Draft Statements

COLLEGE of AMERICAN PATHOLOGISTS

Lower Anogenital Squamous Terminology (LAST) for HPV-Associated Lesions Guideline – 2025 UPDATE

Statements and Strengths of Recommendations

SUMMARY OF EVIDENCE-BASED RECOMMENDATIONS FOR BIOMARKERS IN HPV-ASSOCIATED LOWER ANOGENITAL SQUAMOUR LESIONS
Pathologists should perform p16 when the H&E morphologic differential diagnosis is between high-grade squamous intraepithelial lesion (HSIL, –IN 2 or –IN 3) and a mimic of HSIL (eg, processes unrelated to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting).[1] *Note:* Strong and diffuse block-positive p16 results support a categorization of HSIL (–IN 2 or –IN 3) in this context. ***Conditional Recommendation***
Pathologists should perform p16 IHC to secure a diagnosis for HSIL (-IN 2) for cases with a morphologic differential for LSIL (-IN 1).[2] *Note:* A negative or non–block-positive staining strongly favors an interpretation of LSIL (-IN 1) in this context. ***Conditional Recommendation***
Pathologists should ***NOT*** use p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with unequivocal morphologic differential diagnosis of negative, LSIL (–IN 1) and HSIL (–IN 3).[1] ***Conditional Recommendation***

Abbreviations: ASC, Atypical Squamous Cells; H&E, hematoxylin and eosin stain; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry; -IN, intraepithelial neoplasia; LAT, lower anogenital tract; LSIL, low-grade squamous intraepithelial lesion; NOS, not otherwise specified; p16, CDK4 inhibitor p16-INK4

1 Reaffirmed recommendation statement from 2012 guideline

2 Updated recommendation statement from 2012 guideline

SUMMARY OF GOOD PRACTICE SQUAMOUS INTRAEPITHELIAL LESIONS
The use of a unified histopathological nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the lower anogenital tract (LAT).[1]
The use of a 2-tiered nomenclature is recommended for noninvasive HPV-associated squamous proliferations of the LAT, which ***should*** routinely be further qualified with the appropriate –IN terminology.[2] *Note:* –IN refers to the generic intraepithelial lesion terminology, without specifying the location. For a specific location, the appropriate complete term should be used eg, –IN 3 lesions: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3

Performing p16 IHC is recommended as an adjunct to morphologic assessment for specimens interpreted as ≤ –IN 1 that are at high risk for missed high-grade disease, which is defined as HPV16, 18, or 18/45+; a prior cytologic interpretation of HSIL, ASC-H, AGC*, or AEC *; or a prior histologic diagnosis of HSIL.[1]

Note: Any identified p16-positive area must meet H&E morphologic criteria for HSIL to be reinterpreted as such.

*AGC and AEC: including NOS and favor neoplastic

Abbreviations: ASC-H, Atypical Squamous Cells, cannot exclude HSIL; AGC, Atypical Glandular Cells; AEC, Atypical Endocervical Cells; H&E, hematoxylin and eosin stain; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry; -IN, intraepithelial neoplasia; LAT, lower anogenital tract; LSIL, low-grade squamous intraepithelial lesion; NOS, not otherwise specified; p16, CDK4 inhibitor p16-INK4

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Certainty of Evidence Grades[1]

Grade	Definition
High	There is high confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.
Moderate	There is moderate confidence that available evidence reflects true effect. Further research is likely to have an important impact on the confidence in estimate of effect and may change the estimate.
Low	There is limited confidence in the estimate of effect. The true effect may be substantially different from the estimate of the effect.
Very Low	There is very little confidence in the estimate of effect. The true effect is likely to be substantially different from the estimate of effect. Any estimate of effect is very uncertain.

Strength of Recommendations[1]

Category	Definition	Rationale
Strong Recommendation	Recommend for or against a particular practice (Can include “must” or “should”)	Supported by high or moderate quality of evidence and clear benefit that outweighs any harms.
Conditional Recommendation	Recommend for or against a particular practice (Can include “should” or “may”)	Some limitations in quality of evidence (moderate to very low), balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation.

References

1. Schuenemann H, Brozek J, Guyatt G, Oxman A, eds; The GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations: Gradepro website. Updated October 2013. Accessed February 29, 2024. https://gdt.gradepro.org/app/handbook/handbook.html