5
Growth stimulation

GENOME STRUCTURE OF HPV VIRUS

- Human papillomavirus (HPV) is a circular double-stranded DNA virus belonging to the Papillomaviridae family.

- Its genome consists of approximately 8000 base pairs and is divided into two main parts:

I. **structural genes (L1 and L2) that encode the viral envelope proteins,**

II. **non-essential genes (E1 to E7) that have regulatory and pathogenic roles.**

- Among these genes, E6 and E7 are known as key oncogenes in the carcinogenesis process.

THE PROCESS OF HPV GENOMIC INTEGRATION INTO HUMAN CELLS

- In many cases of HPV infection, the virus remains episomally (outside the host DNA) in the cell nucleus and is eventually cleared by the immune response.

- However, in some situations, especially in chronic and persistent infections with high-risk HPV , the virus can permanently integrate its genome into the host DNA

(HPV integration process) .

- During integration, the E2 gene, which regulates E6/E7 expression, is often destroyed, and as a result, the activity of the E6 and E7 oncogenic genes increases excessively .

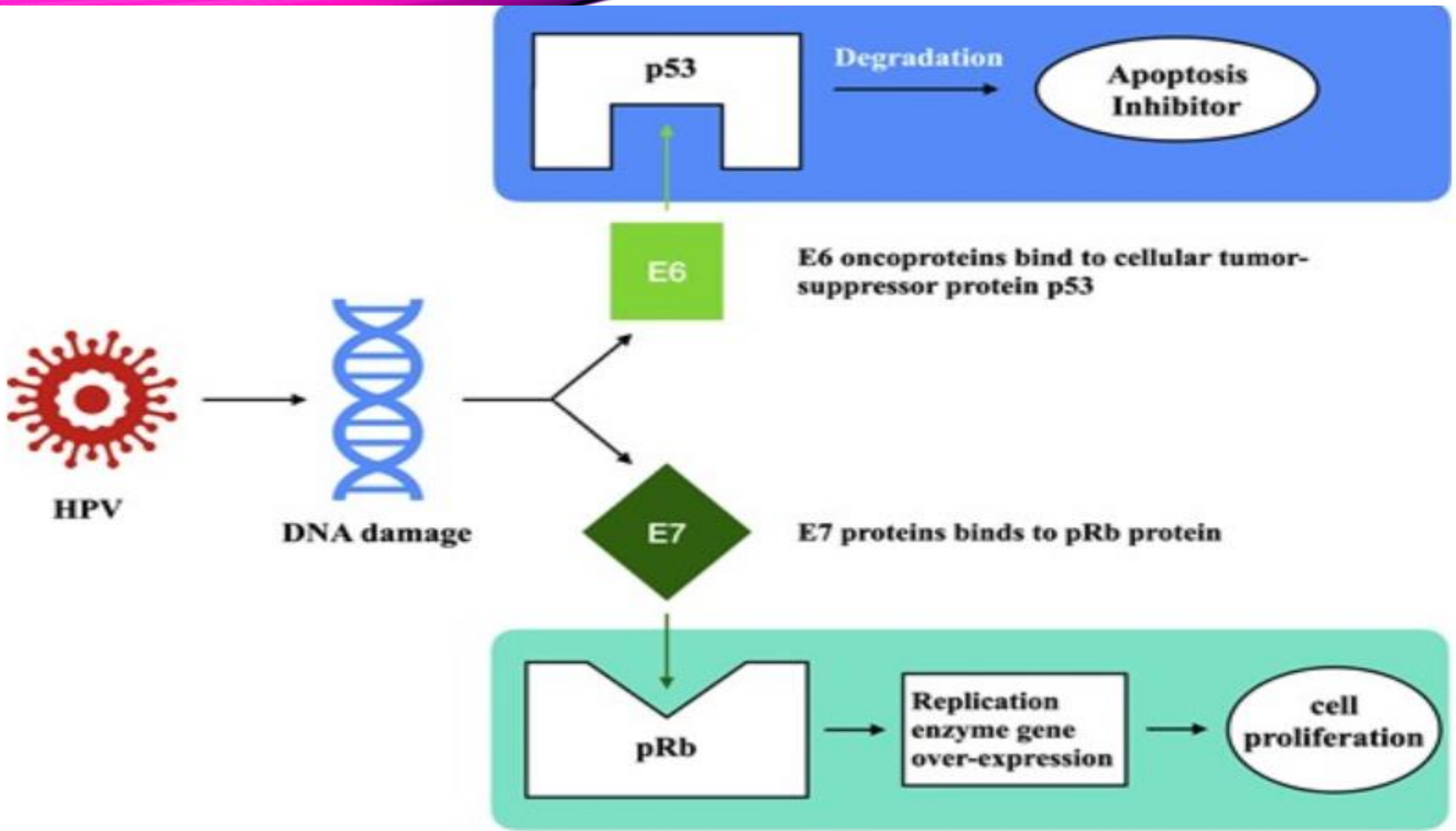
- The HPV carcinogenic nature, as reported in the literature, is linked to its double-stranded circular genome that encodes the two oncoproteins, E6 and E7, which cooperate to overcome cellular apoptotic pathways by interacting with p53 and pRb tumor suppressor proteins.

KEY ROLE OF E6 AND E7 IN CANCER DEVELOPMENT

- By binding to the tumor suppressor protein p53 , E6 deactivates the natural pathway of apoptosis (programmed cell death) and allows damaged cells to survive.

- E7 also inhibits the Rb (Retinoblastoma) protein , which is one of the cell cycle guardians, causing infected cells to divide uncontrollably .

- These genetic abnormalities provide a favorable environment for the development of precancerous lesions (CIN) and ultimately cancer of the cervix, throat, mouth, anus, and other areas .
-


p53
Degradation
Apoptosis Inhibitor
E6
E6 oncoproteins bind to cellular tumor-suppressor protein p53
HPV
DNA damage
E7
E7 proteins binds to pRb protein
pRb
Replication enzyme gene over-expression
cell proliferation

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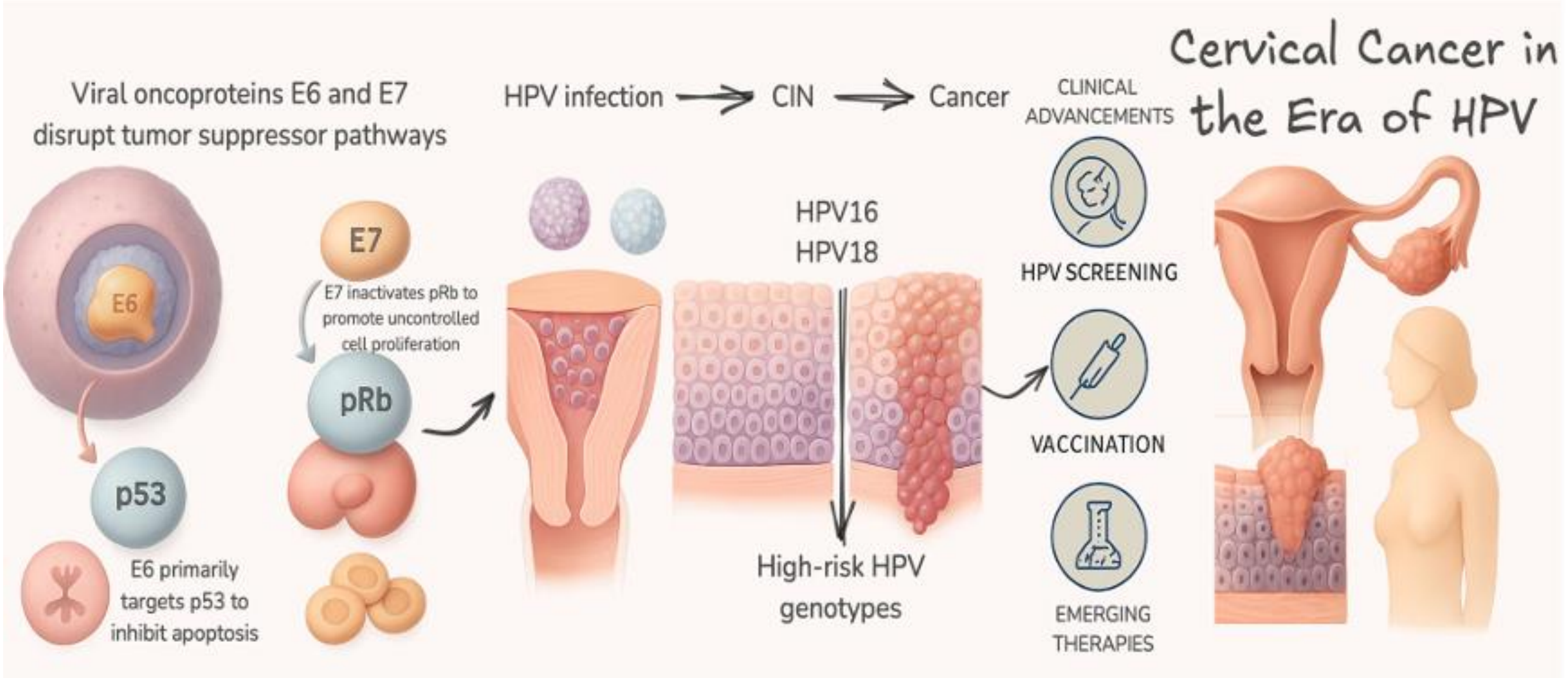
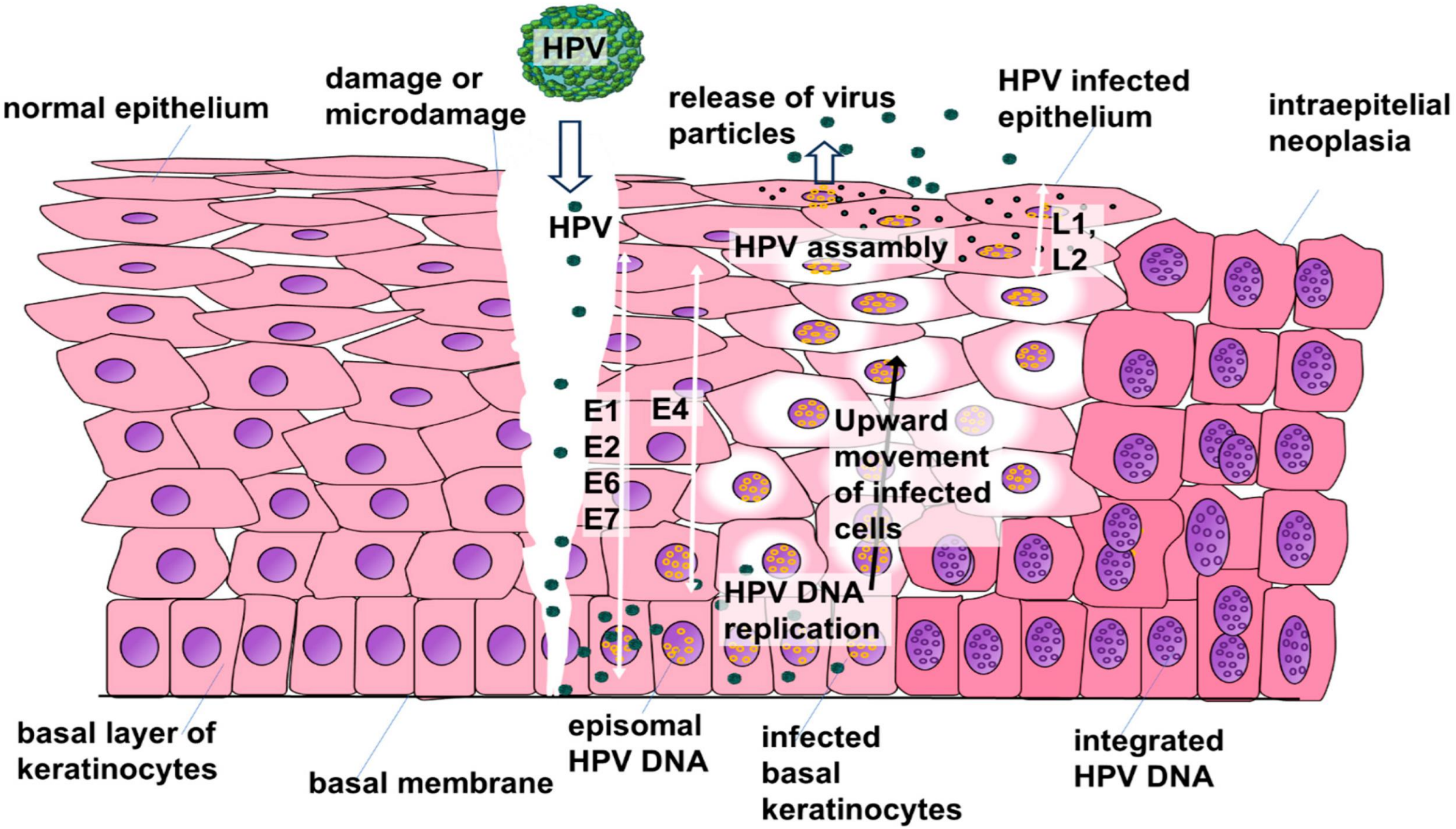
Review

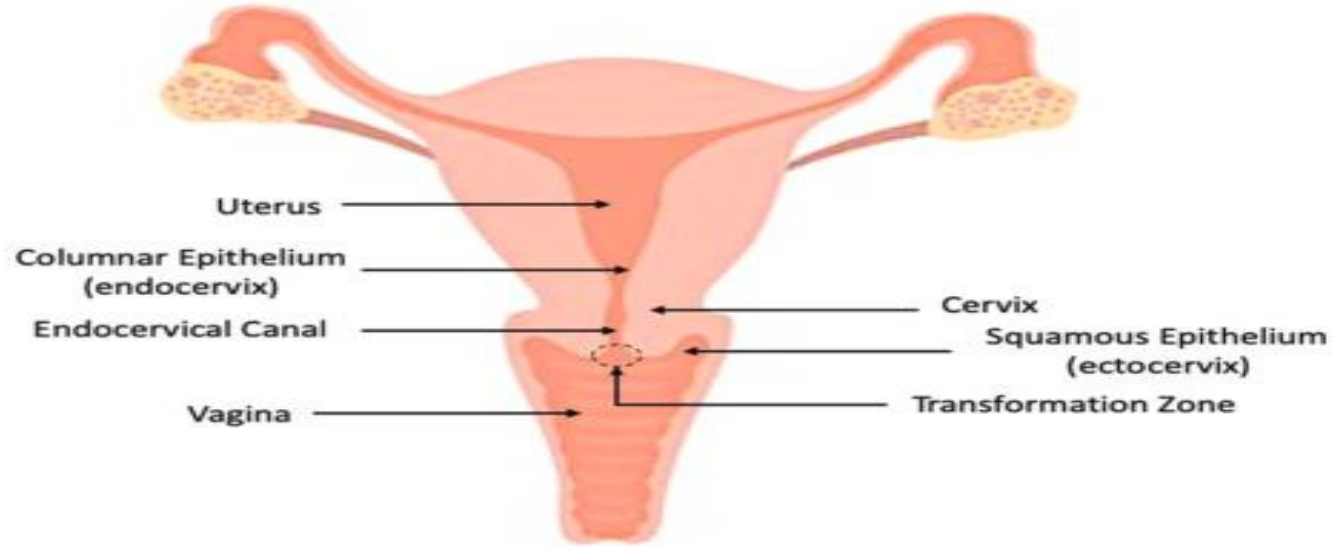
Cervical Cancer in the Era of HPV: Translating Molecular Mechanisms into Preventive Public Health Action

Lidia Boldeanu [1,†], Mohamed-Zakaria Assani [2,3,†], Mihail Virgil Boldeanu [2,*], Isabela Siloși [2,*], Maria-Magdalena Manolea [4], Constantin-Cristian Văduva [4], Alexandru-Dan Assani [3] and Anda Lorena Dijmărescu [4]

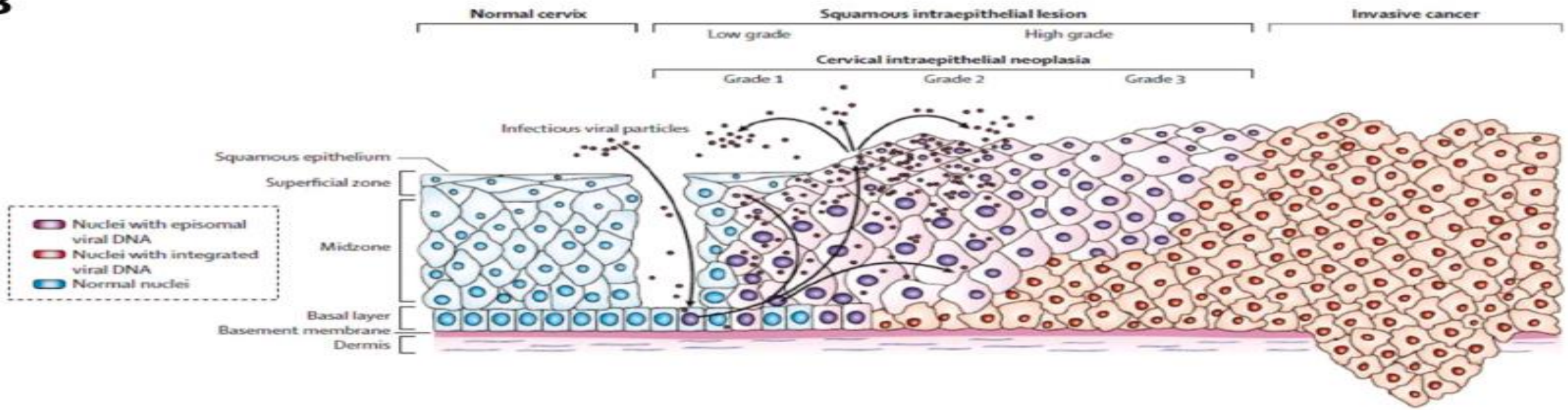



HPV
normal epithelium
damage or microdamage
HPV
release of virus particles
HPV infected epithelium
intraepitelial neoplasia
HPV assambly
L1, L2
E1
E2
E6
E7
E4
Upward movement of infected cells
HPV DNA replication
basal layer of keratinocytes
basal membrane
episomal HPV DNA
infected basal keratinocytes
integrated HPV DNA

A


Uterus
Columnar Epithelium (endocervix)
Endocervical Canal
Vagina
Cervix
Squamous Epithelium (ectocervix)
Transformation Zone

B


Normal cervix
Squamous intraepithelial lesion
Low grade
High grade
Invasive cancer
Cervical intraepithelial neoplasia
Grade 1
Grade 2
Grade 3
Infectious viral particles
Squamous epithelium
Superficial zone
Midzone
Basal layer
Basement membrane
Dermis
Nuclei with episomal viral DNA
Nuclei with integrated viral DNA
Normal nuclei

SYMPTOMS AND SIGNS

- What are the warning signs of cervical cancer?
- Early stages of cervical cancer don't usually involve symptoms and are hard to detect. The first signs of cervical cancer may take time to develop.

❑**Signs and symptoms of Stage I cervical cancer can include**:

➢**Watery or bloody vaginal discharge that may be heavy and can have a foul odor.**

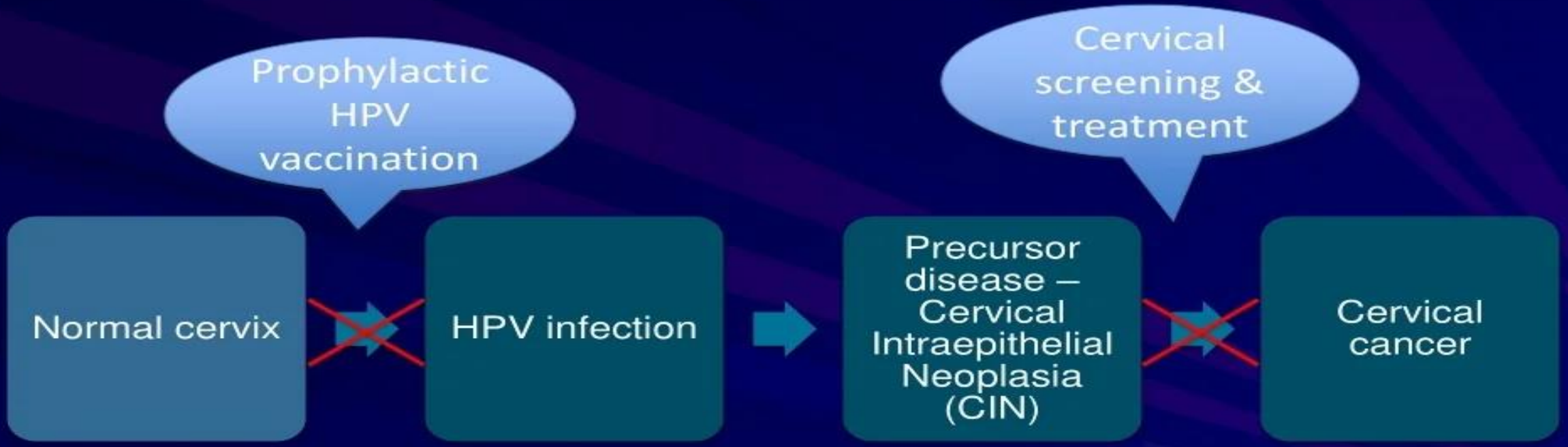
➢**Vaginal bleeding after sex, between menstrual periods or after menopause.**

➢**Pain during sex (dyspareunia).**

❑If cancer has spread to nearby tissues or organs, symptoms may include:

- **Difficult or painful urination, sometimes with blood in urine.**
- **Diarrhea, pain or bleeding from rectum when pooping.**
- **Fatigue, loss of weight and appetite.**
- **A general feeling of illness.**
- **Dull backache or swelling in legs.**
- **Pelvic/abdominal pain.**

2 opportunities to prevent cervical cancer



Cervical Cancer Screening: Importance of Pap Smear and HPV Tests

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

Abbreviations: ASCCP, American Society of Colposcopy and Cervical Pathology; CIN2, cervical intraepithelial neoplasia grade 2; FDA, US Food and Drug Administration; HPV, human papillomavirus.
[a]Cotesting is HPV testing in combination with cytology.

TABLE 3. Cervical Cancer Screening Tests

TEST	DEFINITION	FDA-APPROVED TEST	GENOTYPE
Cytology (also known as Pap test or Pap smear)	Examination of the cells in a sample taken from the cervix under a microscope to check for the presence of abnormal cells (abnormal cells may be precancerous or cancerous cells)		
Primary HPV test	A test to detect the DNA of oncogenic (high-risk) types of HPV in a sample taken from the cervix	cobas® HPV (approved 2014)	HPV types 16 and 18
	HPV is the causal agents of almost all cervical cancers	Onclarity HPV (approved 2018)	HPV types 16, 18, 45, 31, 51, 52, 33+58, 35+39+68, 56+59+66
Cotest (cytology and HPV test administered together)	A test that combines cytology to look at cells under a microscope and test for HPV DNA in the same sample taken from the cervix	Digene HC2 (approved 2003)	No
		Cervista HPV HR (approved 2009)	No
		Cervista HPV16/18 (approved 2009)	HPV types 16 and 18
		Aptima HPV (approved 2011)	No
		Aptima HPV16 and 18/45 (approved 2012)	HPV types 16 and 18/45
		cobas HPV (approved 2011)	HPV types 16 and 18
		Onclarity HPV (approved 2018)	HPV types 16, 18, 45, 31, 51, 52, 33+58, 35+39+68, and 56+59+66

Abbreviations: Aptima HPV, human papillomavirus assay from Hologic, Inc; Cervista HPV HR, high-risk human papillomavirus test (Cervista; cobas HPV, human papillomavirus test (cobas; Digene HC2, hybrid capture 2 test (Digene; FDA, US Food and Drug Administration; Hologic, Inc); HPV, human papillomavirus; Onclarity HPV, human papillomavirus assay from Becton, Dickinson & Company; Pap, Papanicolaou; Qiagen); Roche Molecular Systems).

Adapted from: US Food and Drug Administration. FDA Executive Summary: New Approaches in the Evaluation for High-Risk Human Papillomavirus Nucleic Acid Detection Devices. Prepared for the March 8, 2019 meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee (see FDA 2019[14]).

- **The ACS recommends :**

➢ that individuals with a cervix initiate cervical cancer screening at age 25 years and undergo primary HPV testing every 5 years through age 65 years (preferred).

➢ If primary HPV testing is not available, individuals aged 25 to 65 years should be screened with cotesting (HPV testing in combination with cytology) every 5 years or cytology alone every 3 years (acceptable) **(strong recommendation)**

MANAGEMENT OF HPV POSITIVE

- **Complete Algorithm for HPV-Positive Patients (ACOG/ASCCP 2025)**

❑ **HPV Positive, Cytology NILM**(Negative for Intraepithelial Lesion or Malignancy)

➢**HPV 16 or 18 positive** ⟶ **Immediate colposcopy.**

➢**Other high-risk HPV types** ⟶ **Repeat HPV-based testing in 1 year.**

Persistent positivity (2 consecutive tests) ⟶ **Colposcopy**.

❑ HPV Positive with Abnormal Cytology

➢ASC-US or LSIL + HPV positive ⟶ Colposcopy.

➢HSIL or ASC-H + HPV positive ⟶ Immediate colposcopy or expedited treatment.

Expedited treatment (without biopsy) is acceptable if immediate CIN3+ risk ≥60%. Colposcopy is acceptable if risk is lower.

❑HPV Positive with AGC (Atypical Glandular Cells)

- Colposcopy + endocervical sampling.

- Consider endometrial sampling if ≥35 years or risk factors for endometrial neoplasia.


Thank you for your attention