

Lower Anogenital Squamous Tract

Similar terminology is used for all HPV-associated squamous lesions of the lower anogenital tract (See LAST project)

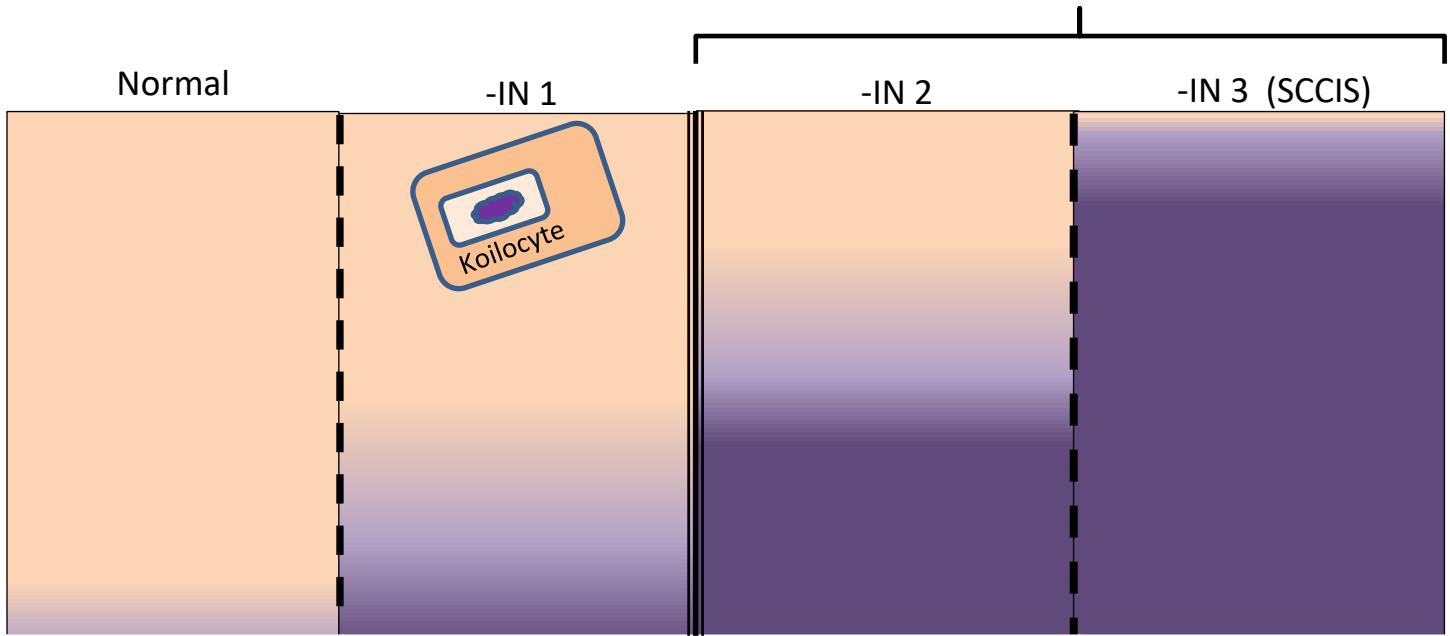
HPV-infection can follow two main paths:

Type 1 → Infects epithelium to support virion production → LSIL/Condyloma (often transient, self-limited, infection regresses)

Type 2 → Viral oncogene overexpression drives a clonal production of undifferentiated cells → HSIL (precancerous, persistent infection)

Low-Grade Squamous Intraepithelial Lesion (LSIL)

High-Grade Squamous Intraepithelial Lesion (HSIL)



	Normal	-IN 1	-IN 2	-IN 3 (SCCIS)
Koilocytosis	None	Present	Maybe	Maybe
Dysplastic basal cells	Absent, but nerves may be more prominent	Limited to lowest 1/3	Extend to 2/3	Full-Thickness
Mitoses	Basal layer only	Limited to lowest 1/3	Extend to 2/3	Full-Thickness
P16 IHC	Negative	Often negative	Block Positive	Block Positive

LAST Project: Darragh TM, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions. Arch Pathol Lab Med. 2012 Oct;136(10):1266-97.

Different abbreviations for different sites:

Site abbreviation + IN

AIN: Anal Intraepithelial Neoplasia

PaIN: Perianal Intraepithelial Neoplasia

PeIN: Penile Intraepithelial Neoplasia

CIN: Cervical Intraepithelial Neoplasia

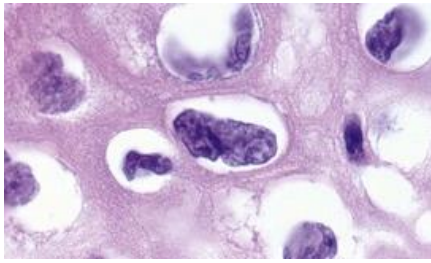
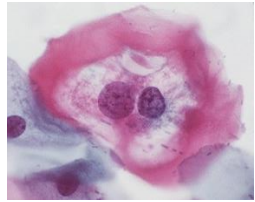
VaIN: Vaginal Intraepithelial Neoplasia

VIN: Vulvar Intraepithelial Neoplasia

LSIL Cytologic changes

Mature Keratinocytes (with lots of cytoplasm) with:

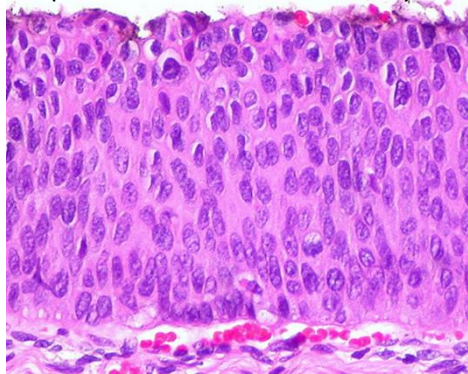
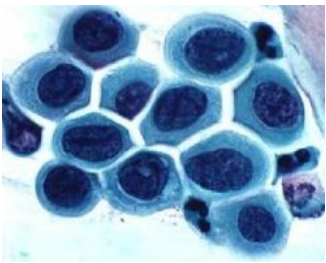
- **Enlarged nuclei** (>3x normal intermediate cells)
- Nuclear **membrane irregularities**
- Hyperchromasia (“Rasinoid”)
- Perinuclear **halos**
- **Multinucleation**



HSIL Cytologic changes

Immature keratinocytes (minimal cytoplasm, High N/C ratios) with:

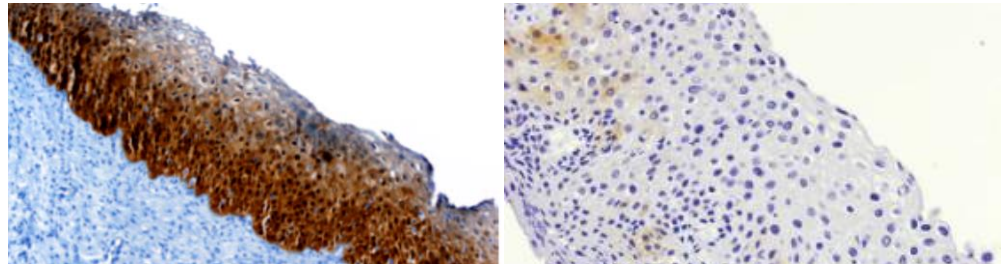
- **Irregular nuclear contours** (*Hint: think in 3-dimensions*)
- Increased nuclear size
- Increased mitoses



When to use P16 Immunohistochemistry:

Used as surrogate marker of High-risk HPV infection

- When the morphologic DDX is **between HSIL (P16 +) and a mimic**, such as squamous metaplasia (P16 -)
- When you are considering a **Dx of -IN2**, which should be P16+ (vs. LSIL, which should be P16 -)
- When there is **disagreement** between pathologists
- When there is a **high-risk** for missed HSIL disease (e.g., HPV +)



P16 Positive

Strong, diffuse, nuclear and cytoplasmic, block staining along the basal layer going at least 1/3 of the way up

P16 Negative

Weak/Patchy
i.e., Anything but “Block” positive

When P16 Immunohistochemistry will NOT help:

- When the biopsy is unequivocally LSIL, HSIL, or Negative morphologically
- When the DDX is between LSIL and Negative, as both processes are P16 negative (usually).

Just Remember:

- p16 has no value outside of morphologic context (LSIL can be positive !)
- p16 has a very good negative predictive value for HSIL

Human Papilloma Virus (HPV)

Sexually Transmitted Disease

Serotypes: **16 & 18** → High Risk → Most associated with **HSIL/SCC**

6 & 11 → Low Risk → Most associated with **LSIL/Condylomas**

HPV-associated oncoprotein E6 inactivates p53, E7 inactivates Rb

Usually infects transition zone between squamous and glandular mucosa.