

Cervical Squamous Intraepithelial Lesions

HPV pathogenesis · morphology · classification · natural history

A pathology teaching lecture

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Learning outcomes

- Relate HPV biology to LSIL and HSIL morphology
- Translate dysplasia/CIN terminology into two-tier SIL categories
- Use epithelial maturation, koilocytic change, p16 and Ki-67 in lesion interpretation
- Interpret Robbins natural-history estimates and clinical implications

Why SIL matters

- A cervical squamous intraepithelial lesion is an epithelial abnormality associated with HPV infection
- Some lesions are precursors of invasive squamous carcinoma
- The long interval before many invasive cancers creates an opportunity for detection
- Grade informs the distinction between surveillance-oriented and treatment-oriented pathways

Cervical tissue compartments

SCHEMATIC — epithelial transition, not a histologic specimen



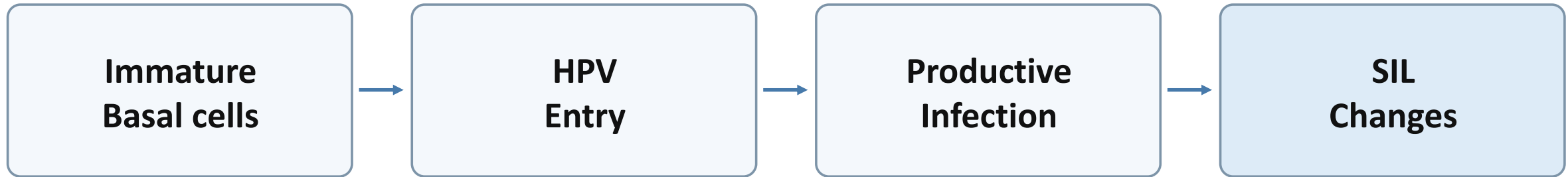
Stratified squamous



Columnar epithelium

The squamocolumnar junction is a transition between epithelial phenotypes

The transformation zone creates vulnerability



- HPV requires access to immature basal epithelial cells
- Mature, intact squamous surfaces ordinarily resist productive entry
- Repair and immature squamous metaplasia expose susceptible epithelial populations
- Cervical transformation-zone biology helps explain lesion predilection

A lesion is not equivalent to invasive cancer

Intraepithelial

Atypical cells within epithelial compartment

Architectural and nuclear change assessed above stroma

Invasive

Malignant epithelium penetrates the underlying stroma

A separate entity beyond the SIL classification

Invasive carcinoma is a distinct diagnostic endpoint

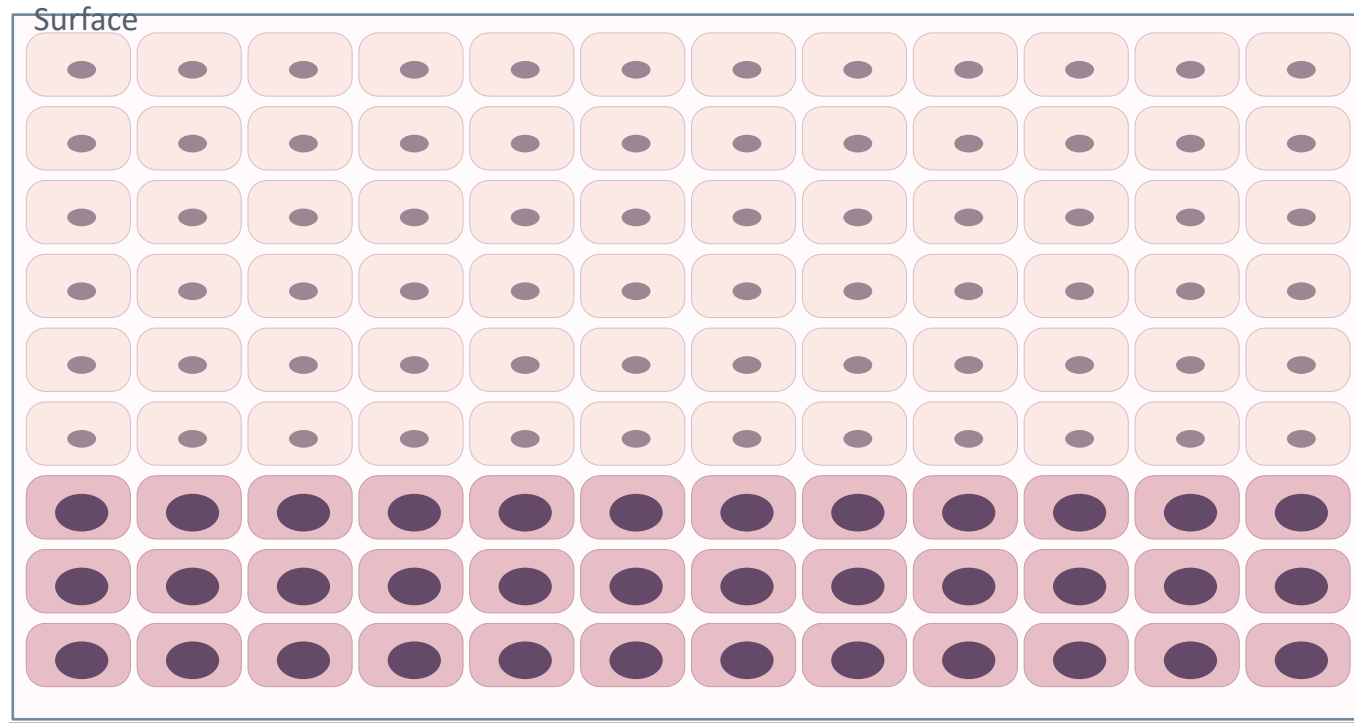
Three successive classification vocabularies

Historical dysplasia	CIN system	Two-tier SIL
Mild	CIN 1	LSIL
Moderate	CIN 2	HSIL
Severe / carcinoma in situ	CIN 3	HSIL

Older vocabulary: Mild, moderate, and severe dysplasia; Carcinoma in situ

LSIL maps to CIN 1

CIN 1 / LSIL



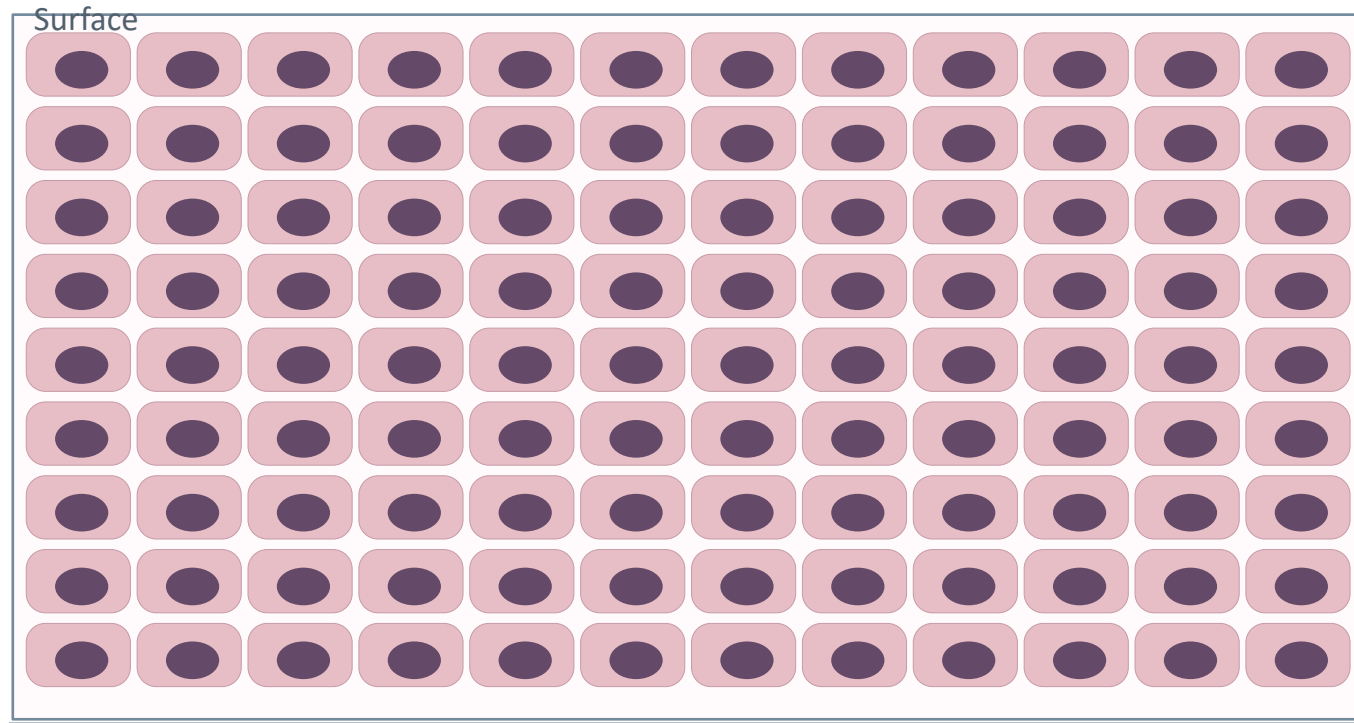
Stromal side

Editable schematic — not histology

- LSIL corresponds to mild dysplasia / CIN 1
- Immature atypical cells largely occupy the lower epithelial third
- Maturation is retained in the upper epithelial layers
- Koilocytic changes commonly signal productive HPV replication

HSIL unifies CIN 2 and CIN 3

Normal



Stromal side

Editable schematic — not histology

- HSIL includes CIN 2 and CIN 3 in the two-tier terminology
- Abnormal proliferating immature cells expand beyond the lower third
- CIN 3 may show nearly full-thickness loss of maturation
- The higher-grade category is clinically important because progression risk is greater

Why two-tier terminology is useful

LSIL

Usually transient productive infection

Common spontaneous regression

HSIL

Deregulated cell growth

Greater concern for malignant progression

Management still requires case-specific clinical evaluation

HPV is central to cervical squamous neoplasia

- Human papillomaviruses are DNA viruses classified by oncogenic risk
- High-risk types are central to cervical precursor lesions and carcinoma
- Many genital HPV infections are asymptomatic
- Viral presence alone is not equivalent to a histologic SIL

High-risk and low-risk are biologic groups

High-risk HPV

E6/E7 strongly impair tumour suppressor control

Associated with cervical precursors and cancer

Low-risk HPV

Different E6/E7 interactions

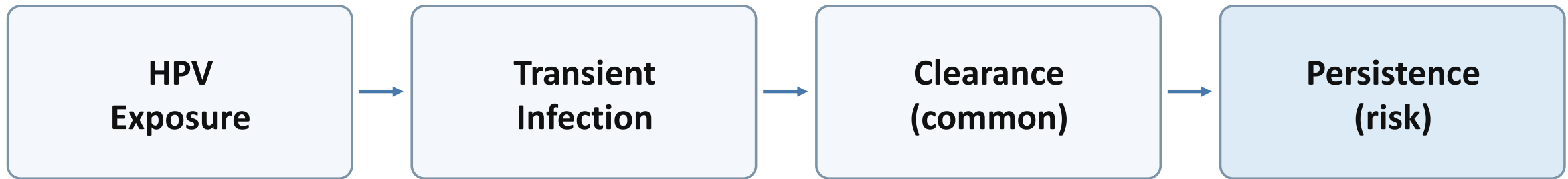
Commonly causes condylomata

Risk designation concerns oncogenic potential, not whether infection is symptomatic

HPV-16 is prominent

- HPV-16 as the most common type in LSIL and HSIL
- The text reports high-risk HPV association in >80% of LSIL and 100% of HSIL
- These figures summarize the textbook source rather than a universal individual test rule
- HPV type alone cannot determine a lesion's outcome

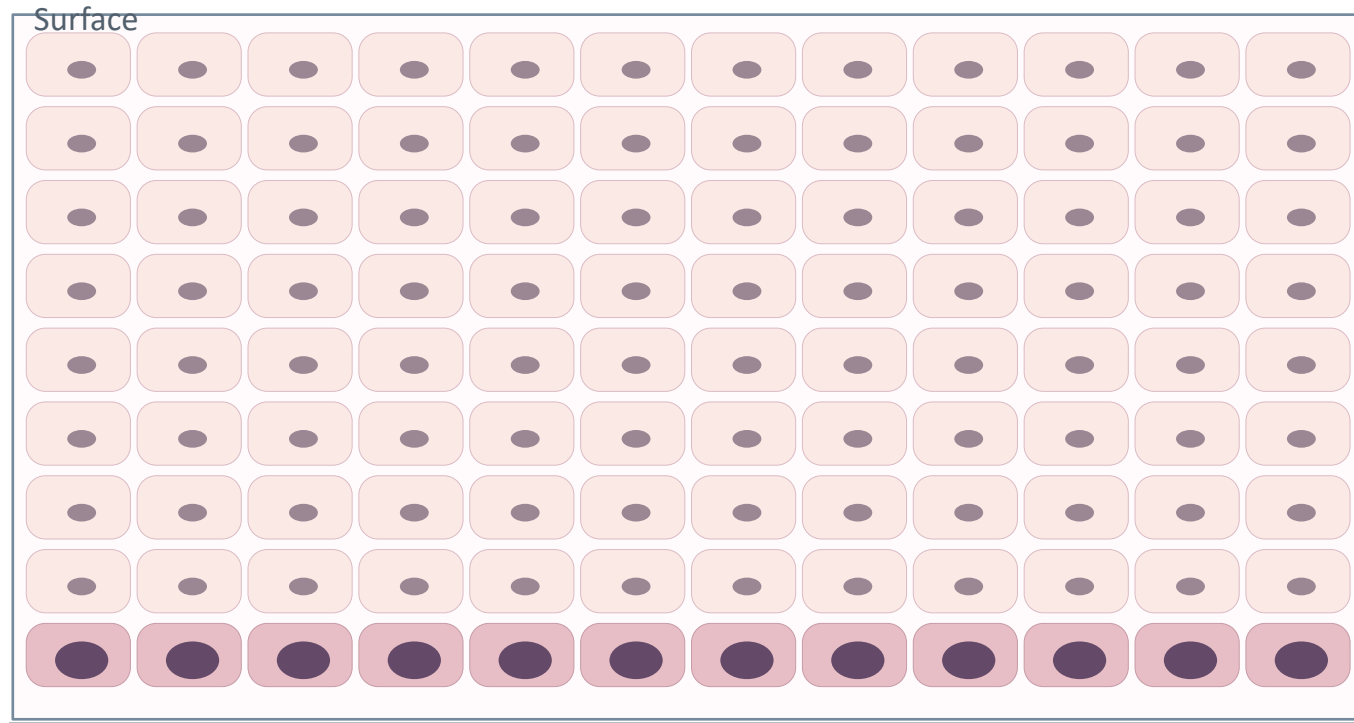
HPV infection is common; Persistence is selective



- The source reports clearance of ~50% of infections within 8 months
- Approximately 90% clear within 2 years
- High-risk infections persist longer on average than low-risk infections
- Persistence increases the chance of precursor lesions and carcinoma

Basal-cell infection precedes surface changes

Normal

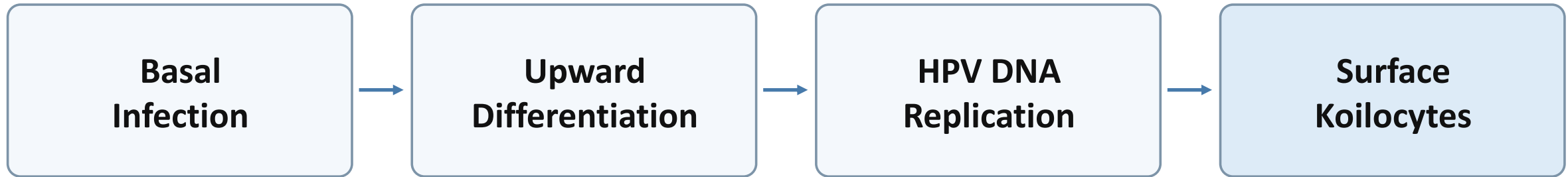


Stromal side

Editable schematic — not histology

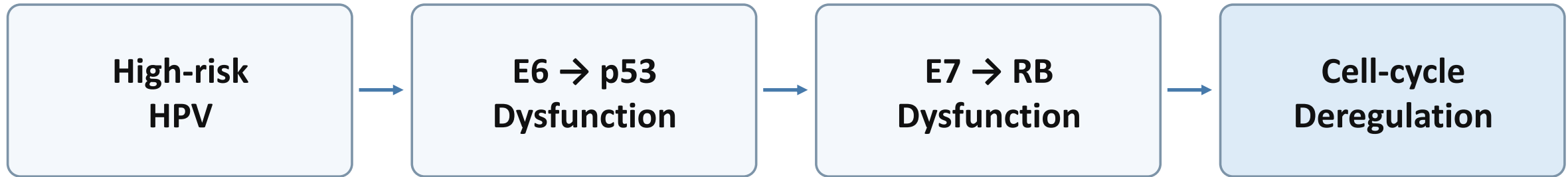
- Entry occurs in immature basal epithelial cells
- Virus replication is amplified in differentiating cells above the basal layer
- The infected epithelium becomes abnormal in a stratified, layer-dependent fashion
- These differences produce diagnostic histologic and biomarker patterns

Productive infection: A layered viral life cycle



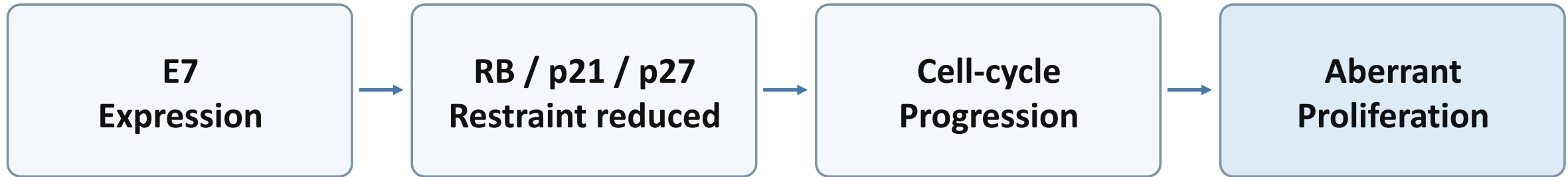
- Basal cells maintain an infected population
- Maturing keratinocytes support substantial HPV DNA replication
- Superficial koilocytes can contain particularly abundant viral DNA
- Superficial proliferative activity is abnormal for normal squamous epithelium

E6 and E7 help force cell-cycle progression



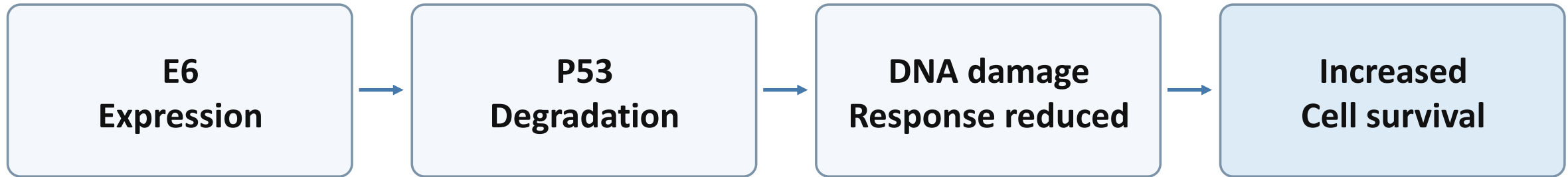
- High-risk HPV E7 interferes with the RB pathway
- High-risk HPV E6 promotes loss of p53 function
- The combined effect favors cell cycling despite maturation cues
- Impaired growth control facilitates additional genetic alterations

E7 disrupts the RB checkpoint



- Proteasomal degradation of RB by E7
- E7 also interferes with the cell-cycle inhibitors p21 and p27
- Reduced checkpoint restraint promotes continued cell-cycle transit
- The consequences are important in differentiated epithelial layers

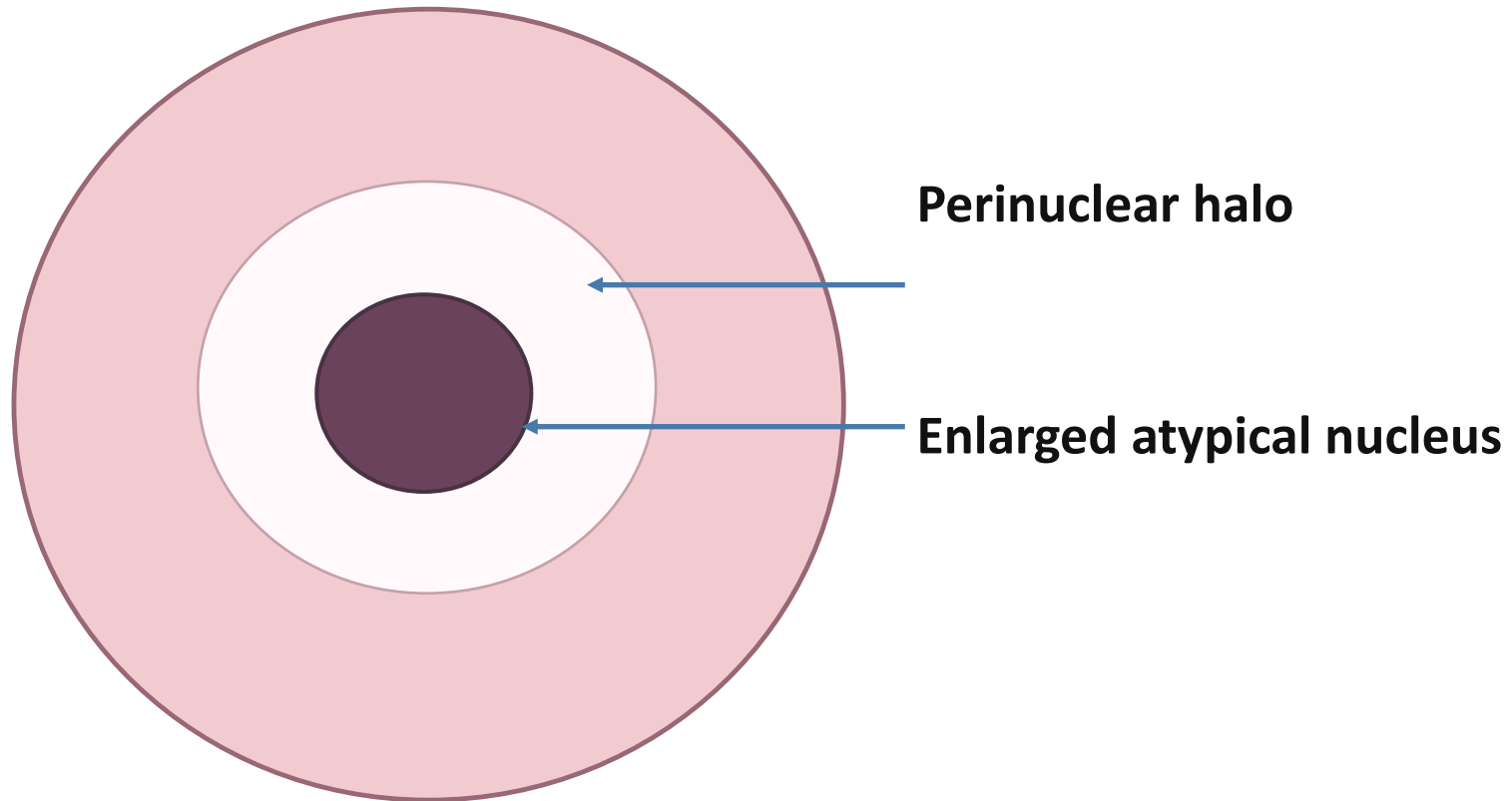
E6 weakens p53 surveillance



- High-risk HPV E6 promotes proteasome-mediated p53 degradation
- P53 loss weakens the response to DNA injury
- E6 can up-regulate telomerase, favoring replicative persistence
- These changes contribute to cellular immortalization and progression potential

E5 contributes to koilocytic morphology

SCHEMATIC — koilocyte features, not a clinical specimen



The visible nuclear changes plus halo constitute koilocytic atypia

Episomal and integrated HPV are not synonymous

Episomal pattern	Integrated pattern
Common in precursor lesions	Frequent in established carcinomas
Supports productive viral genome maintenance	May further deregulate E6/E7 expression

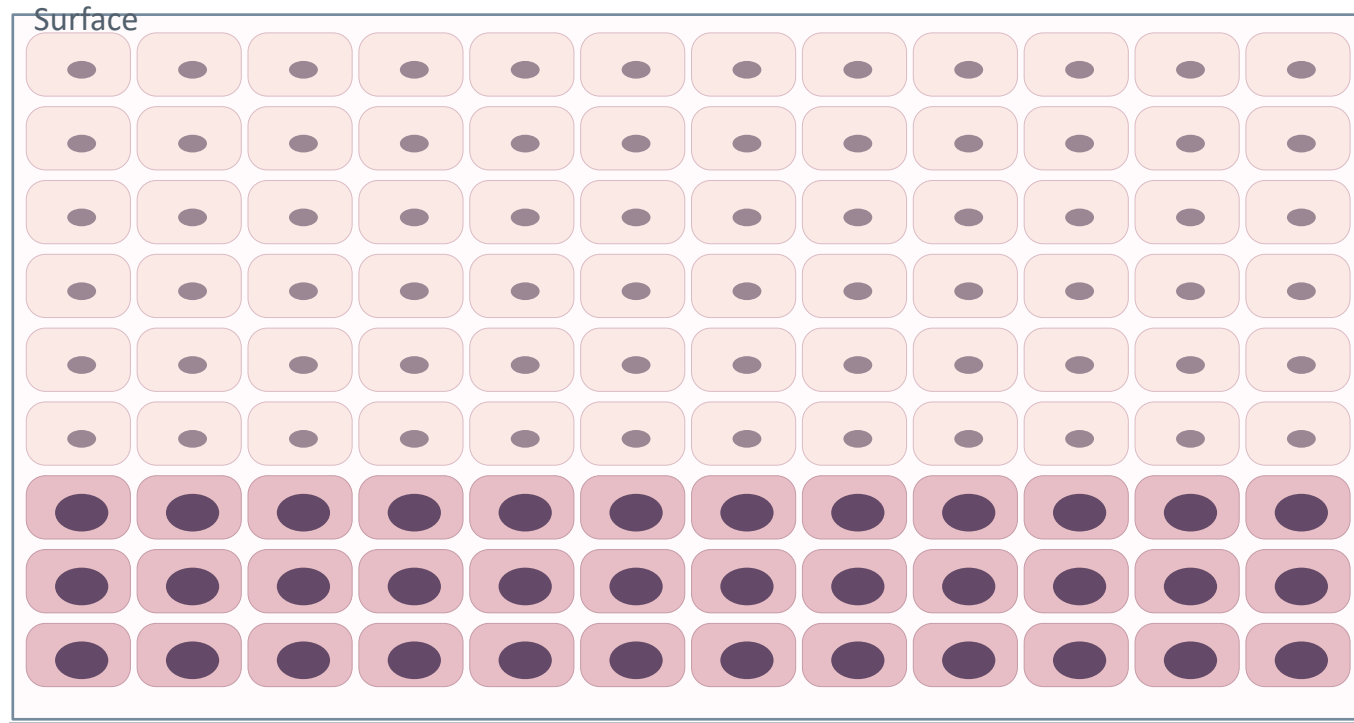
This contrast is a general pathogenetic association, not a stand-alone SIL grading test

Why infection does not always progress

- Most infections resolve rather than become persistent
- The host immune response influences viral clearance
- Co-carcinogenic exposures and host factors modify progression risk
- A molecular risk genotype cannot predict a specific patient's clinical course

LSIL: Productive viral infection dominates

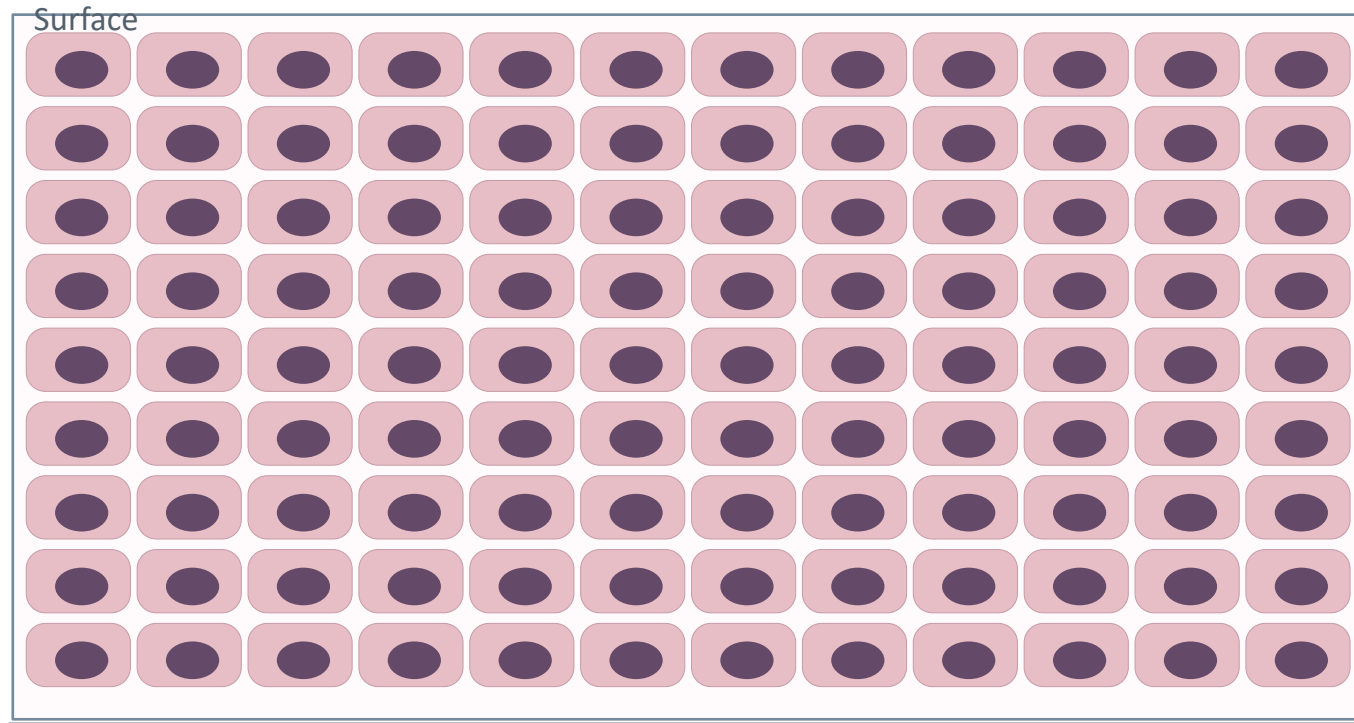
CIN 1 / LSIL



- High epithelial viral replication is a defining biologic theme
- Host growth regulation is disturbed, but maturation remains evident
- Koilocytes are characteristic cytopathic correlates
- Spontaneous regression is more common than malignant progression

HSIL: Cellular deregulation dominates

Normal



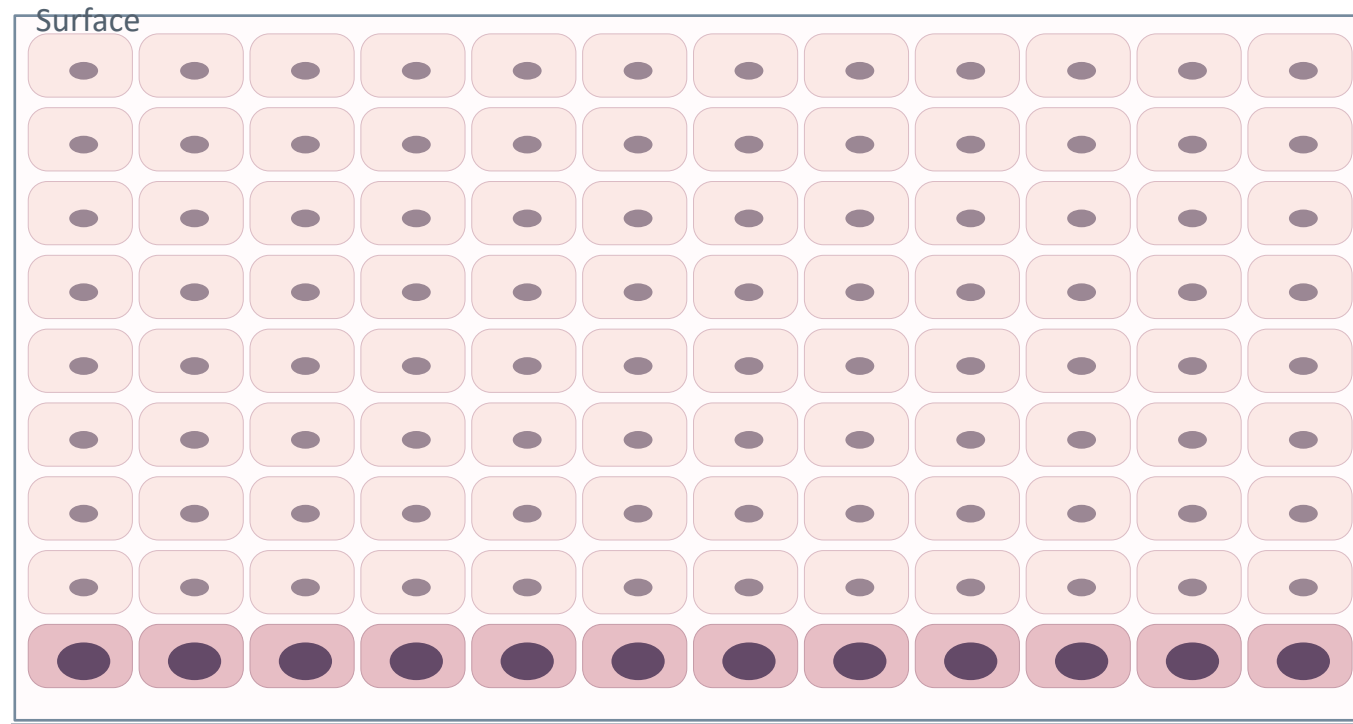
Stromal side

Editable schematic — not histology

- Expansion of proliferating immature squamous cells is prominent
- Epithelial maturation is markedly reduced or arrested
- Viral replication is lower than in productive LSIL
- Cell-cycle derangement may become irreversible

The normal squamous baseline

Normal



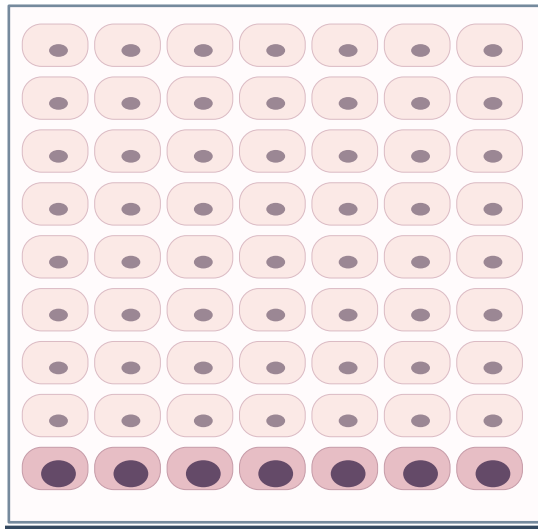
Stromal side

Editable schematic — not histology

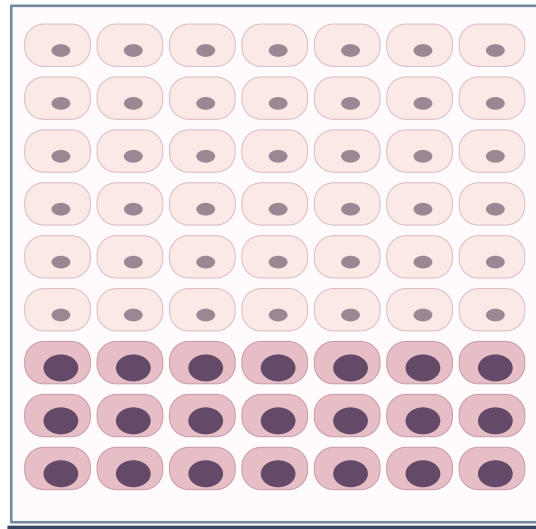
- Basal immature cells ordinarily form a thin proliferative compartment
- Maturation increases toward the epithelial surface
- Nuclei become less conspicuous in upper layers
- Comparing altered tissue to this baseline is essential

The grading principle is vertical extent

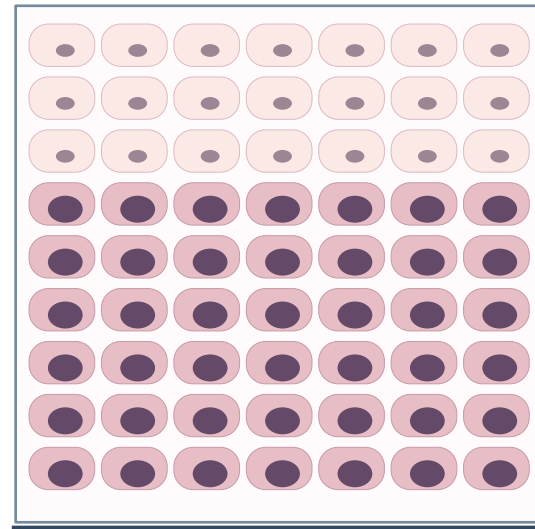
Normal



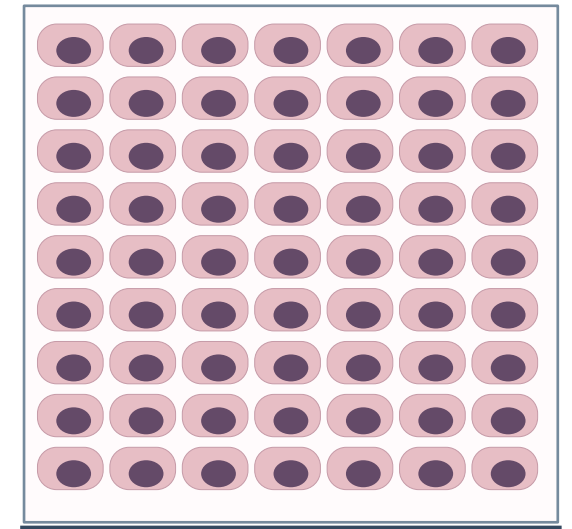
CIN 1 / LSIL



CIN 2 / HSIL



CIN 3 / HSIL

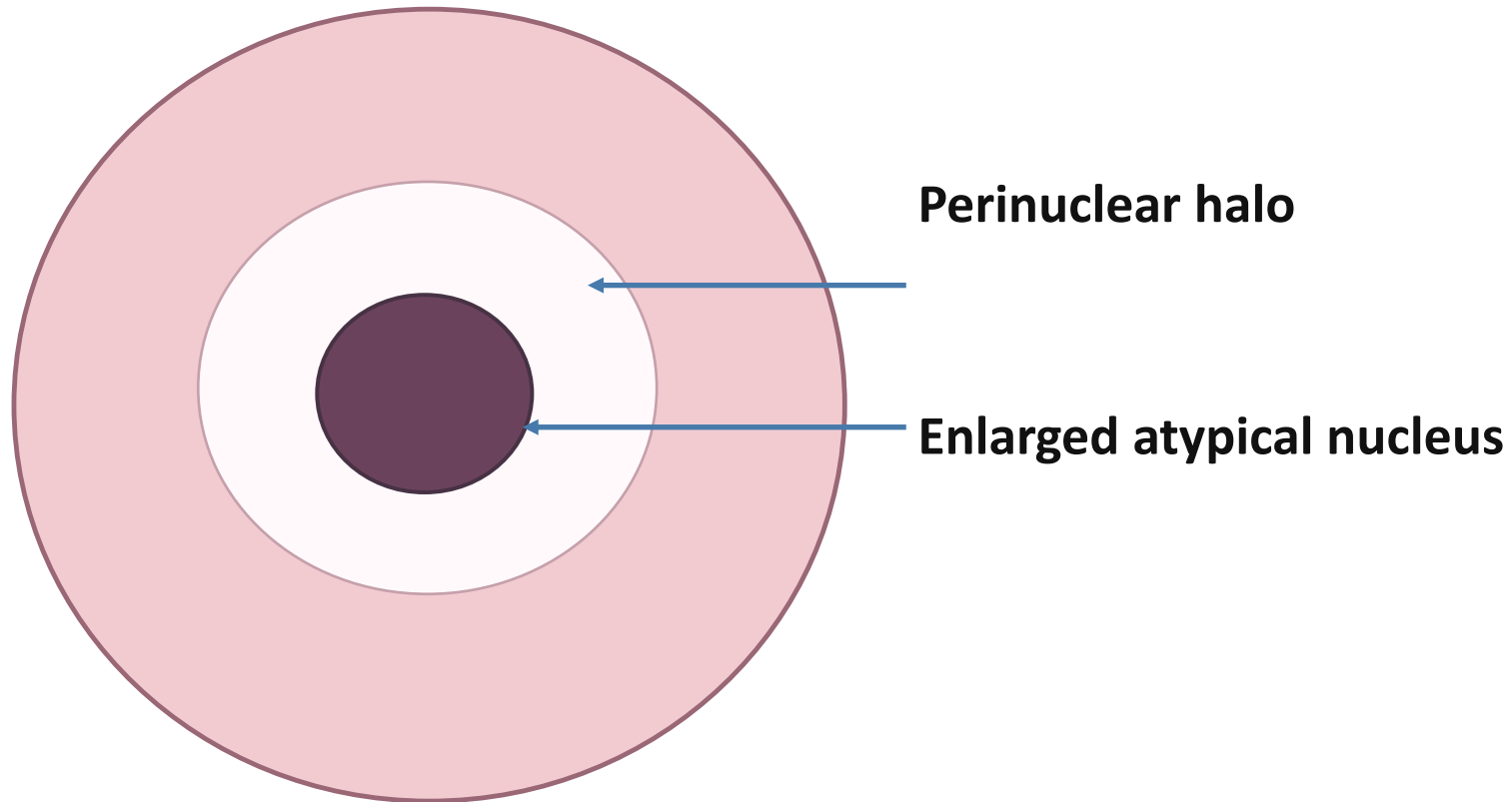


Assess how far immature atypical cells extend above the basal layer

Schematic epithelial compartments — not a histologic specimen

Nuclear enlargement signals atypia

SCHEMATIC — koilocyte features, not a clinical specimen



Architecture and cytology should be read together

Hyperchromasia and coarse chromatin

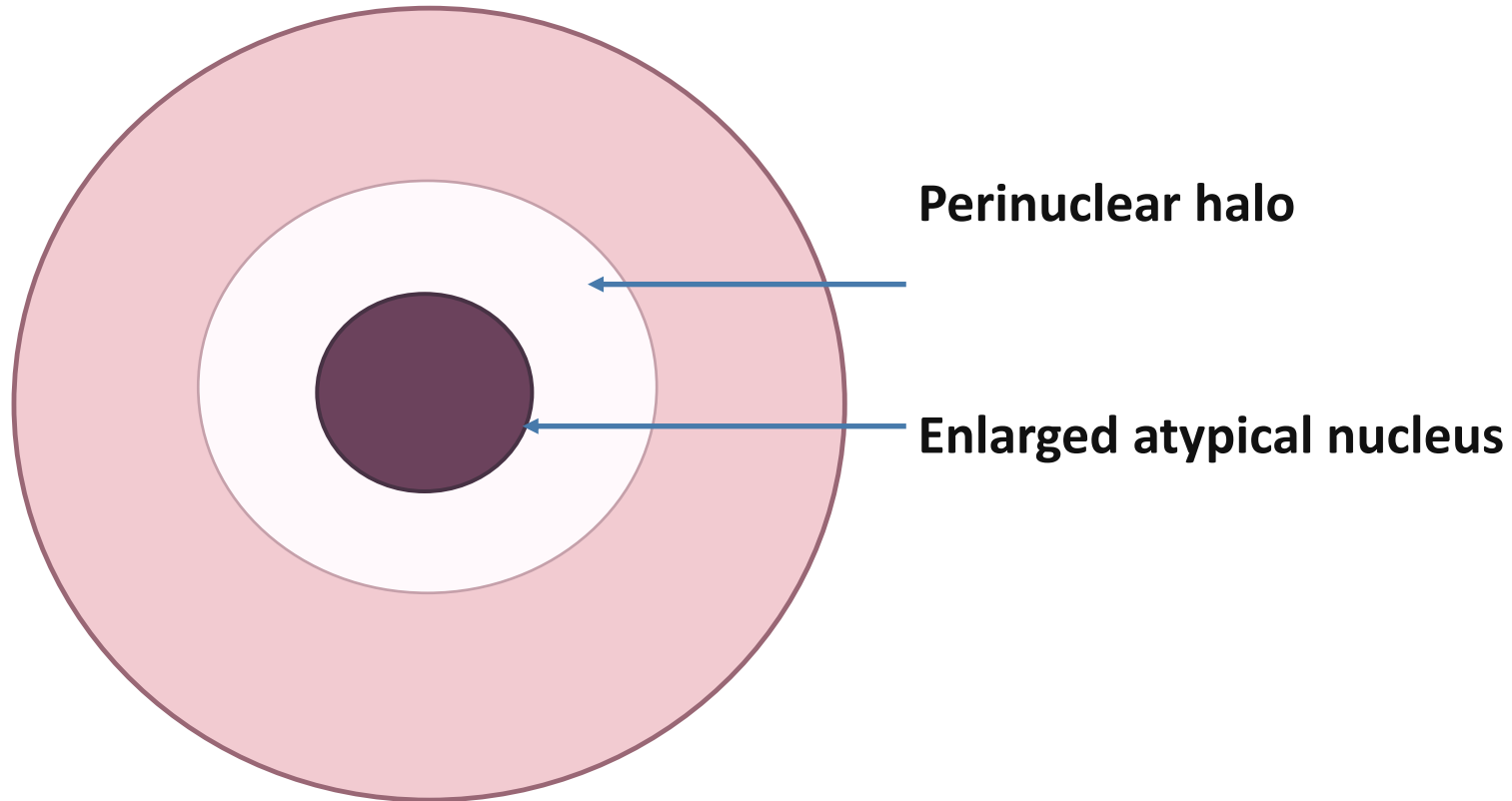
- Hyperchromasia denotes unusually dark-staining nuclei
- Coarse nuclear chromatin is part of Robbins' diagnostic description
- These features accompany irregular proliferation and differentiation
- Neither feature by itself determines LSIL versus HSIL

Variation in nuclear size and shape

- Nuclear pleomorphism occurs within abnormal squamous epithelium
- Assess variability across cells, not just one atypical nucleus
- Anatomic location of atypical cells changes the grade interpretation
- Koilocytic change provides an HPV-associated cytopathic context

Koilocytosis combines two findings

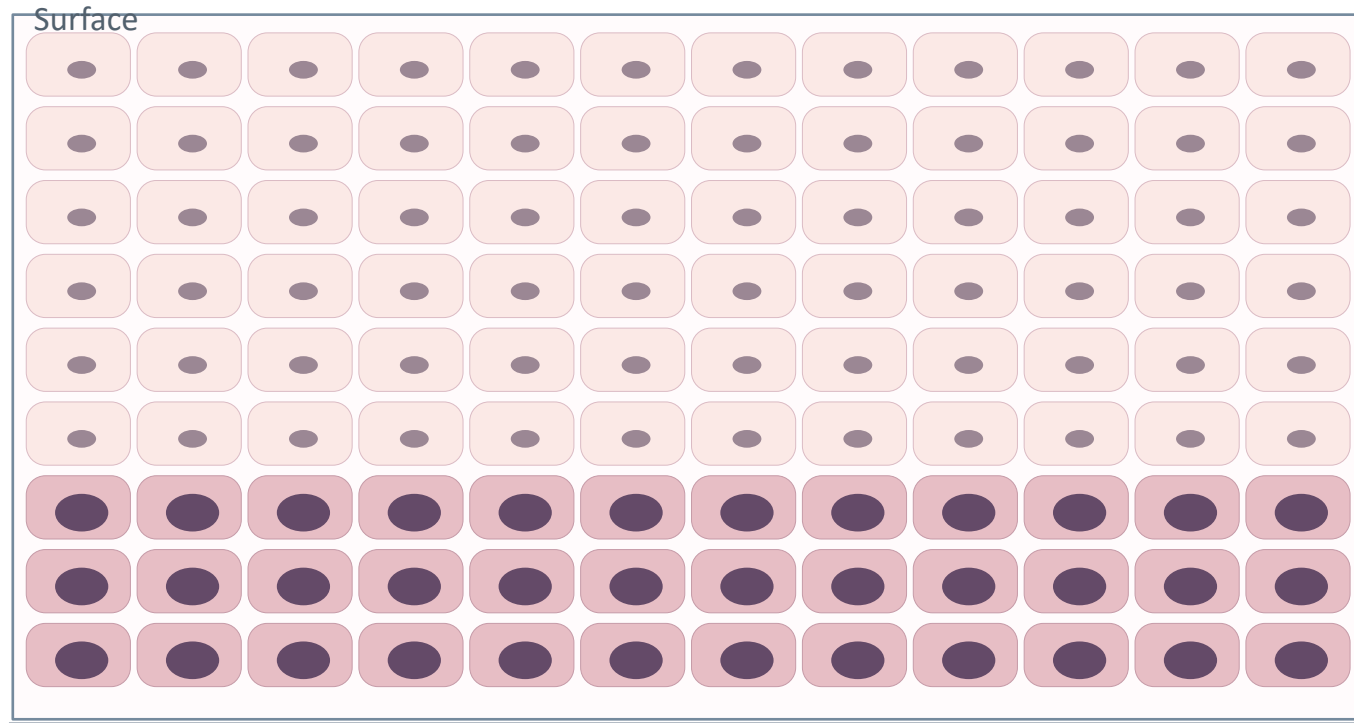
SCHEMATIC — koilocyte features, not a clinical specimen



Koilocytosis is a morphologic sign of productive HPV effect

LSIL: Maturation is retained

CIN 1 / LSIL



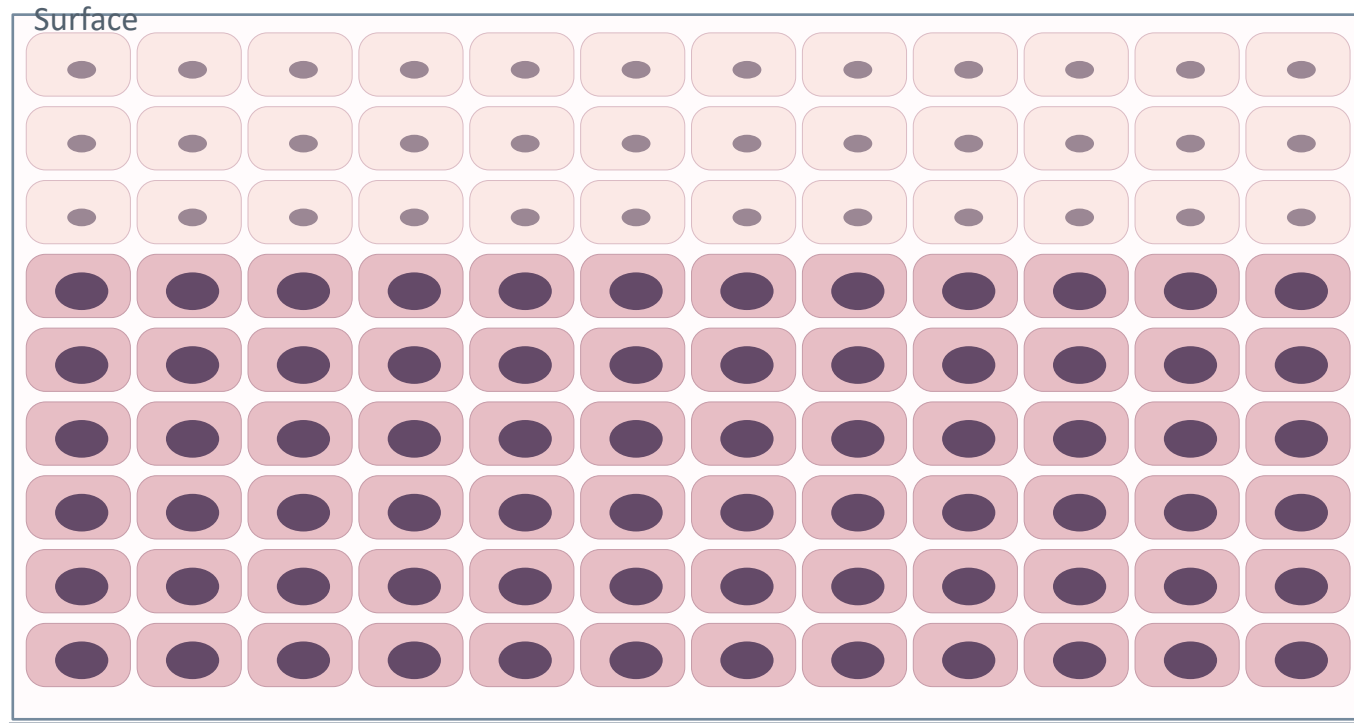
Stromal side

Editable schematic — not histology

- The abnormal immature compartment is limited mainly to the lower third
- Superficial squamous differentiation remains visible
- Koilocytic atypia may be apparent in maturing upper cells
- This architecture aligns with an active productive infection

CIN 2: Atypia rises into intermediate layers

CIN 2 / HSIL



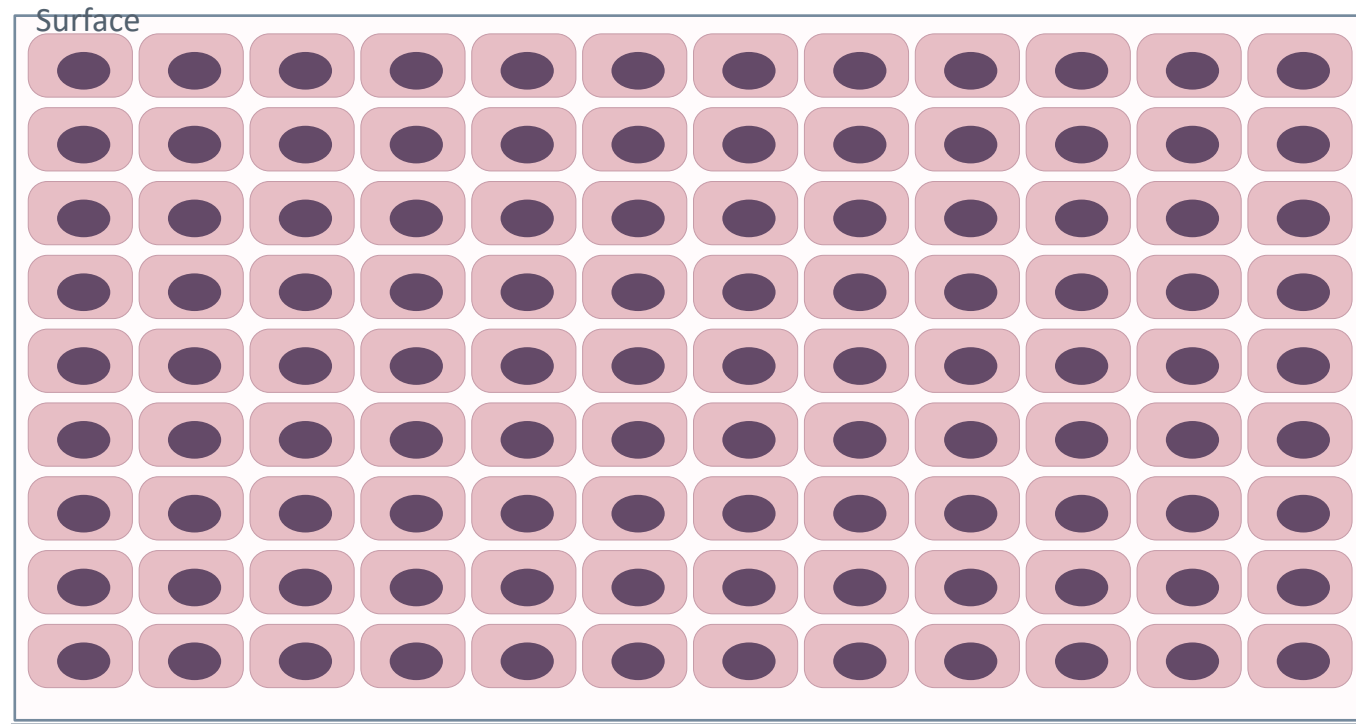
Stromal side

Editable schematic — not histology

- Atypical immature cells extend above the epithelial lower third
- Surface maturation is reduced relative to LSIL
- This pattern falls within HSIL under the two-tier system
- The CIN 2 designation expresses its location within a continuum

CIN 3: Maturation may be lost throughout

CIN 3 / HSIL



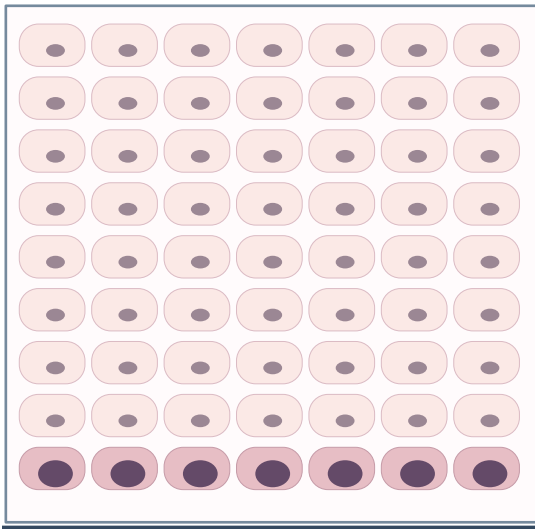
Stromal side

Editable schematic — not histology

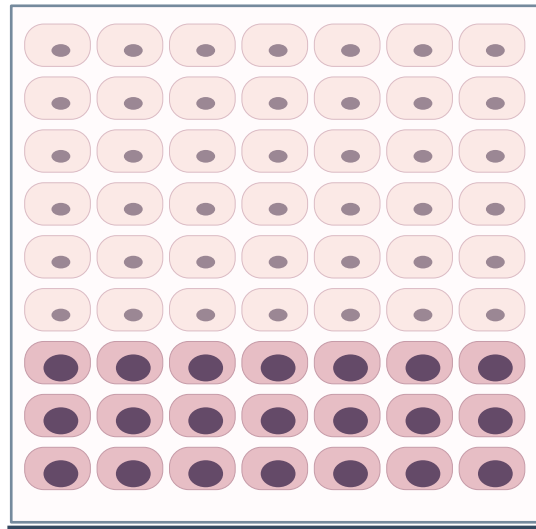
- Immature atypical cells extend to the epithelial surface
- Atypia is diffuse across much or all of epithelial thickness
- The architecture corresponds to severe dysplasia / carcinoma in situ
- CIN 3 is still an intraepithelial lesion unless stromal invasion is demonstrated

Read the full epithelial column

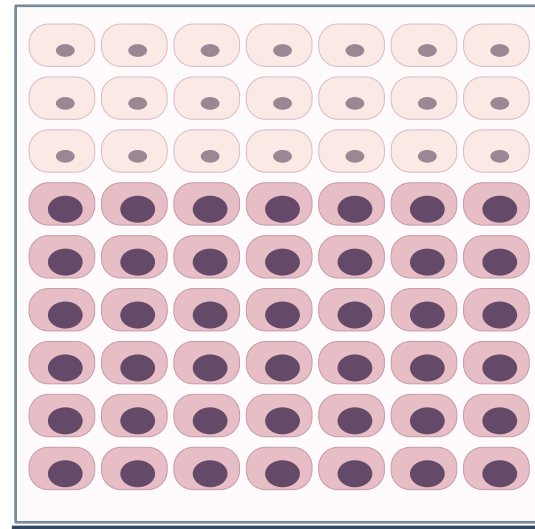
Normal



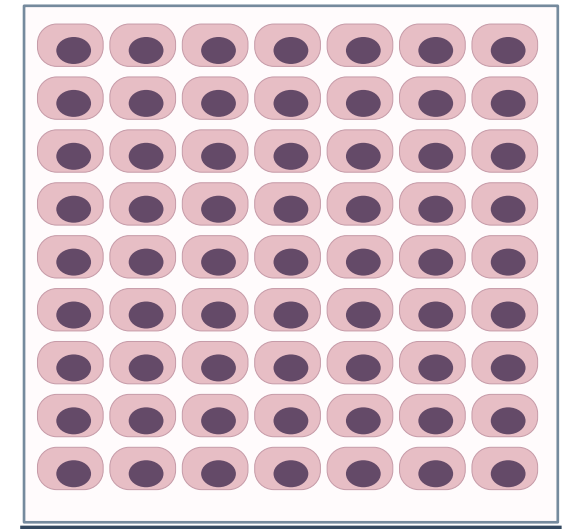
CIN 1 / LSIL



CIN 2 / HSIL



CIN 3 / HSIL



Locate the basement-membrane side and the luminal surface

Schematic epithelial compartments — not a histologic specimen

Do not confuse grade with invasion

Grade	Invasion
Degree of epithelial maturation loss	Relation to epithelial–stromal boundary
Distribution of atypical cells	Presence of malignant cells in stroma

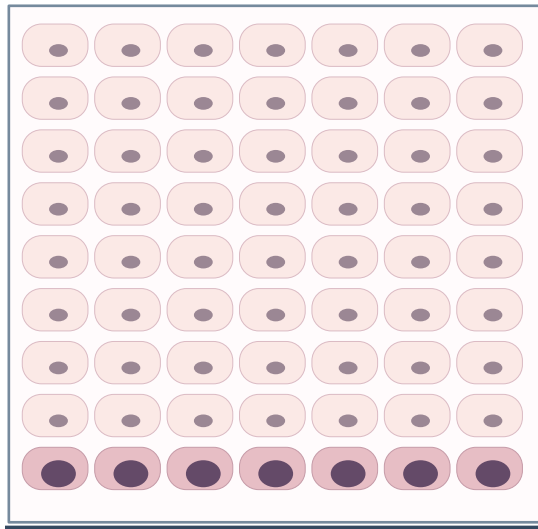
A complete tissue assessment is needed when invasion is suspected

Atypia must be assessed in context

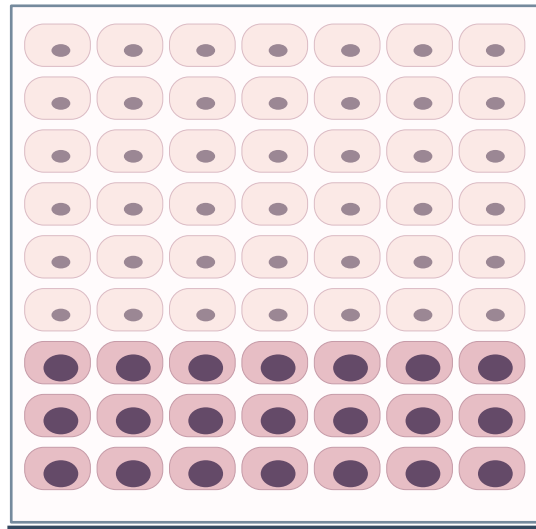
- Inflammation and repair can cause atypical-appearing squamous cells
- Marked cervicitis can disturb Pap cytology
- Cytology abnormalities require appropriate diagnostic correlation
- Avoid equating isolated nuclear atypia with tissue-confirmed HSIL

Morphologic spectrum: A single visual framework

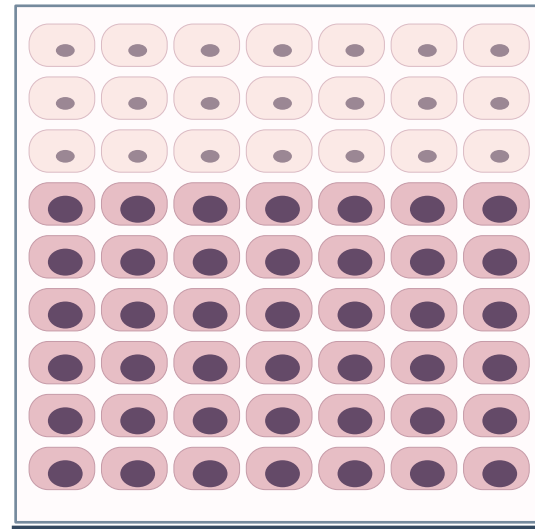
Normal



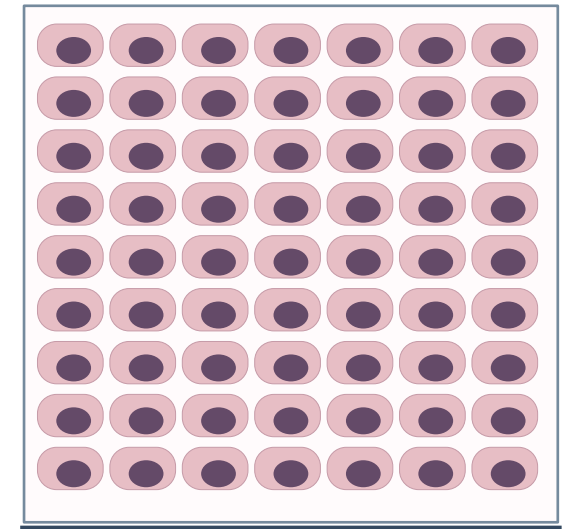
CIN 1 / LSIL



CIN 2 / HSIL



CIN 3 / HSIL



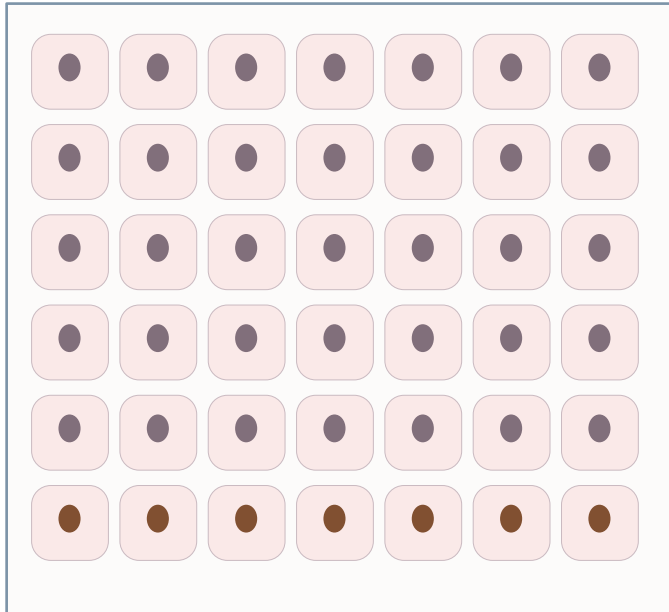
Normal epithelium maintains an organized maturation gradient

Schematic epithelial compartments — not a histologic specimen

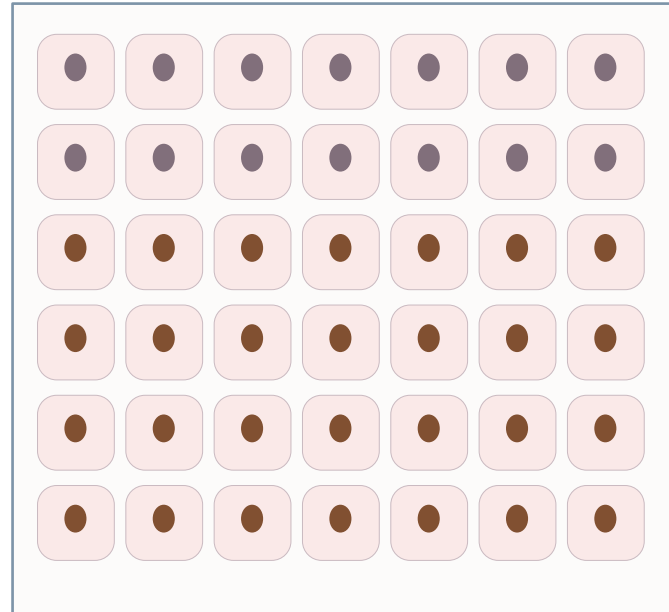
Ki-67 is a marker of proliferative activity

SCHEMATIC — vertical staining distributions; Not clinical immunohistochemistry

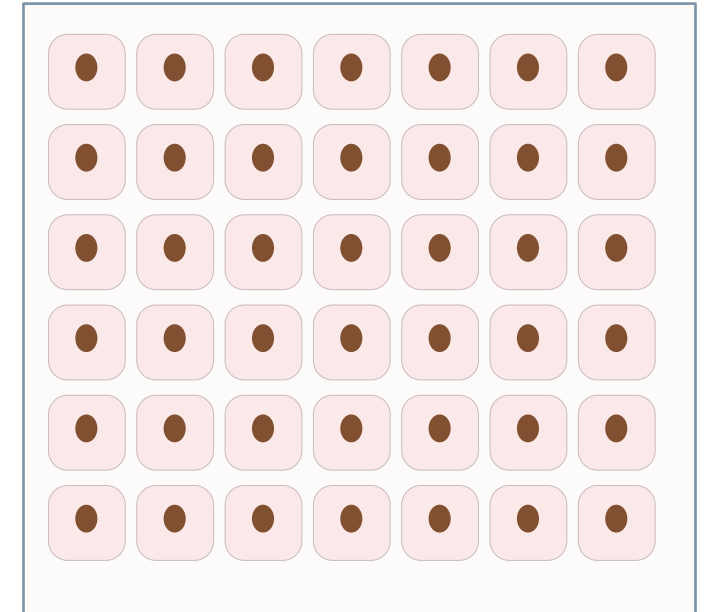
Normal proliferation



Upward Ki-67



P16 overexpression

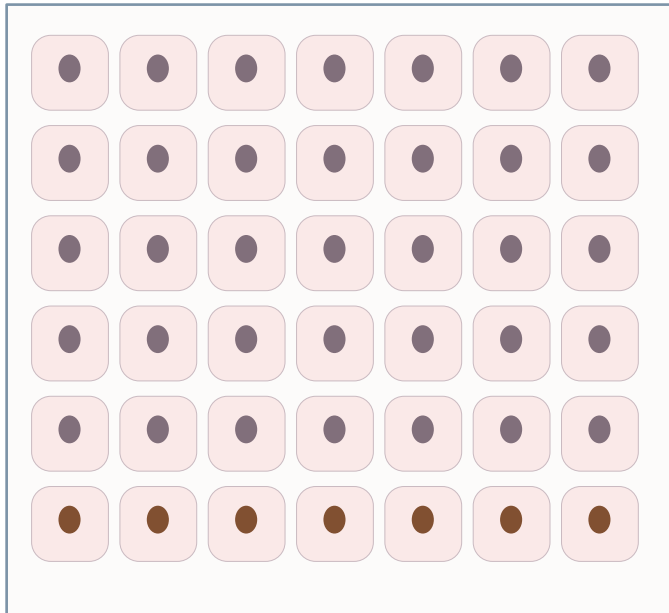


- Normal squamous epithelium restricts proliferation largely to basal cells
- HPV-related lesions show Ki-67-positive cells higher in the epithelium

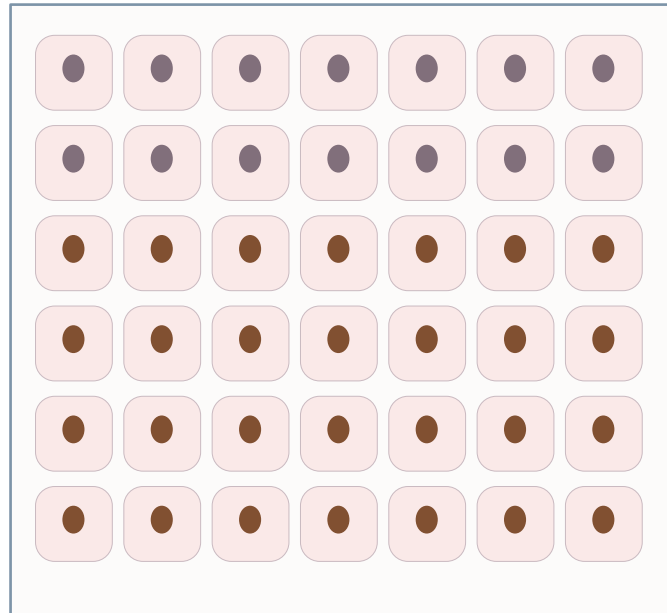
P16 reflects disturbed cell-cycle control

SCHEMATIC — vertical staining distributions; Not clinical immunohistochemistry

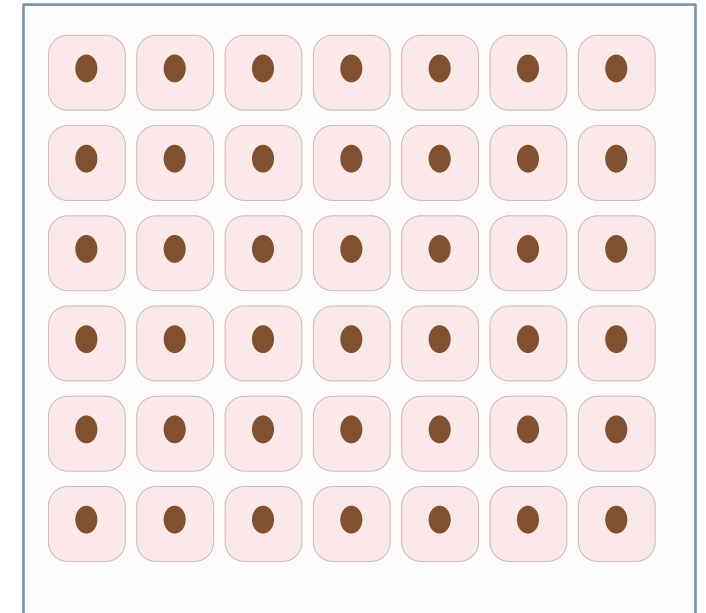
Normal proliferation



Upward Ki-67



P16 overexpression



- P16 is a cyclin-dependent kinase inhibitor
- Its overexpression in high-risk HPV-associated SIL

P16 and Ki-67 answer different questions

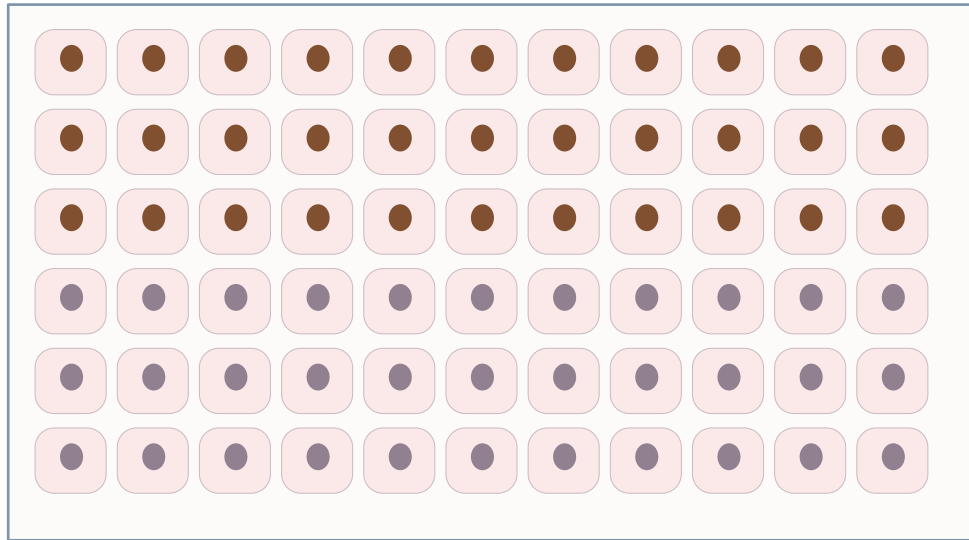
Test	Question answered	Interpretive caution
H&E	What is the tissue architecture and atypia?	Primary morphologic assessment
Ki-67 IHC	Where are cycling cells located?	Evaluate vertical distribution
p16 IHC	Is the cell-cycle response altered?	Interpret pattern and H&E together
HPV DNA assay	Is viral DNA detected?	Detection is not synonymous with HSIL

Ki-67 reflects where cells are actively cycling

HPV DNA localizes to maturing keratinocytes

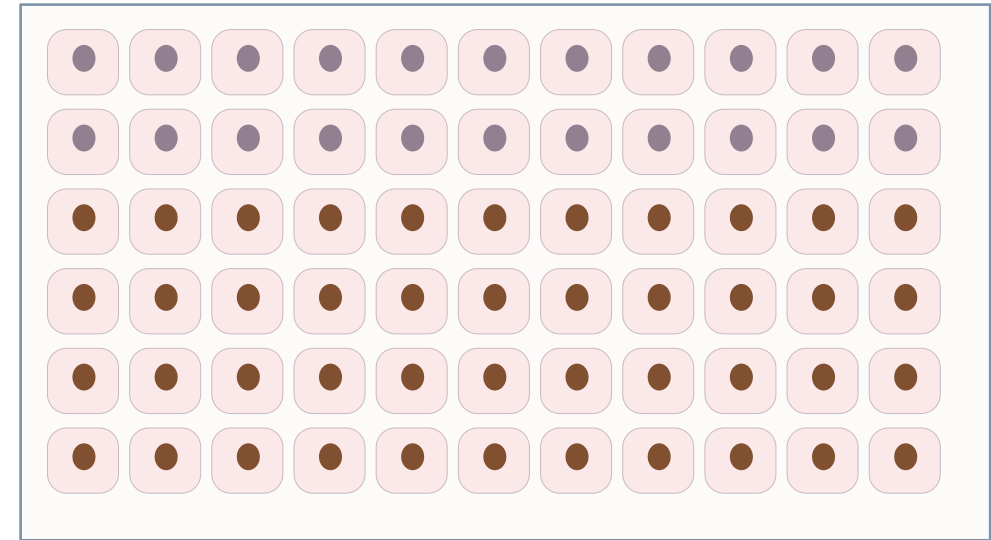
SCHEMATIC — viral DNA and Ki-67 localize to different epithelial compartments

HPV DNA: Mature upper cells



Viral replication predominantly above

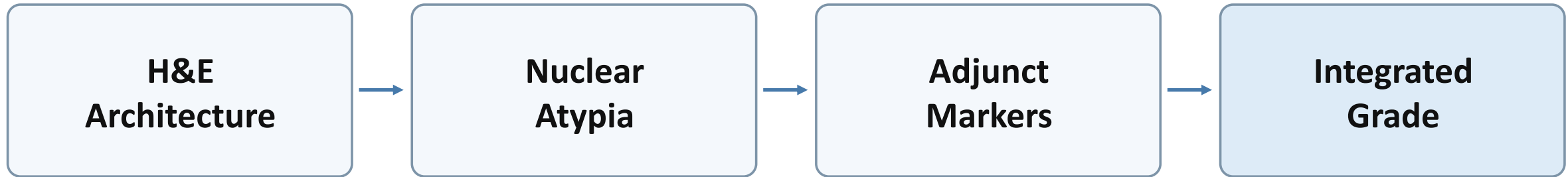
Ki-67: Aberrant upward cycling



Proliferation extends beyond basal layer

- Robbins Fig. 22.15 describes abundant HPV DNA in superficial koilocytes
- In situ hybridization demonstrates viral DNA within the tissue

Diagnostic layers must be integrated



- Begin with full-thickness H&E assessment
- Interpret koilocytosis and the position of atypical immature cells
- Use p16 and Ki-67 when the histology is equivocal
- Correlate molecular/cytologic information without conflating assay types

Pap cytology reflects exfoliated surface cells

Pap test

Exfoliated-cell nuclear/cytoplasmic features

Screening and detection context

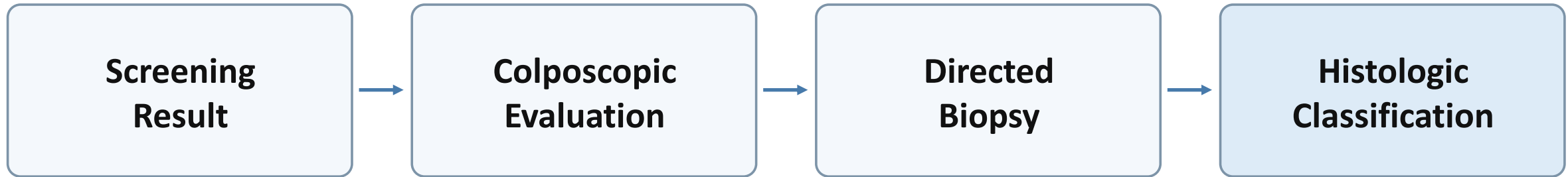
Biopsy

Entire epithelium and stromal interface

Histologic grading context

Biopsy supplies tissue architecture for histologic grading

Screening identifies, tissue assessment classifies



- A Pap smear can detect squamous precursor abnormalities
- High-risk HPV testing detects viral nucleic acid
- Colposcopy localizes suspicious cervical areas for biopsy
- The definitive morphologic interpretation depends on tissue when sampled

HPV testing and cytology are not interchangeable

Dimension	Cervical cytology	High-risk HPV test
Analyte	Exfoliated-cell morphology	Viral nucleic acid
Robbins comparison	Lower sensitivity; higher specificity	Higher sensitivity; lower specificity
Positive result	Cellular change detected	Virus detected
Histologic grade?	No	No

HPV DNA testing is more sensitive and less specific than the Pap test in the Robbins comparison

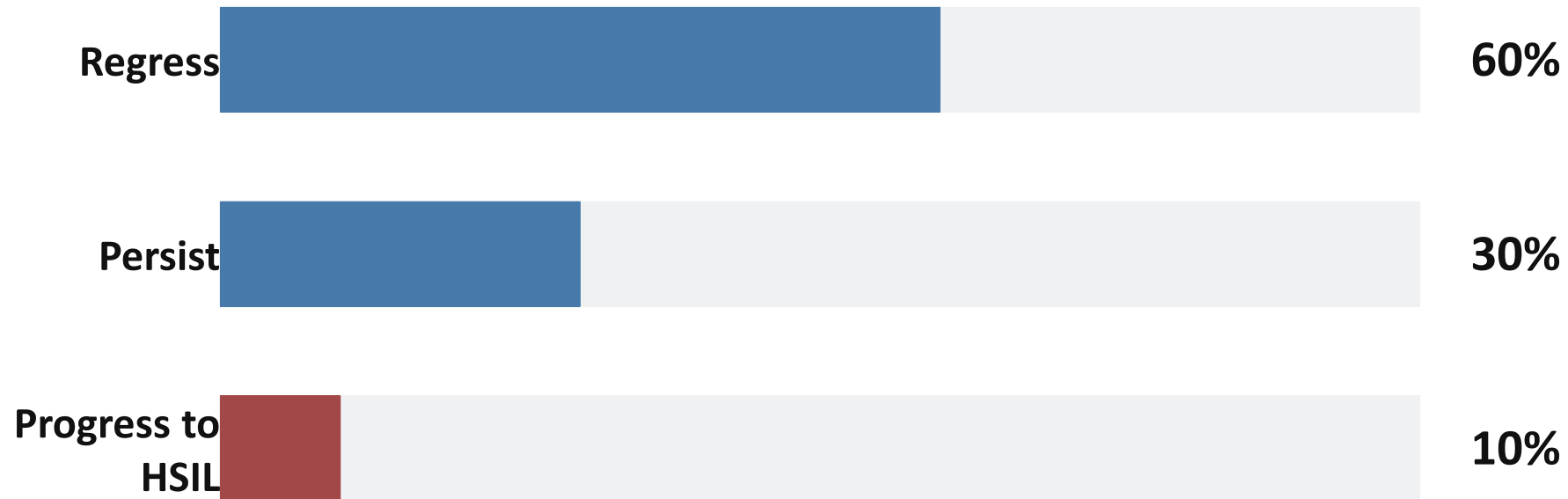
Colposcopy and biopsy connect tests to tissue

- Acetic acid highlighting abnormal epithelium
- Colposcopy aids site selection for biopsy
- Tissue shows the distribution of immature atypical cells
- The biopsy is interpreted in the clinical and screening context

LSIL is substantially more common than HSIL

- LSIL is approximately tenfold more common than HSIL
- This reflects the common productive infection pathway
- Prevalence alone should not be used to classify an individual biopsy
- The contrast in frequency must be considered with different progression risks

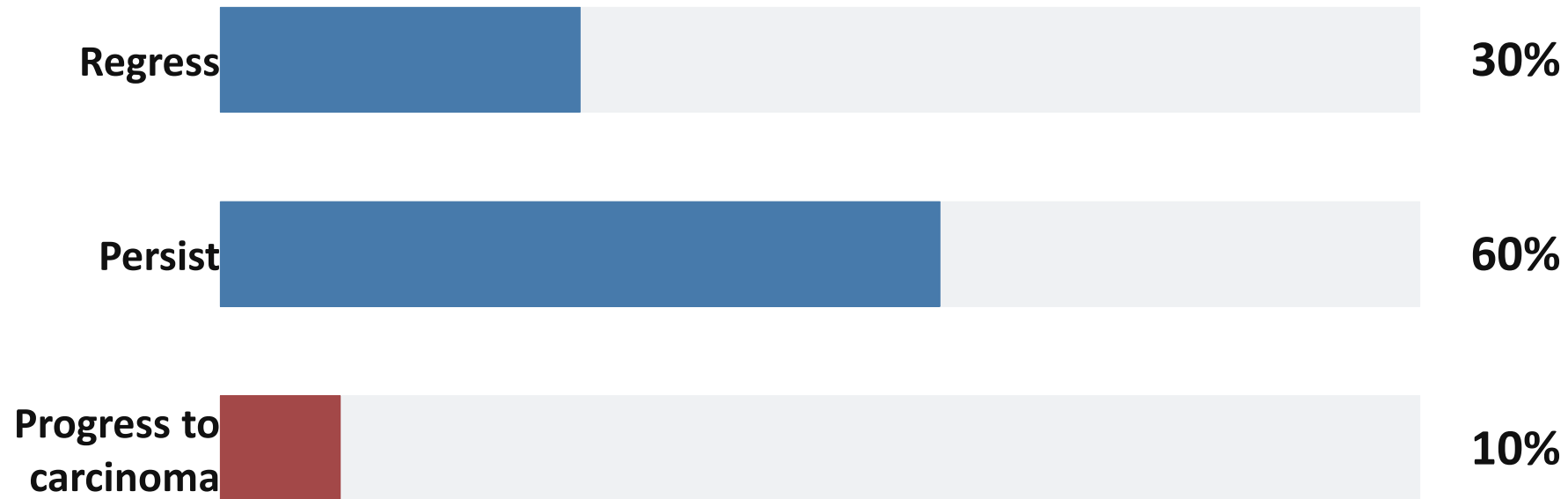
LSIL natural history: Approximate source values



Source: Robbins Table 22.1 — approximate estimates

These are aggregated estimates rather than individualized probabilities

HSIL natural history: Approximate source values



Source: Robbins Table 22.1 — approximate estimates

The data do not justify predicting a single patient's outcome

The time frame changes interpretation

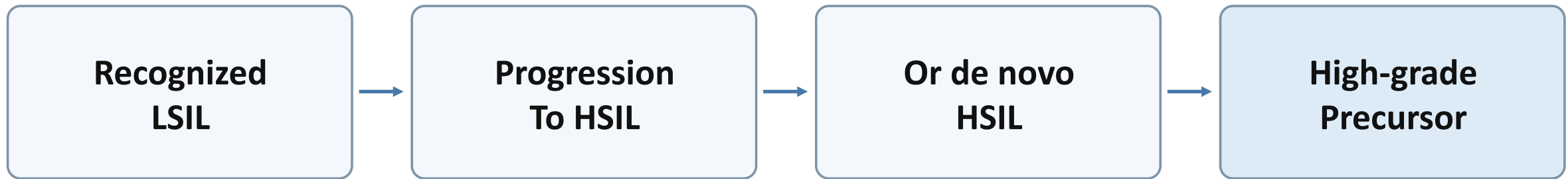
Statement	Time qualifier	Interpretive point
SIL fate table	Approx. 2-year follow-up	Regression/persistence estimates
HSIL → carcinoma	2–10 years (table note)	Progression fraction uses different window
Invasive evolution	Often decades overall	Long precursor phase

The table heading describes an approximate 2-year follow-up

Most LSIL does not evolve into HSIL

- Regression is the predominant course reported for LSIL
- LSIL often represents a productive, self-limited viral infection
- The malignancy-prevention concern is greatest when high-grade disease develops
- Follow-up decisions must be individualized beyond a textbook percentage

Not every HSIL has a recognized LSIL precursor



- Most HSIL develops from LSIL
- About 20% of HSIL is reported to arise de novo
- This challenges the idea that every case follows a documented stepwise sequence
- Absence of known prior LSIL does not exclude HSIL

Risk varies beyond viral genotype

- HPV-16 infection is associated with greater progression risk
- Immune factors can influence persistence or clearance
- Co-carcinogenic influences also modify risk
- One HPV result cannot forecast a defined histologic outcome

Clinical implications differ by grade

LSIL

Spontaneous regression frequent

Conservative follow-up often appropriate

HSIL

Greater progression concern

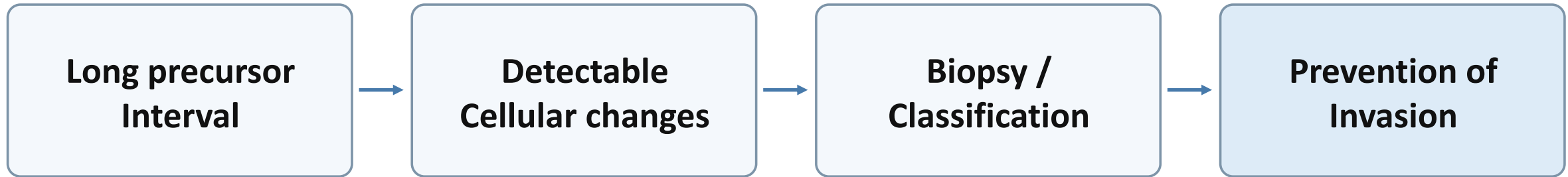
Treatment commonly considered

Histologic findings should be interpreted alongside the clinical scenario

Prevention begins before morphologic HSIL

- HPV vaccination targets relevant viral genotypes
- Prevention and screening interrupt the pathway to invasive cancer
- Robbins stresses continuation of screening despite vaccination
- Recommendations depend on updated jurisdictional guidance

Why screening is effective for cervical lesions



- Precursor lesions can shed abnormal cells before invasion
- The cervix is accessible to cytology, HPV testing, and colposcopy
- Progression is often sufficiently prolonged for detection
- These factors underpin the success of cervical cancer prevention

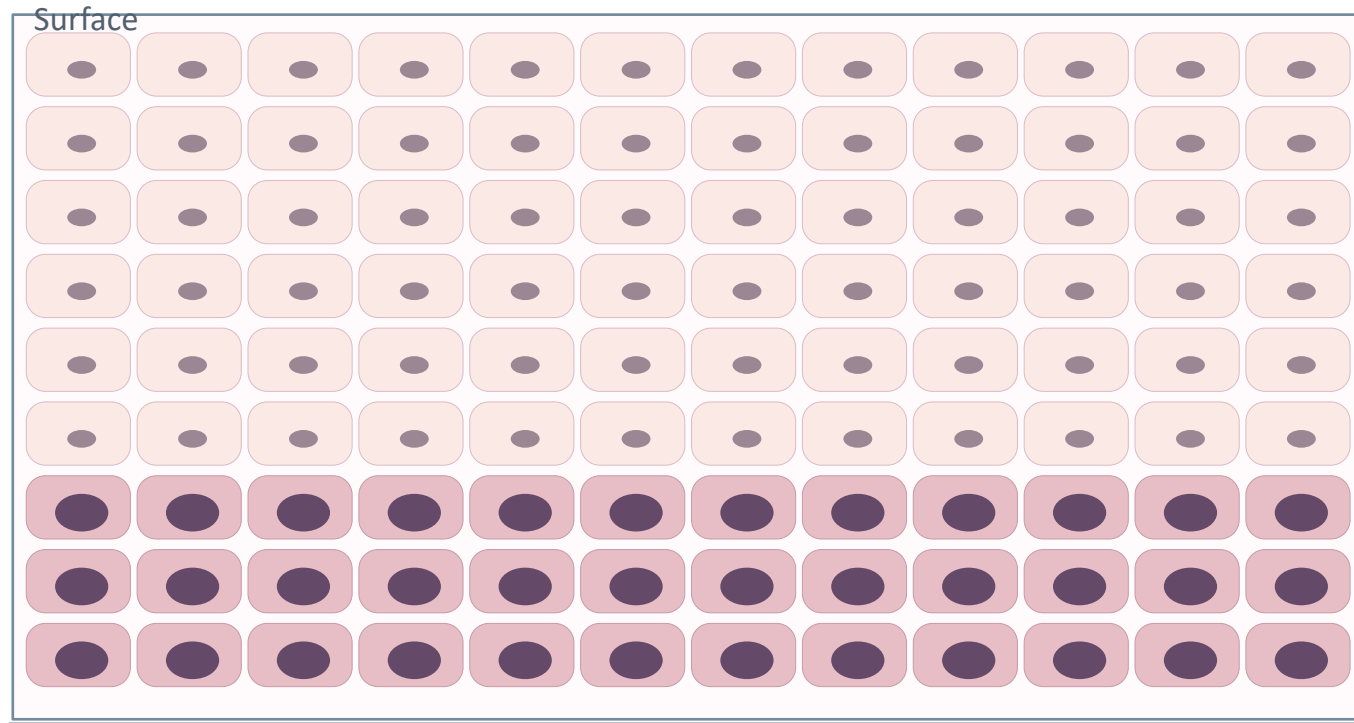
Case 1: Koilocytosis with surface maturation

Clinicopathologic reasoning

- Biopsy shows atypia concentrated in the lower epithelial third
- Upper squamous layers mature; Cells show perinuclear halos with abnormal nuclei
- Question: Which SIL grade is most compatible with this pattern?
- What underlying viral program does the architecture suggest?

Case 1 interpretation: Productive LSIL

CIN 1 / LSIL



Stromal side

Editable schematic — not histology

- CIN 1 / LSIL best fits lower-third atypia with maturation
- Koilocytic nuclear changes support a cytopathic HPV effect
- Productive replication is greatest in differentiating upper cells
- Many such lesions regress; Severity is not determined by HPV detection alone

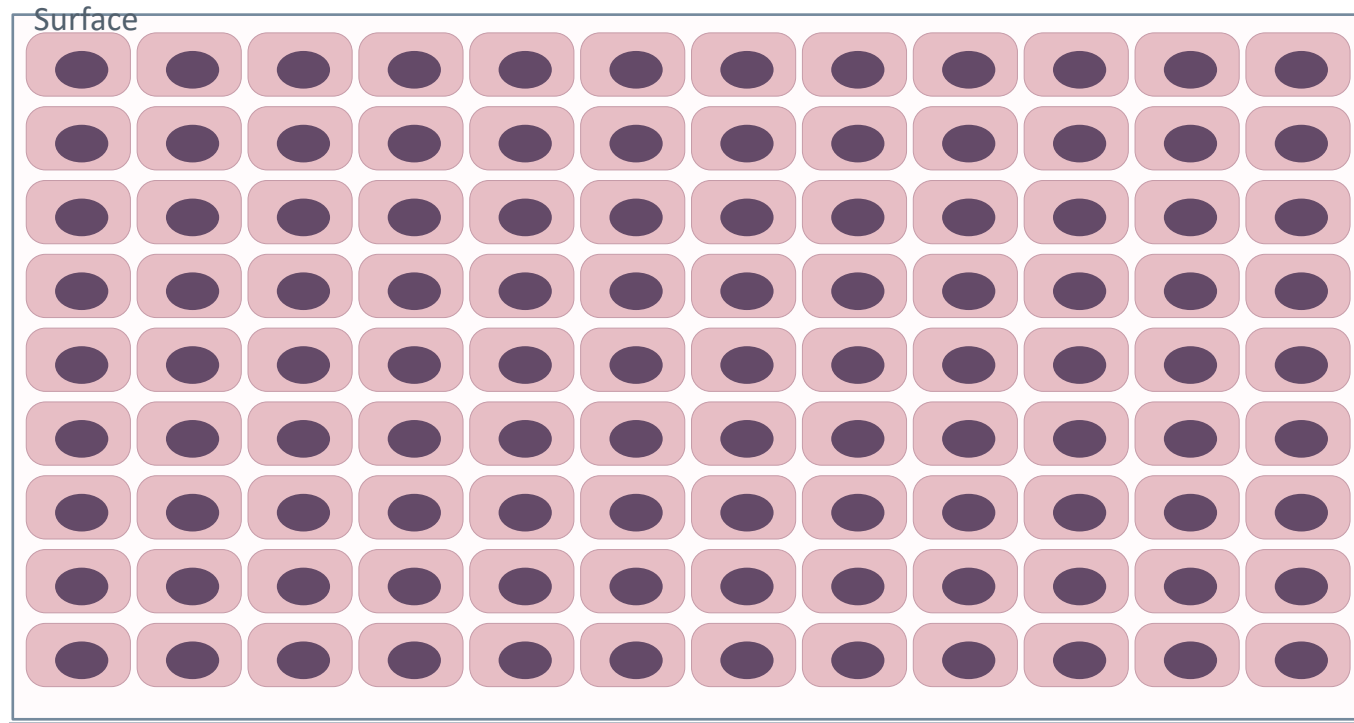
Case 2: Widespread immature cells

Clinicopathologic reasoning

- Biopsy shows atypical nuclei extending toward the surface
- There is little residual epithelial maturation
- Question: Which SIL category is appropriate?
- What additional relationship must be assessed before diagnosing invasion?

Case 2 interpretation: HSIL, not necessarily invasion

CIN 3 / HSIL



Stromal side

Editable schematic — not histology

- Diffuse atypia and maturation loss support HSIL / CIN 3
- Full epithelial thickness does not establish stromal invasion
- Confirm the epithelial–stromal relationship in the tissue sample
- Proliferation and altered p16 patterns may offer supportive evidence

Case 3: A positive HPV test without tissue atypia

Clinicopathologic reasoning

- A screening sample is positive for a high-risk HPV genotype
- No biopsy-confirmed SIL has been demonstrated
- Question: Can HSIL be inferred directly from the viral test?
- What additional information would establish a tissue diagnosis?

Case 3 interpretation: Viral detection ≠ HSIL

Information	What it establishes
HPV DNA positive	Viral nucleic acid detected
Abnormal Pap	Cytomorphologic change detected
Biopsy with architecture	Histologic SIL grade can be assigned

HPV positivity indicates viral DNA detection, not histologic grading

Case 4: Interpreting biomarkers

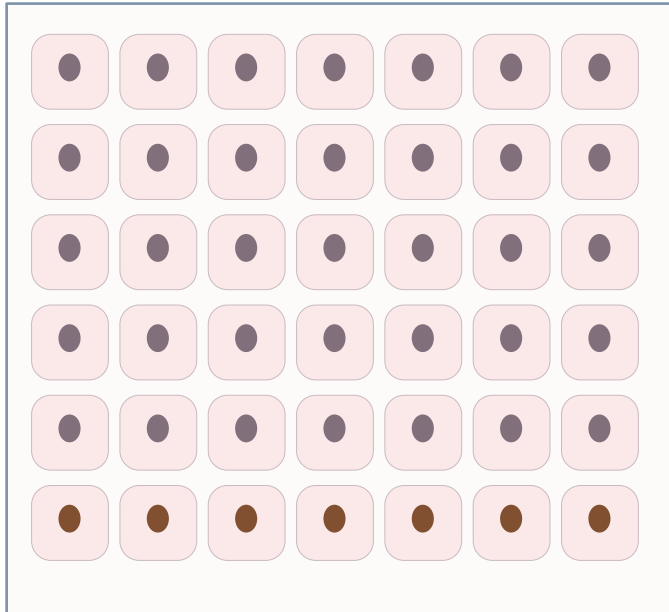
Clinicopathologic reasoning

- A cervical biopsy has equivocal nuclear atypia
- Ki-67 labeling is increased well above the basal layer
- P16 expression is increased
- Question: How should these findings be used in the final interpretation?

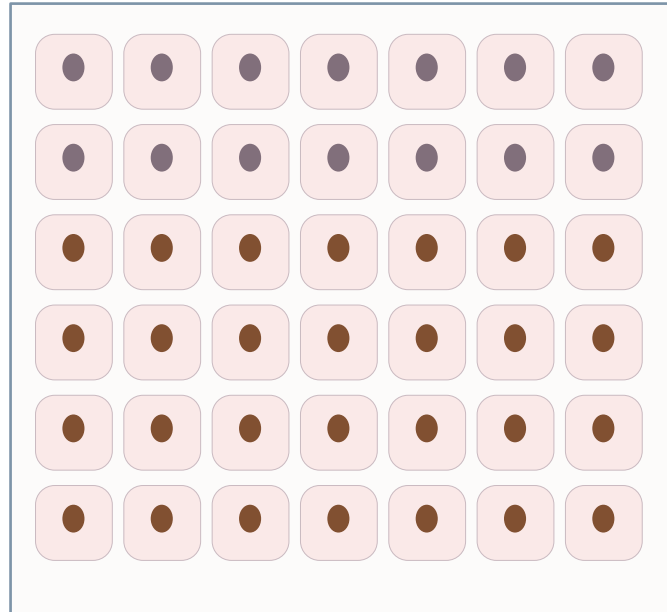
Case 4 interpretation: Biomarkers are adjuncts

SCHEMATIC — vertical staining distributions; Not clinical immunohistochemistry

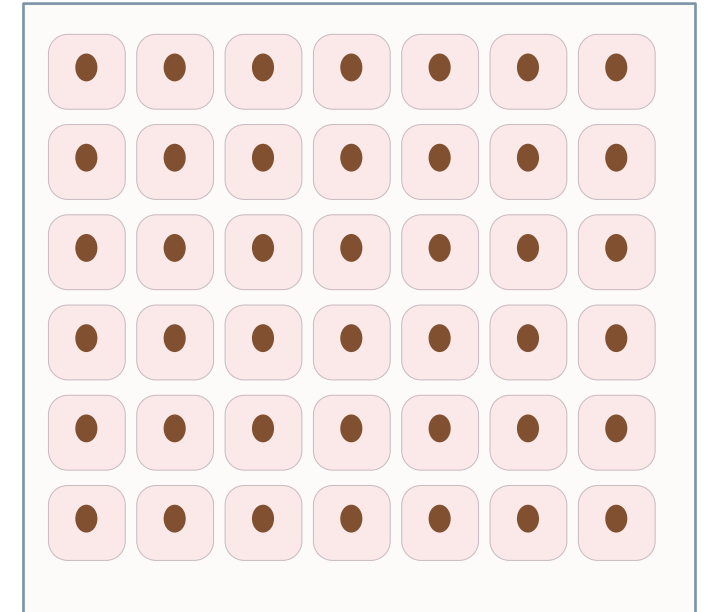
Normal proliferation



Upward Ki-67



P16 overexpression



- Ki-67 demonstrates altered proliferative distribution
- P16 supports an HPV-associated cell-cycle response

Integrated LSIL–HSIL comparison

Feature	LSIL / CIN 1	HSIL / CIN 2–3
Immature atypical cells	Predominantly lower third	Extend beyond lower third
Surface maturation	Substantially retained	Reduced or lost
HPV replication	High/productive	Relatively lower
Typical course	Frequent regression	Higher progression risk

Atypia thickness, maturity, viral replication and behavior are linked

Common interpretive errors to avoid

- Do not call an isolated perinuclear halo koilocytosis without nuclear atypia
- Do not equate positive HPV DNA with histologic HSIL
- Do not call full-thickness dysplasia invasive carcinoma without stromal invasion
- Do not read the natural-history estimates as individual prognoses

Five ideas to retain

- CIN 1 maps to LSIL; CIN 2 and CIN 3 map to HSIL
- Extent of immature atypical cells and maturation is the grading backbone
- Koilocytosis reflects productive HPV cytopathic effects
- P16 and Ki-67 provide context to H&E morphology
- Persistence, genotype and host factors influence risk, but outcomes vary

Core references and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 22, pp. 905–910
- Primary SIL section: pp. 906–907; Fig. 22.14 and morphology text
- Adjacent context: HPV pathogenesis, Fig. 22.15, Table 22.1, screening overview
- Native epithelial drawings are schematic; authentic slide images not reproduced