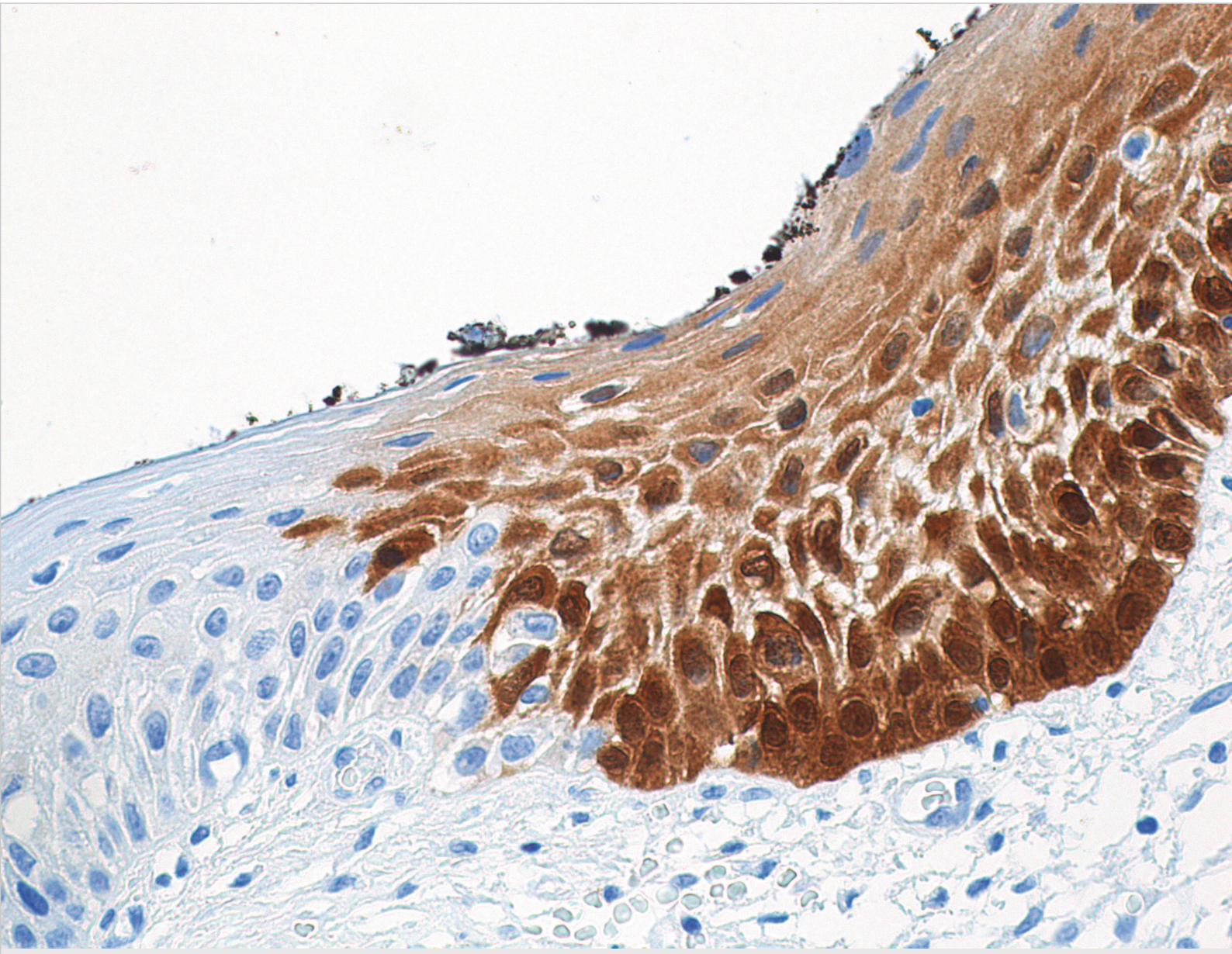
CINtec® HISTOLOGY

Roche

WHO Implements the LAST Consensus Recommendations

Guidance to help improve diagnostic agreement with p16 IHC testing



WHO Global Recommendations now include p16 IHC testing for improved diagnosis of HPV-associated lesions

The World Health Organization (WHO) has published guidance for the clinical use of p16 immunohistochemistry (IHC) to improve the detection of precancerous cervical lesions. The WHO guidelines and the Lower Anogenital Squamous Terminology (LAST) consensus recommendations align to strongly recommend the adjunctive use of p16 biomarker detection to support consistent diagnosis of cervical precancer.[1,2]

The WHO guidelines describe, for pathologists, the practical, clinical implementation of the LAST consensus recommendations in the context of cervical histopathology as it relates to the natural history of the development of human papillomavirus (HPV)-associated cervical lesions. The LAST recommendations were developed by an interdisciplinary team led by the College of American Pathologists (CAP) and the American Society for Colposcopy and Cervical Pathology (ASCCP), and provide direction to:

- Standardize histopathologic diagnostic terminology for cervical squamous epithelial lesions associated with the human papillomavirus (HPV)
- Guide optimal use of p16 immunohistochemistry in cervical biopsy specimens

Unified terminology

The new recommendations introduce unified diagnostic terminology for HPV-associated squamous lesions of the cervix, 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 subcategorization of squamous intraepithelial lesions using the applicable "CIN" 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 cervical tissue.

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

- To aid in differential diagnosis between CIN2/CIN3 and a mimic of precancer (e.g., 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).)

This work group concluded that the p16 biomarker is the only biomarker "…with sufficient evidence on which to make a recommendation regarding use in (cervical) squamous lesions."[2]

—Darragh, et al. (CAP/ASCCP LAST Project group)

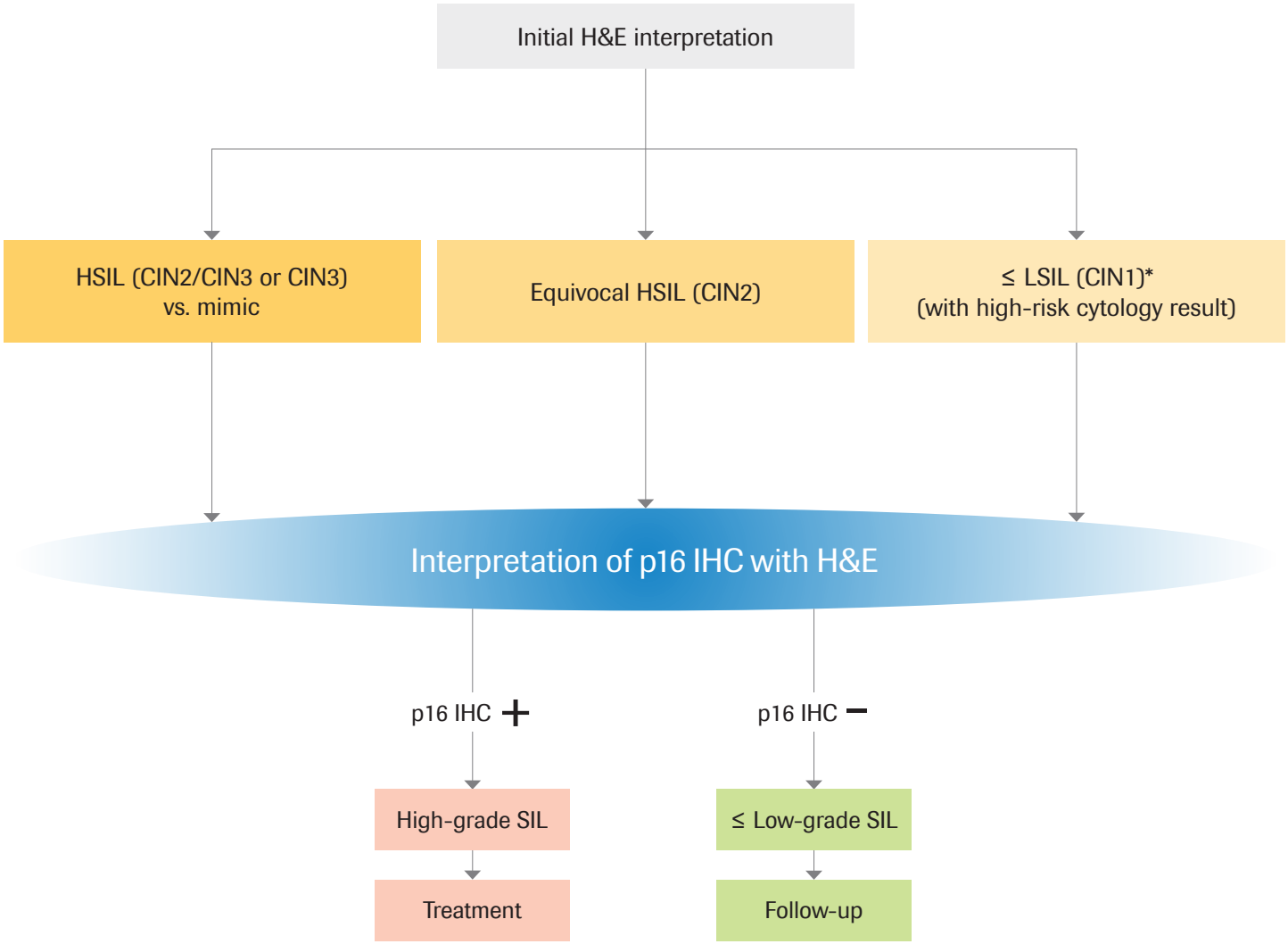


Figure 1. Use of p16 immunohistochemistry to evaluate morphologic CIN1 (with high-risk cytology result), CIN2 and the differential diagnosis of a mimic of high-grade precancer and HSIL.** (Figure modified with permission, courtesy of Teresa M. Darragh.)

* ≤ LSIL (CIN1) diagnosis with prior cytologic interpretation of ASC-US/HPV16+, HSIL, ASC-H, or AGC(NOS).
** At present, no recommendation for p16 immunohistochemistry use has been made for morphologic ≤ LSIL (CIN1) (with prior low-risk cytologic findings such as LSIL and ASC-US/hrHPV+ results other than HPV 16) or for morphologically determined CIN3.

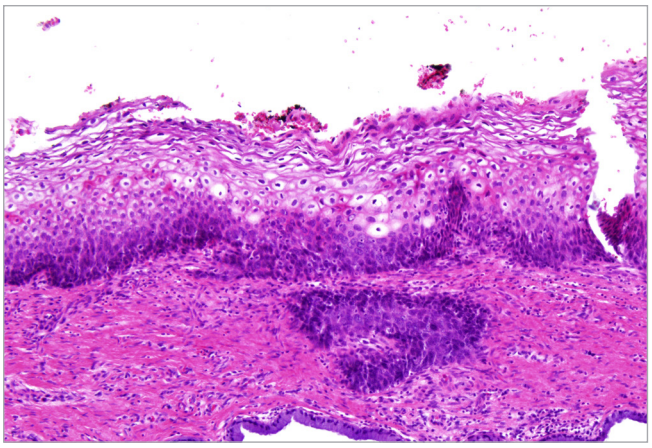


Figure 2, panel A: H&E-stained cervical biopsy specimen (case 1). Magnification 10x

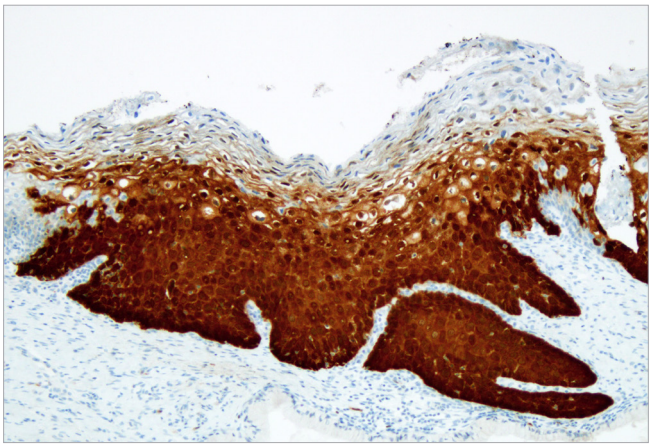


Figure 2, panel B: CINtec® Histology-stained cervical biopsy specimen (case 1) demonstrating diffuse, positive CINtec® Histology status. Magnification 10x

CINtec® Histology

Confidently interpret cervical biopsies

CINtec® Histology is the only clinically validated test that uses advanced biomarker technology to provide definitive yes/no confirmation of cervical precancerous lesions, so 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 product is the only IVD product on the market 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.[3, 4, 5, 6]

"The clinical utility of p16 immunohistochemistry is directly related to the performance characteristics of a particular clone in the literature…"[2]

—Darragh, et al. (CAP/ASCCP LAST Project group)

The CINtec® Histology product is for use with the VENTANA BenchMark ULTRA IHC/ISH instrument using VENTANA OptiView DAB IHC.

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

References:

1. Stoler M, Bergeron C, Colgan TJ, et al. Tumours of the Uterine Cervix. In Kurman, RJ, Carcangiu, ML, Herrington, CS, Young, RH (Eds.), WHO Classification of Tumours of Female Reproductive Organs. Lyon, France: IARC and WHO, 2014:169-206.

2. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol.* 2013 Jan;32(1): 76-115. doi: 10.1097/PGP.0b013e31826916c7. Erratum in: Int J Gynecol Pathol. 2013 Mar;32(2):241. Int J Gynecol Pathol. 2013 Jul;32(4):432. Original publication in *J Low Genit Tract Dis.* 2012;16(3):205-242, and *Arch Pathol Lab Med.* 2012;136:1266-1297.

3. Bergeron C, Ordi J, Schmidt D, et al. Conjunctive p16INK4a testing significantly increases accuracy in diagnosing high-grade cervical intraepithelial neoplasia. *Am J Clin Pathol.* 2010;133(3):395-406.

4. Ordi J, Garcia S, del Pino M, et al. p16INK4a immunostaining identifies occult CIN lesions in HPV-positive women. *Int J Gynecol Pathol.* 2009;28(1):90-97.

5. Galgano M, Castle P, Atkins K, et al. Using biomarkers as objective standards in the diagnosis of cervical biopsies. *Am J Surg Pathol.* 2010;34(8):1077-1087.

6. Roche data on file.

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