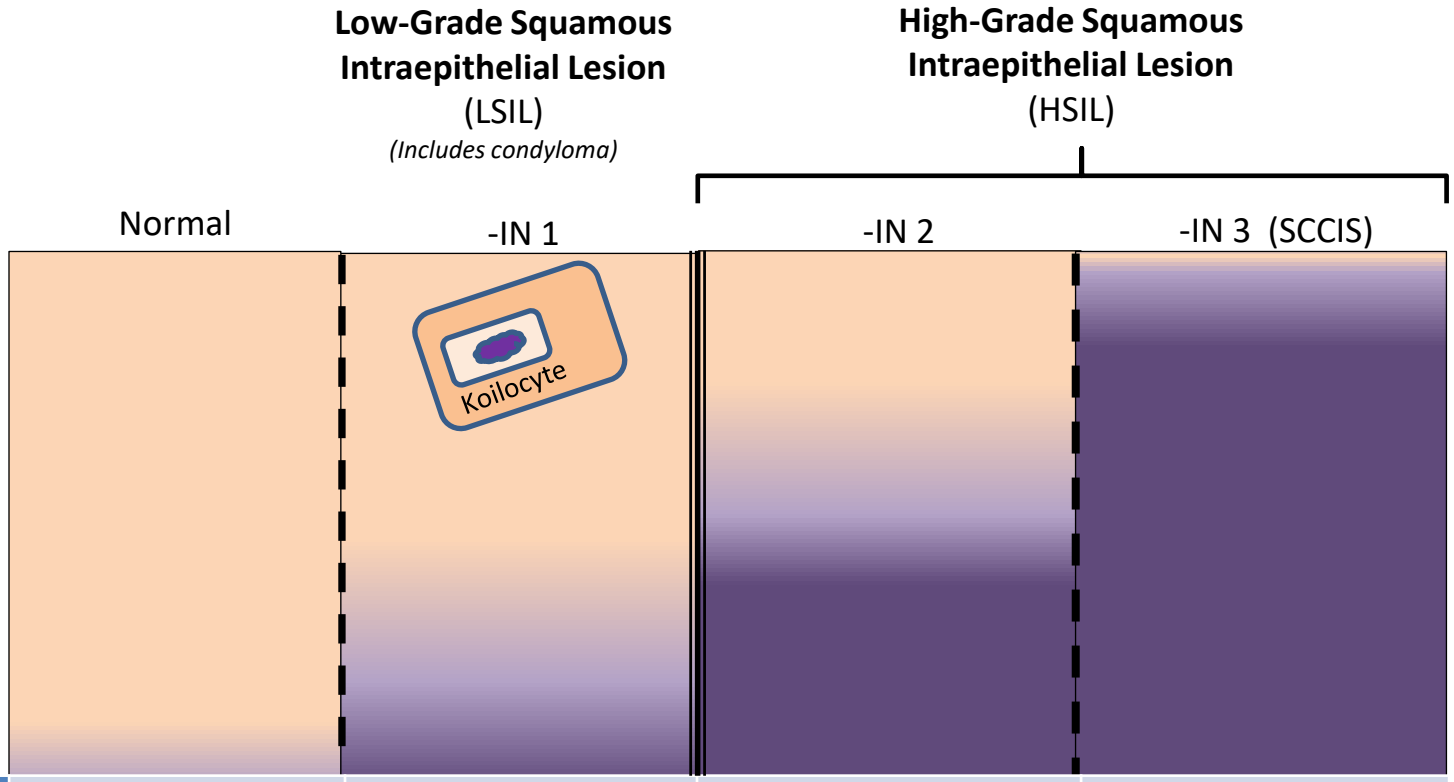
Prepared by Dr. Kurt Schaberg

Lower Anogenital Squamous Tract

Most Squamous cell carcinomas of the lower anogenital tract are caused by HPV (Human Papilloma Virus)
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:

1→ Infects epithelium to support virion production → LSIL/Condyloma (often transient, self-limited, infection regresses)→ **Low-risk**
2→ Viral oncogene overexpression → clonal production of undifferentiated cells → HSIL (precancerous, persistent infection) → **High-risk**



	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

Different abbreviations for different sites:

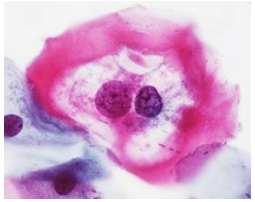
Site abbreviation + IN

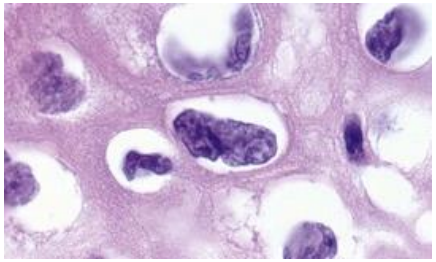
AIN: Anal Intraepithelial Neoplasia
PaIN: Perianal Intraepithelial Neoplasia
PeIN: Penile Intraepithelial Neoplasia
CIN: Cervical Intraepithelial Neoplasia
VaIN: Vaginal Intraepithelial Neoplasia
VIN: Vulvar Intraepithelial Neoplasia

LSIL Cytologic changes

Mature Keratinocytes (with lots of cytoplasm) with:

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

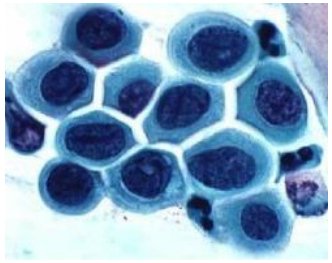


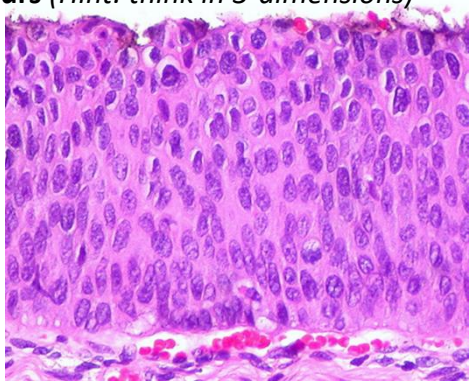


HSIL Cytologic changes

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

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

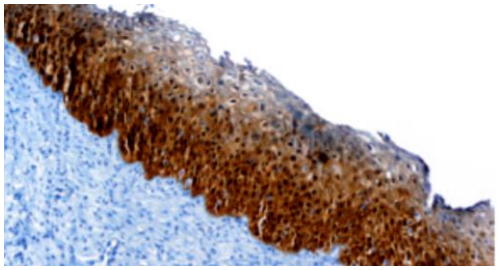


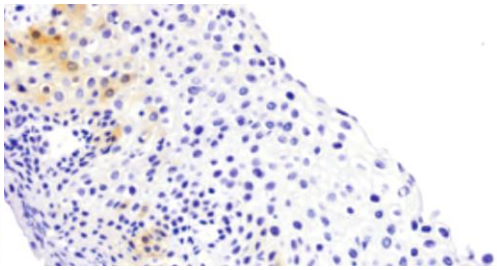


When to use P16 Immunohistochemistry:

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 usually 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)

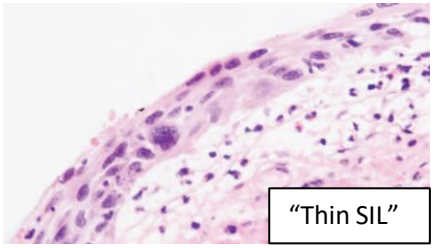
Sexually **T**ransmitted **D**isease
Serotypes: **16 &18** → High Risk→ Most associated with **HSIL/SCC**
6 &11 → Low Risk→ Most associated with **LSIL/Condylomas**

HPV-associated oncoprotein E6 inactivates p53, E7 inactivates Rb

Usually infects transition zone between squamous and glandular mucosa.

Special circumstances to call HSIL: *(that may go against prior rules)*

- Significant nuclear atypia and abnormal mitoses
- "Thin SIL" (<10 cells thick)
- "Keratinizing SIL": A markedly atypical (often pleomorphic) keratinizing proliferation. More often seen on cutaneous sites.
- Dysplasia extending into endocervical glands



"Thin SIL"

"Keratinizing SIL"

Superficially invasive squamous cell carcinoma

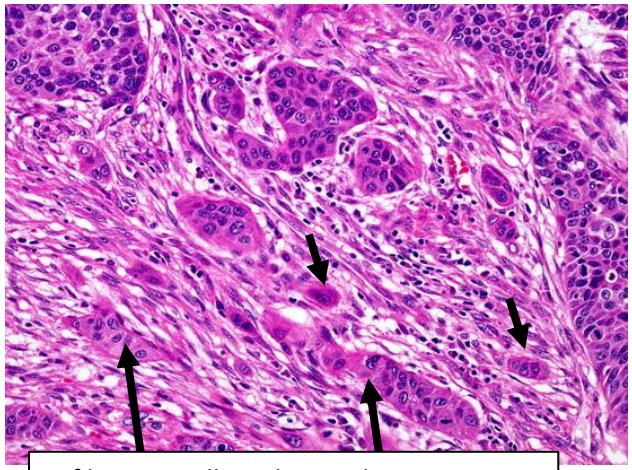
Term recommended for minimally invasive SCC that has been completely excised and might be amenable to local excisional (conservative) treatment only.

General requirements:

- Invasive depth of ≤ 3 mm from the basement membrane of the point of origin, AND
- Horizontal spread of ≤ 7 mm in maximal extent, AND
- Completely excised

(also report presence/absence of LVI, multifocality)

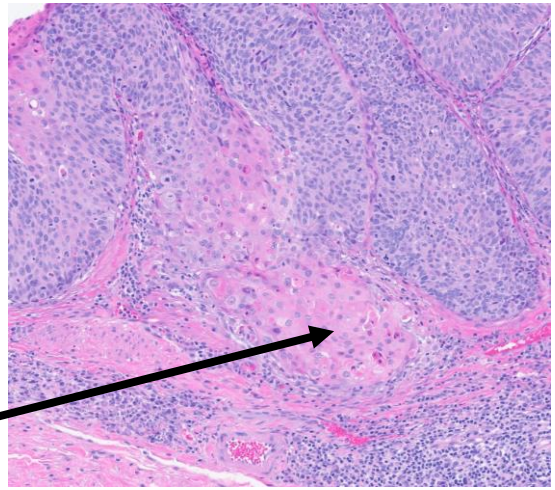
If a SCC doesn't meet these requirements→ *Invasive Squamous cell carcinoma*
(i.e., just leave off "superficial")



Infiltrating cells in desmoplastic stroma

Clues to Invasion:

- Infiltrative growth (often jagged) with desmoplastic/inflamed stroma
- Paradoxical (reverse) maturation
- Perineural or lymphovascular invasion
- Infiltrating single cells
- Complex architecture (after excluding tangential sectioning)



"Paradoxical" (Reverse) Maturation
When the cells get pinker/more keratinizing as they go deeper (the opposite of what you'd expect!