The LAST Consensus Recommendations

p16 IHC testing is the global standard of care

CINtec® HISTOLOGY

The LAST recommendations – p16 IHC testing is the global standard of care

In 2012, the College of American Pathologists (CAP) and the American Society for Colposcopy and Cervical Pathology (ASCCP) issued the Lower Anogenital Squamous Terminology (LAST) recommendations.[1]

The LAST recommendations provide direction to:

- Standardise histopathologic diagnostic terminology for cervical and lower anogenital tract squamous epithelial lesions associated with the human papillomavirus (HPV)
- Guide optimal use of p16 immunohistochemistry in these tissues

In 2014, the World Health Organization (WHO) adopted the LAST consensus recommendations; the adjunctive use of p16 IHC in evaluation of cervical biopsies is now considered recommended standard of care.[2]

Unified terminology

The LAST recommendations introduce unified diagnostic terminology for HPV-associated squamous lesions of the cervix and lower anogenital tract, a measure intended to improve communication among pathologists and physicians, allowing for appropriate patient management.

Terminology recommendations:

- A two-tiered nomenclature system to describe noninvasive HPV-associated lesions (similar to the Bethesda System)
  - LSIL: low-grade lesions
  - HSIL: high-grade lesions
- Further sub-categorisation of squamous intraepithelial lesions using the applicable "_IN" designation in parentheses.*
  - LSIL (CIN1)
  - HSIL (CIN2)
  - HSIL (CIN3)

Adjunctive use of p16 immunohistochemistry

The LAST biomarker work group reviewed more than 2,000 scientific publications, evaluating the natural history of HPV-mediated disease and use of molecular markers in conjunction with H&E morphology in lower anogenital tract tissues.

p16 IHC is recommended for use along with H&E (Figure 1):*

- To aid in differential diagnosis between CIN2/CIN3 and a mimic of pre-cancer (eg, immature metaplasia, reparative epithelial changes, atrophy or tangential cutting)
- Anytime a morphologic CIN2 diagnosis is considered
- As an adjudication tool for cases with professional disagreement
- As an adjunct to morphologic assessment for biopsy specimens interpreted as ≤CIN1 that are at high risk for missed high-grade disease. (Defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV 16+ or AGC (NOS).)

p16 IHC is not recommended as an adjunct to H&E for assessment of cervical biopsies with clear H&E morphologic interpretations of negative for dysplasia, CIN1 and CIN3.

p16 IHC aids in the identification of CIN

In normal cervical tissues, p16 is expressed at low levels typically not detectable by p16 IHC. Strong overexpression of p16 in pre-cancerous and cancerous tissues is associated with transforming HPV infections.[3,4,5,6] The overexpression of p16 in squamous cervical lesions is detectable by p16 IHC (Figure 2).

The vast majority of high-grade CIN lesions will demonstrate positive p16 IHC staining (ie, positive CINtec® Histology status). In addition, typically 40 to 60% of CIN1 lesions may demonstrate positive p16 IHC staining (ie, positive CINtec® Histology status).[7,8,9,10,11]

Positive p16 IHC staining suggests the presence of CIN. Final diagnosis of a case as CIN1, CIN2 or CIN3 is based on the routine morphological criteria on the H&E-stained slide taking into account the p16 IHC staining result.

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*This work group concluded that the **p16 biomarker is the only biomarker** "…with sufficient evidence on which to make a recommendation regarding use in lower anogenital tract squamous lesions."* [1]

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* Examples given for cervical squamous epithelial tissue. Similar "_IN" sub-categorisation and interpretation criteria are recommended for squamous tissue of other lower anogenital body sites. Site-specific lower anogenital intraepithelial neoplasia terminology include: Anus = AIN; Perianus = PAIN; Penis = PeIN; Vagina =VaIN; Vulva = VIN; and Cervix = CIN.

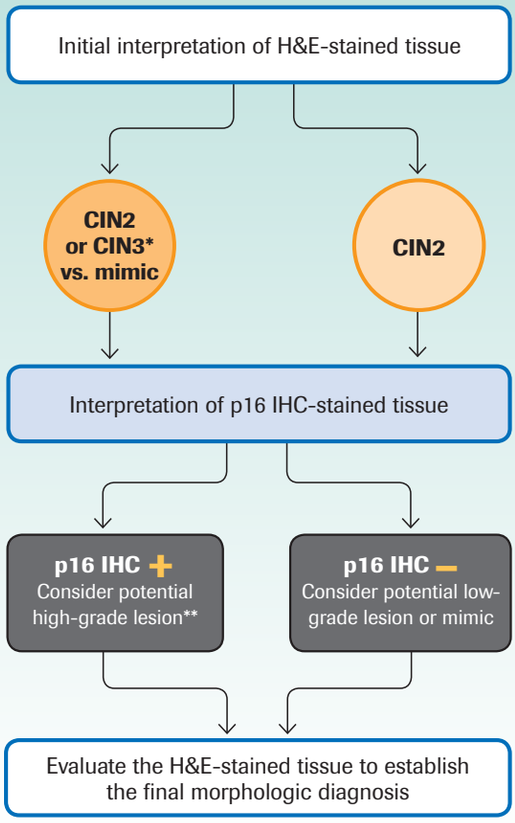
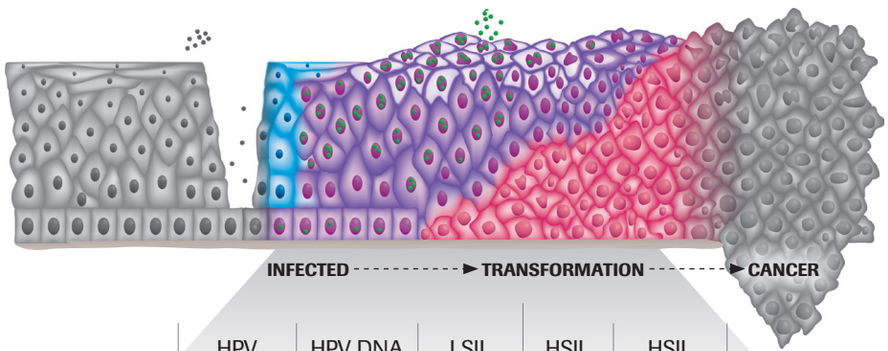


Figure 1. Use of p16 immunohistochemistry to evaluate CIN2, and in the differential diagnosis of high-grade pre-cancer (CIN2 or CIN3) versus its morphologic mimic.**



	HPV infection	HPV DNA replication	LSIL (CIN1)	HSIL (CIN2)	HSIL (CIN3)
p16 IHC result	–	–	– or +	+	+

Figure 2. The overexpression of p16 in transforming HPV infections is detectable by p16 immunohistochemistry (IHC) within the (cervical) squamous epithelium.

* p16 IHC is not recommended as an adjunct to H&E for assessment of cervical biopsies with clear H&E morphologic interpretations of CIN3.

** Positive p16 IHC staining does not necessarily indicate the lesion is high-grade. 40 to 60% of CIN1 lesions may demonstrate positive p16 IHC staining (ie, positive CINtec® Histology status).

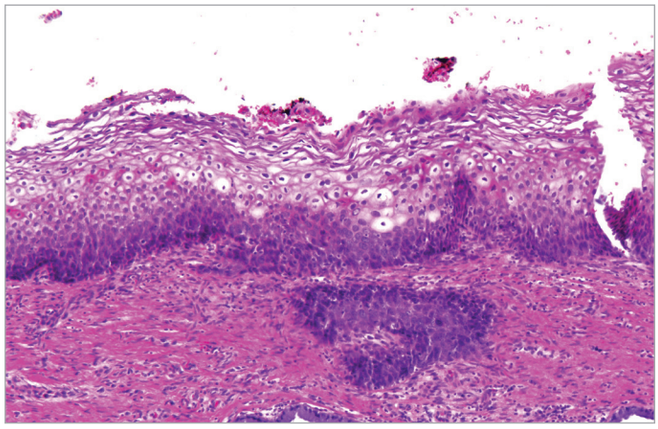


Figure 3: H&E-stained cervical biopsy specimen. Magnification 10x

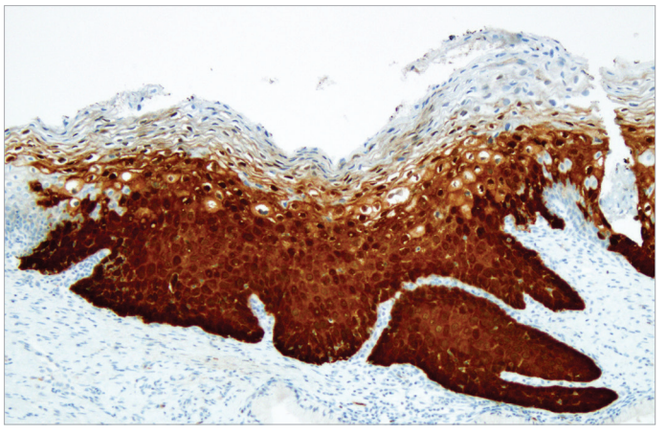


Figure 4: The same cervical biopsy specimen as in Figure 3 stained using CINtec® Histology. This specimen demonstrates diffuse p16 immunostaining, representing positive CINtec® Histology status. Magnification 10x

CINtec® Histology: Confidently interpret cervical biopsies more accurately

CINtec® Histology is the only clinically validated test that uses advanced biomarker technology to confirm the presence or absence of cervical lesions due to transforming HPV infections so that healthcare professionals can be sure they are prescribing appropriate intervention for their patients.

The p16 ^{INK4a} protein is overexpressed in cervical tissue as a consequence of a transforming HPV infection and is the only recommended biomarker for detecting high-grade cervical disease. The Roche CINtec® Histology test is the only *de novo* 510(k) p16 IHC product cleared by the FDA for detecting the overexpression of p16 within cervical biopsies. The clinical value of CINtec® Histology has been demonstrated in controlled clinical trials and population-based studies conducted by leading cervical cancer researchers.[10,11,12]

The CINtec® Histology product is for use with VENTANA BenchMark ULTRA, BenchMark XT and BenchMark GX IHC/ISH staining instruments* using VENTANA OptiView DAB IHC or VENTANA *ultra*View DAB detection. The CINtec® Histology Kit is available for manual use or use with semi-automated IHC instruments.

Contact your local Roche representative with questions regarding the LAST recommendations, or to learn more about CINtec® Histology.

*The BenchMark GX IHC/ISH instrument is not available in all countries.

"The clinical utility of p16 immunohistochemistry is directly related to the performance characteristics of a particular clone in the literature…"[1]

References

1. Darragh et al. *Arch Pathol Lab Med.* 2012;136(10):1266-1297. **2.** Stoler et al. *Tumours of the uterine cervix.* In Kurman el al. (Eds.), *WHO classification of tumours of female reproductive organs.* Lyon, France: IARC and WHO,2014;169-206. **3.** Sano et al. *Am J Pathol.* 1998;153:1741-1748. **4.** von Knebel Doeberitz M., Vinokurova S. *Arch Med Res.* 2009;40(6):435-442. **5.** Negri et al. *Virchows Arch.* 2004;445:616-620. **6.** Wentzensen N, von Knebel Doeberitz M. *Dis Markers.* 2007;23(4):315-330. **7.** Cuschieri K, Wentzensen N. *Cancer Epidemiol Biomarkers Prev.* 2008;17:2536-2545. **8.** Tsoumpou et al. *Cancer Treat Rev.* 2009;35:210-220. **9.** Dijkstra et al. *J Clin Pathol.* 2010;63(11):972-977. **10.** Bergeron et al. *Am J Clin Pathol.* 2010;133:395-406. **11.** Galgano et al. *Am J Surg Pathol.* 2010;34:1077-1087. **12.** Ordi et al. *Int J Gynecol Pathol.* 2009;28(1):90-97.

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