Title

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

Journal

Archives of Pathology & Laboratory Medicine, 136(10)

ISSN

0003-9985

Authors

Darragh, Teresa M
Colgan, Terence J
Cox, J Thomas
et al.

Publication Date

2012-10-01

DOI

10.5858/arpa.lgt200570

Peer reviewed

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

Teresa M. Darragh, MD;[1] Terence J. Colgan, MD;[2] J. Thomas Cox, MD;[3] Debra S. Heller, MD;[3] Michael R. Henry, MD;[4] Ronald D. Luff, MD;[5,6] Timothy McCalmont, MD;[1] Ritu Nayar, MD;[7] Joel M. Palefsky, MD;[1] Mark H. Stoler, MD;[8] Edward J. Wilkinson, MD;[9] Richard J. Zaino, MD;[10] David C. Wilbur, MD,[11] for members of the LAST Project Work Groups

The following LAST Steering Committee members, Work Group members, and/or Conference Moderators have no perceived conflicts of interest to report: Jill Allbritton, Sarah Bean (advisor), Joel Bentz, Debra Heller, Gene Herbeck, Rodolfo Laucirica, Christopher Otis, Stanley Robboy, Mary Schwartz, Mark Welton, and Barbara Winkler.

Steering Committee: Dr Darragh serves on the advisory boards of OncoHealth and Arbor Vita Corporation; she owns stock in OncoHealth and receives grants from the National Institutes of Health (NIH)/National Cancer Institute (NCI) and NIH/National Institute of Allergy and infectious Disease. In addition, she receives fees for lecturing for the American College of Obstetricians and Gynecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP), Society of Gynecologic Oncologists (SGO), Planned Parenthood, and the American Society for Clinical Pathology (ASCP). Dr Henry receives royalties from the College of American Pathologists (CAP). Dr Luff is an employee of Quest Diagnostics and holds stock ownership in the corporation. Quest Diagnostics receives grants from GlaxoSmithKline, BD TriPath, and Hologic to support clinical trials. Dr Luff received coverage for his travel to an Endo Pharmaceuticals investigators' meeting. He serves on the Foundation Board of the American Society of Cytopathology (ASC). Dr McCalmont receives lecture fees from the Pennsylvania State University, University of Washington, and the Oregon Dermatological Society. He serves as an expert witness for Filice, Brown and receives consultancy fees from various law firms. Dr Wilbur serves as an expert witness for MCIC Vermont, Ohio State University, Promutual, Memorial Sloan-Kettering Cancer Center, CMIC, Lavin, O'Neill, CRICO, Claims Management, and the Mayo Clinic. He serves as a consultant for Becker Consulting. He receives lecture fees from CAP, Cornell University, and the University of Iowa and receives royalties from both CAP and Elsevier. He serves on an advisory board for Corista LLC and VisionGate. He receives grants from the US State Department and the US Agency for International Development. Dr Wilkinson serves as a consultant for Hologic and Guided Therapeutics and serves on the advisory boards of Merck, Inc, and the ASCCP. He receives royalties from Lippincott, Williams, and Wilkins and grants from MTM Laboratories. Dr Wilkinson owns stock in Johnson & Johnson and Procter & Gamble.

Work Group 1: Dr Cox serves on the advisory boards for Gen-Probe, Graceway, and Roche; he also serves on the Merck HPV Vaccine Data and Safety Monitoring Board. Dr Cox receives lecture fees from BD Diagnostics, Veregen, GlaxoSmithKline, and Onco-Health. Dennis O'Connor serves as a consultant to the National Children's Tissue Bank. He receives lecture fees from the Indian Health Service and the ASCCP and grants from the Gynecologic Oncology Group. R. Kevin Reynolds receives lecture fees from

[1]University of California – San Francisco, San Francisco, CA; [2]Mount Sinai Hospital, Toronto, Ontario, Canada; [3]UMDNJ-New Jersey Medical School, Newark, NJ; [4]Mayo Clinic, Rochester, MN; [5]Quest Diagnostics, Teterboro, NJ; [6]Thomas Jefferson University, Philadelphia, PA; [7]Northwestern University Feinberg School of Medicine, Chicago, IL; [8]University of Virginia Health System, Charlottesville, VA; [9]University of Florida College of Medicine, Gainesville, FL; [10]Hershey Medical Center, Penn State University, Hershey, PA; and [11]Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Reprint requests to: Teresa M. Darragh, MD, Departments of Pathology and Obstetrics, Gynecology and Reproductive Science, University of California – San Francisco/Mt Zion Medical Center, 1600 Divisadero St, Room B618 San Francisco, CA 94115. E-mail: teresa.darragh@ucsf.edu.

This guideline was developed through a collaboration between the American Society for Colposcopy and Cervical Pathology and the College of American Pathologists, and has been jointly published by invitation and consent in both the *Journal of Lower Genital Tract Disease* and the *Archives of Pathology & Laboratory Medicine*. It has been edited in accordance with the standards established at the *Journal of Lower Genital Tract Disease*.

Published as an Early Online Release June 28, 2012.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the Web site of the *Archives* (www.archivesofpathology.org) and the *Journal of Lower Genital Tract Disease* (www.jlgtd.com).

Dr Cox has retired from Santa Barbara Student Health Service, University of California, Santa Barbara, CA.

The American Society for Colposcopy and Cervical Pathology (ASCCP) and College of American Pathologists (CAP) provided the funding for this project; no industry funds were used in the development of the consensus statements and recommendations.

ACOG, ASCCP, and the Michigan Hematology Oncology Association. James Scurry (advisor) owns stocks in Sonic Health Care, Impedimed, Nib Holdings Limited, and Biota Holdings. M. Angelica Selim received a grant from NIH/NCI. For Dr Wilkinson, see Steering Committee listing.

Work Group 2: David Chelmow serves on the eMedicine Editorial Board and Medscape Reference Editorial Board. He has served as an expert witness for various obstetrical cases. He receives lecture fees from ACOG District IV. Leona Council is a part-time employee of LabCorp and receives grants from the Minority Health Research Committee. Hope Haefner has received lecture fees from ACOG, ASCCP, Toledo Hospital, Society of Obstetricians and Gynecologists of Canada (SOGC), Florida OBGYN Society, Kentucky ACOG Section, Indiana ACOG Section, ACOG District V, Miami Grand Rounds, Missouri OBGYN Associates, Ohio Dermatologic Association, Flint Hospital, University of Wisconsin, University of Connecticut, and the Turkish Society. She serves as an expert witness for Kitch Attorneys & Counselors. For Dr Henry, see Steering Committee listing. Lydia Howell serves on an advisory board for the American Council on Education and as an expert witness for Ubaldi and McPherson, LLC. She has received grants from NIH and lecture fees from Washington University in St Louis. Kieron Leslie serves both as a consultant and as an advisory board member for Novartis. Dr Leslie receives lecture fees from Meridian Conferences. Alice Lytwyn provides expert review and consulting for the Program for Appropriate Technology in Health. She receives lecture fees from the SOGC and Merck Frosst. Dr Lytwyn also receives grants from Merck Frosst. For Dr McCalmont, see Steering Committee listing. Joel Palefsky serves on the advisory boards of Merck and Co, Pharmajet, Inc, Aura Biosciences, Inc, and the Arbor Vita Corporation. He serves as a consultant and receives grants and travel expenses from Merck and Co. Dr Palefsky receives lecture fees from the Gilead Biosciences, American Social Health Association, University of Ottawa, Thai Red Cross, University of Minnesota, University of Illinois, University of British Columbia, Louisiana State University, American Association for Cancer Research, ASCCP, Gynecologic Oncology Society of Canada, University of Alberta, and the European Society for Sexual Medicine. He serves as an expert witness for the Schoenberg Law Firm. He receives grants from Aura Biosciences and NIH for research and royalties from UpToDate. Jennifer Roberts (advisor) receives lecture fees from the Australian Society for Colposcopy and Cervical Pathology. Brigitte Ronnett receives grants from NIH/NCI and Merck Research Laboratories. She serves as a consultant to Merck Research Laboratories and receives lecture fees from MTM Laboratories. She also receives royalties from Springer Verlag. Christopher Shea serves on the Editorial Board of the *Journal of American Academy of Dermatology*. He receives lecture fees from Meriter Foundation. Dr Shea serves as an expert witness for Healthcare Litigation Support, LLC, Wicker, Smith, O'Hara, McCoy & Ford, PA, Gary Osborne & Associates, Eichorn and Eichorn, and Benito H. Diaz, Esq. He receives grants from the University of Chicago, Chicago Dermatology Society, and NIH. Paul Staats receives lecture fees from Harvard Medical School. Alan Waxman serves on advisory boards for ACOG, ASCCP, the American Cancer Society Cervical Cancer Screening Work Group. He receives a partial salary grant from NIH and lecture fees from ACOG, ASCCP, Oakstone Medical Publishing, the National Library of Medicine, the New Mexico Department of Health/Center for Health Training, Center for Health Training (Austin, TX), SouthEast Alaska Regional Health Corporation, Arctic Slope Native Association, Yukon Kuskokwim Health Corporation, and Breast Cancer Detection of Alaska. Dr Waxman also receives a retirement pension from the United States Public Health Service.

Work Group 3: J. Michael Berry receives lecture fees from Sutter Medical Center of Santa Rosa Medical, AIDS Healthcare Foundation of Los Angeles, American Society of Colon and Rectal Surgeons, and ASCCP. He serves as a consultant for the Cancer Research Center of Hawaii. Dr Berry is employed by the University of California - San Francisco, which holds contracts and receives grants for the performance of research from Merck and Company and the NIH/AMC Working Group. He serves on an advisory board for Arbor Vita Corporation. Terence Colgan is a consultant for LifeLabs and Ontario Medical Associates. He receives lecture fees from the ASCCP and grants from the Canadian Institute of Health Research, Institute of Science & Technology Partnerships, Canada, and the Canadian Health Research Institute. He has patents pending or received relative to protein markers of endometrial cancer and endometrial biomarkers. He receives honoraria for serving as the Associate Editor of *Cancer Cytopathology*. For Dr Darragh, see Steering Committee listing. Levi Downs receives grants from GlaxoSmithKline. Olga Ioffe receives lecture fees from the ASCP. Nancy Joste serves on the Board of Directors for both Grounds for Health (NGO) and Planned Parenthood of New Mexico. She receives grants from the NIH/NCI. Oscar Lin receives grants from NIH and lecture fees from the ASC. Richard Zaino holds a consultancy with the United States Food & Drug Administration and serves as the co-chair of the NCI Uterine Task Force. He receives lecture fees from Hartford Hospital, PA Association of Pathologists, Gynecologic Oncology Group, CAP, Scientific Symposium International (travel reimbursement included), ASCP, and the Medical University of South Carolina.

Work Group 4: Christina Kong serves as an expert witness for PG&E, Rissman, Barrett, Hurt, Donahue, & McLain, PA, Garrett Hemann Robertson, PC, Martin & Jones, LLC, Cabaniss, Johnston, Gardner, Dumas, and O'Neal, LLP, and Andrada & Associates. She receives lecture fees from the California Society of Pathologists and grants from Burrough's Wellcome Fund and NIH. She received travel reimbursement from the Philippine Society of Pathologists. Bradley Quade serves as an expert witness for William E. Artz, PC, Bonezzi, Switzer, Murphy, Polito & Hupp, Co, LPA, Risk Management Foundation, Margolis Edelstein, Professional Casualty Association, Mary Hitchcock Memorial Hospital, University Hospitals Health System, Kline & Specter, Berman and Simmons, Martin, Magnuson, McCarthy & Kenney, Trobh, Heisler & Piampiano, and Foster & Eldridge. He serves on an advisory board for the Columbia Hospital Research Foundation and he receives a grant from NIH/National Institute of General Medical Sciences. Mark Stoler serves as a consultant to Merck Research Labs, Roche, Gen-Probe, Qiagen, BD, Ventana Medical Systems, MTM Laboratories, and Abraxis. For Dr Wilbur, see Steering Committee listing.

Work Group 5: Alicia Carter (advisor) is employed by Laboratory Corporation of America Holdings. Philip E. Castle serves as a consultant for Merck, Inc, and Roche. Maire Duggan receives grants (materials only, no funding) from Hologic for the PALS Trial. Francisco Garcia is employed by the University of Arizona, which holds contracts for the performance of research with Roche, Innovio, Photocure, Hologic, and BDD. Marc Goodman (advisor) is a consultant for Vanderbilt University, University of Iowa, the North American Association of Central Cancer Registries, and Moffitt Cancer Center. He serves on the Board of Scientific Counselors of NCI and receives grants from NIH for SEER, ovarian, and HPV research. For Dr Luff, see Steering Committee listing. Ann Moriarty is employed by AmeriPath and serves on the Cancer Support Community Physicians Advisory Board. She receives lecture fees from the ASC and serves as an expert witness for Eichorn and Eichorn, LLP. Ritu Nayar serves on the Cytopathology Test Development Committee for the American Board of Pathology and as an Associate Editor for Cancer (Cytopathology). She receives lecture fees from Indiana University, McGill University, and the United States & Canadian Academy of Pathology and receives grants from MTM Laboratories. Margaret Neal (advisor) serves on an advisory board for PathPAC. George Niedt serves as a consultant to Bronx Lebanon Hospital and Jacobi Hospital. Vijaya Reddy (advisor) receives royalties from both Cambridge Publishers and Elsevier. Mona Saraiya (advisor) serves on the American Cancer Society Steering Committee for Gynecologic Cancer. Susan Spires (advisor) receives lecture fees from CAP and ASC. Steve Silverberg (advisor) receives royalties from Elsevier, Wolters Kluwer, and the American Registry of Pathology. He

receives lecture fees from the ASCP. Herschel Lawson (conference moderator) receives lecture fees from the University of New Mexico School of Medicine and the ASCCP. Thomas Wright (technical reviewer) serves as a consultant for GlaxoSmithKline, Roche Molecular Diagnostics, Merck, Inc, i3 Innovus, MTM Laboratories, Gen-Probe, and BD. He also serves on advisory boards for BD, Merck, Inc, and Roche. He receives lecture fees from BD, Merck, Inc, and Roche. Evan Myers (LAST methodologist) serves as a consultant for Gen-Probe, Merck, Inc, and GlaxoSmithKline. He serves on an advisory board for Merck, Inc and receives fees for lecturing for Gen-Probe. Dr Myers receives grants from Gen-Probe, GlaxoSmithKline, and the Agency for Healthcare Research and Quality (AHRQ).

• ***Abstract.***—**The terminology for human papillomavirus (HPV)–associated squamous lesions of the lower anogenital tract has a long history marked by disparate diagnostic terms derived from multiple specialties. It often does not reflect current knowledge of HPV biology and pathogenesis. A consensus process was convened to recommend terminology unified across lower anogenital sites. The goal was to create a histopathologic nomenclature system that reflects current knowledge of HPV biology, optimally uses available biomarkers, and facilitates clear communication across different medical specialties. The Lower Anogenital Squamous Terminology (LAST) Project was cosponsored by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology and included 5 working groups; 3 work groups performed comprehensive literature reviews and developed draft recommendations. Another work group provided the historical background and the fifth will continue to foster implementation of the LAST recommendations. After an open comment period, the draft recommendations were presented at a consensus conference attended by LAST work group members, advisors, and representatives from 35 stakeholder organizations including professional societies and government agencies. Recommendations were finalized and voted on at the consensus meeting. The final, approved recommendations standardize biologically relevant histopathologic terminology for HPV-associated squamous intraepithelial lesions and superficially invasive squamous carcinomas across all lower anogenital tract sites and detail the appropriate use of specific biomarkers to clarify histologic interpretations and enhance diagnostic accuracy. A plan for disseminating and monitoring recommendation implementation in the practicing community was also developed. The implemented recommendations will facilitate communication between pathologists and their clinical colleagues and improve accuracy of histologic diagnosis with the ultimate goal of providing optimal patient care.**

Key Words.—**squamous intraepithelial lesion, human papillomavirus, superficially invasive carcinoma, p16, terminology**

(*Arch Pathol Lab Med*. 2012;136:1266–1297; doi: 10.5858/arpa.LGT200570)

The biology of the human papillomavirus (HPV) and its critical role in cancers of the lower anogenital tract (LAT) have been delineated during the last several decades. Human papillomavirus interacts with squamous epithelia in 2 basic ways. In the first, the squamous epithelium supports virion production, but lesions are transient. Historically, these processes have been termed *low-grade lesions*, *grade 1 intraepithelial neoplasia*, *mild dysplasia*, or, in the appropriate architectural background, *condyloma*. Human papillomavirus–infected squamous epithelia produce a morphologic low-grade lesion at some point in the complete life cycle of the virus, although it may be undetected clinically. In contrast, the second form of HPV-epithelial interaction is characterized by lesions that are broadly classified as precancerous. These are lesions in which the coordinate control between viral gene expression and epithelial differentiation is broken. It is postulated that viral oncogene overexpression drives cell proliferation to produce a clonal expansion of relatively undifferentiated cells characterized clinically by persistent viral detection, persistent and growing colposcopic abnormalities, and, over time, a substantial risk of malignant transformation. These precancers are morphologically indistinguishable from each other by routine histologic morphology regardless of the sex of the individual or the site of the lesion (see Figure 1) [1–4].

Despite these 2 well-established patterns of viral-epithelial interaction, the histopathologic terminology of HPV-associated processes in the LAT remains disparate and complex. This is primarily the result of terms evolving from different interest groups, particularly those in the areas of gynecology and gynecologic pathology and dermatology and dermatopathology, but also from specialty groups focused on specific body sites. These differing terminologies, for biologically equivalent lesions, have created the potential for miscommunication as pathologists attempt to reconcile the various terminologies with identified lesions and clinicians guide patient management based on these pathologic diagnoses. To optimize this communication, diagnostic terms should be consistent across body sites that share disease commonalities, and convey meaning, grounded in science, that allows for appropriate patient management.

The field of cytopathology had a similar terminology problem before the Bethesda conferences of 1988, 1991, and 2001. These conferences formulated a new terminology for reporting cytologic abnormalities in gynecologic and anal cytology. This terminology, now commonly known as *The Bethesda System* (TBS), created standard reporting terms and criteria for each interpretive category. It has been widely implemented in the United States and internationally and has led to improved and more reliable communication between pathologists and clinicians and among those in different medical specialties [5]. In addition, TBS was designed to be consistent with the current knowledge of HPV-associated disease. Until the introduction of TBS, morphologic terminologies were tied to older, less accurate understanding of the disease process. The Bethesda System also enabled the development of clinical management guidelines linked to standardized terminology.

The role of colposcopy and biopsy is to identify high-grade disease. Both colposcopic and biopsy interpretation have limited reproducibility and accuracy [6–9]. Biopsies represent potentially limited samples within fields of possible disease that may be of varying grade. Sampling issues may lead to underrepresentation of the actual disease present. Larger biopsies and increased numbers of biopsies more accurately assess each patient's "true" biology or cancer risk [6, 7]. Biopsy interpretation also has inherent issues of reproducibility [10]. Biomarkers are routinely used for histopathologic evaluation and lead to greater diagnostic reproducibility. Although changes to clinical management strategies are not explicitly addressed by the LAST recommendations, the ability to more accurately and

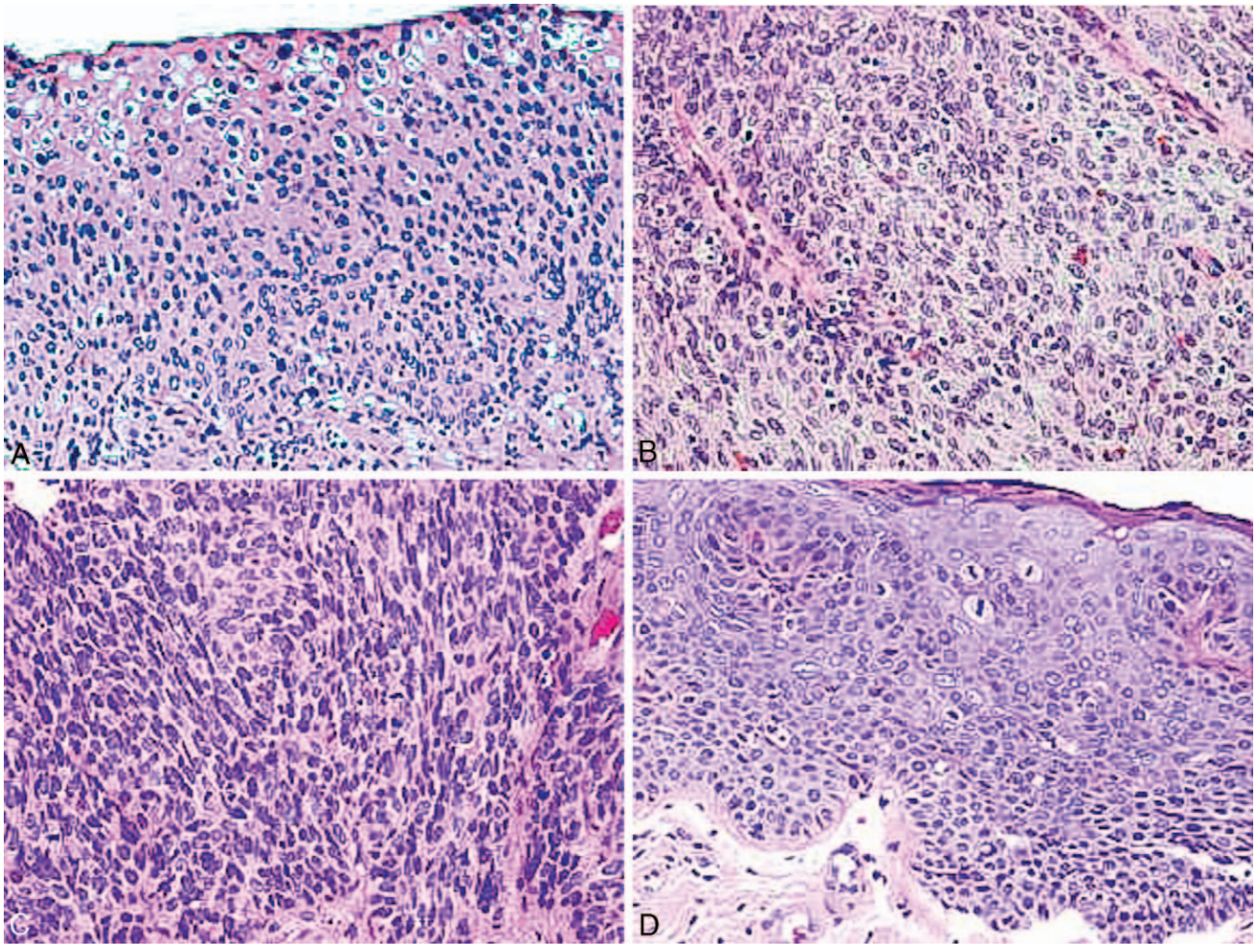

Figure 1. The similarity of morphology between LAT sites and between sexes is shown. Each is an example of a precancerous HSIL. If reviewed without knowledge of biopsy site or sex of the patient, they would be impossible to distinguish from one another. A to D, Medium power, H&E: A, CIN 3 (female); B, AIN 3 (female); C, AIN 3 (male); D, PeIN 3 (male).

reproducibly define patients' cancer risk based on their histopathologic diagnosis will ultimately lead to improved patient care.

The goal of clinical management is to identify and treat high-grade disease to decrease the risk of developing invasive cancer. Not all precancers will progress to cancer. Currently, we cannot predict which lesion would eventually become malignant if not treated. The potential harms of overtreatment of precancer compared with the risk of developing invasive disease if these lesions are not treated need to be balanced. The risks of cancer progression from HPV-associated precancer to invasive cancer are perceived to be different for different body sites. This perception is driven mostly by the relative frequency of LAT cancers and a marked paucity of long-term natural history data. The 30-year progression risk of invasive cancer is 30% to 50% for untreated high-grade cervical disease [11, 12]. Although data are not as robust, similar progression risk is seen for untreated vulvar precancer [13, 14]. Similar long-term data are lacking for anal cancer precursors and other LAT squamous cancers [15]. Long-term prospective studies of outcomes for patients with untreated high-grade precursors will be difficult to achieve.

On the basis of these underlying principles of HPV-associated disease (see Table 1) and issues related to terminology, a consensus process was conceived and sponsored by the College of American Pathologists (CAP) and the American Society for Colposcopy and Cervical Pathology (ASCCP). The Lower Anogenital Squamous Terminology (LAST) Project was designed to comprehensively evaluate the terminology of HPV-associated squamous lesions of the LAT, including the cervix, the vagina, the vulva, the perianus, the anus, the penis, and the scrotum. The project had several specific objectives carried out by 5 work groups (WGs; see Table 2):

1. To develop a historical perspective of the origins of terminologies in the LAT, with an emphasis on how nomenclature has influenced management.
2. To address whether the biology of HPV-associated disease in all of these sites allowed for unification of terminology.
3. To propose terminology for intraepithelial lesions and early invasive carcinoma.
4. To perform a review to determine whether currently available biomarkers support any proposed terminology

Table 1. General Principles Underlying the LAST Project

- There is unified epithelial biology to HPV-related squamous disease.
- Each cytologic or histologic sample is only a statistical representation of the patient's true biology.
- The more samples or data points available, the more accurate the assessment of the patient's true biology.
- The true biology represents the risk for cancer at the current time and, to a lesser extent, the risk for cancer over time.
- Diagnostic variation can be improved by:
  - aligning the number of diagnostic terms with the number of biologically relevant categories and
  - the use of biologic markers.

Table 2. LAST Project WGs

WG1: Historical review of LAT HPV-associated squamous lesion terminology
WG2: Squamous intraepithelial lesions, with subgroups:
Cervix and vagina
Vulva, penis, and scrotum
Anal canal and perianus
WG3: Superficially invasive squamous cell carcinoma (SISCCA), with subgroups:
Cervix and vagina
Vulva, penis, and scrotum
Anal canal and perianus
WG4: Biomarkers in HPV-associated lower anogenital squamous lesions
WG5: Implications and implementation of standardized terminology

recommendations or improve diagnostic reliability and reproducibility of histopathologic interpretation.

5. To facilitate and monitor dissemination and implementation of terminology changes into clinical practice with the goal of optimizing educational, quality assurance, regulatory, and clinical processes.

Final recommendations from the LAST Project are summarized in Table 3.

CAP-ASCCP LAST CONSENSUS PROCESS

A detailed account of the LAST Project is available in the Supplemental Digital Content; http://links.lww.com/LGT/A6. Briefly, the CAP Pathology and Laboratory Quality Center (the CAP Center) and the ASCCP convened a steering committee (SC) and 5 WGs that consisted of experts in the field including surgical pathologists, gynecologic pathologists, dermatopathologists, and medical and surgical specialists including gynecologists, gynecologic oncologists, dermatologists, infectious disease specialists, and surgeons (see A, Supplemental Digital Content; http://links.lww.com/LGT/A6). Work group members and advisors included representatives from both sponsoring organizations and other clinical specialties. Both sponsoring organizations used their respective approval processes for the formal review and appointment of the project chairs and WG members.

MANAGEMENT OF CONFLICTS OF INTEREST

All expert panel members complied with the CAP conflicts of interest policy (in effect, October 2010), which required disclosure of financial or other interests that may have an actual, potential, or apparent conflict (see Appendix, Supplemental Digital Content; http://links.lww.com/LGT/A6). Both ASCCP and the CAP provided the funding for this project; no industry funds were used in the development of the consensus statements and recommendations.

LITERATURE REVIEW AND CONSENSUS PROCESS

A computerized search was conducted for 4 of the 5 WGs using the following electronic databases: OVID MEDLINE, PubMed, Wiley Cochrane Library, and OCLC WorldCat, for English-language articles only. All study designs and publication types were included. Reference lists from identified articles were examined for articles not identified in the searches. The scope, key questions, search terms as defined by the SC, and the literature review results are displayed in the supplemental methodology material (see Appendix, Supplemental Digital Content; http://links.lww.com/LGT/A6). Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Canada) for WG2, 3, and 4.

Each identified article underwent an inclusion-exclusion process, dual-independent reviews conducted by co-chairs and WG members. On the basis of each WG's inclusion-exclusion criteria, articles were kept for full data extraction, as "indirect background material," or excluded from further review. Articles with 2 differing votes were considered in "conflict." Conflicts were adjudicated by both reviewers for WG2 and WG3 and by co-chair referees when conflicts could not be resolved. Co-chairs alone adjudicated WG4 conflicts. Conflicts included the "uncertain" reviews at the title/abstract level and the "indirect background material" reviews at the full text level. Final data extractions were performed by all WG members. After data extractions, WG members crafted draft summations and recommendations. The drafts were posted on the ASCCP Web site for open comment for 26 days from mid-January to mid-February 2012. After review of the open comments, draft recommendations were revised, if needed, before the consensus conference held immediately preceding the March of 2012 ASCCP Biennial Meeting in San Francisco, CA.

Recommendations for terminology of squamous intraepithelial lesions (WG2) and superficially invasive squamous carcinomas (WG3) were based on the expert opinion of WG members and advisors after their comprehensive review of the literature. The recommendations from WG4, on use of biomarkers, were chiefly driven by the specific data from the comprehensive literature review. For this reason, an independent assessment of the strength of the evidence identified to support WG4's recommendations was performed by an expert in evidence evaluation, Dr Evan Myers (Duke University), following WG4's review and development of recommendations.

At the consensus conference, WG members and advisors, along with representatives from 35 participating organizations (see Table 5, Supplemental Digital Content; http://links.lww.com/LGT/A6) and observers, deliberated on, revised, and voted on the final draft recommendations; observers did not vote. At least a two-thirds majority (67%) was required for passage of each recommendation. The LAST Project writing committee was tasked with adding to the documentation the appropriate supporting detail and explanatory material for the recommendations.

The CAP Independent Review Panel, the CAP Transformation Program Office Steering Committee, and the

ASCCP Executive Committee provided final review and approval of the article.

HISTORICAL REVIEW OF LAT HPV-ASSOCIATED SQUAMOUS LESION TERMINOLOGY—WG1

Work group 1 was in charge of framing the historical development of terminology applied to HPV-associated squamous lesions of the LAT and the influence of terminology on clinical management.

The history of terminology for LAT-associated precancer has developed along 2 separate paths depending on whether the epithelial lesion is mucosal or cutaneous. Terminology of mucosal cervical, vaginal, and anal lesions was largely developed by general pathologists, gynecologic pathologists, and gynecologists. In contrast, terminology for cutaneous vulvar, penile, and perianal lesions was largely developed by dermatologists and dermatopathologists. Terminology for HPV-associated disease of the LAT has changed numerous times during the last 120 years along with our understanding of the disease process and the treatment strategies.

Mucosal Terminology

Cervix: Preinvasive Lesions.—The earliest description of intraepithelial precancer was by Sir John Williams in 1888 [16]. Subsequent descriptions of the "earliest histologic changes of cervical cancer" as *surface carcinoma* or *intraepithelial carcinoma,* and later *carcinoma in situ* (CIS), reflected the histologic descriptions of cells that morphologically looked like cancer but had not invaded below the basement membrane [17–19]. The identification of CIS created a 2-tiered clinical approach that fostered hysterectomy for women with CIS and no treatment for women without it (see Figure 2). By the early 1950s, it was increasingly clear that surface lesions existed on the cervix that had abnormal histologic features that did not fulfill the criteria for CIS. These lesions seemed to have lower risk for progressing to cancer than CIS does. A variety of confusing terms were developed for these surface lesions, including *anaplasia* and *basal cell hyperplasia*. In 1952, Reagan and Hicks [20] coined the term *atypical hyperplasia* for cervical abnormalities with "greater degrees of differentiation than CIS and less risk for subsequent development of cancer." In the following year, they replaced this with "*dysplasia,*" which they graded mild, moderate, or severe [21]. The word "dysplasia" is derived from the Greek word *dys* for "bad" and *plasia* for "molding" and has been used in many areas of medicine, usually to describe a nonmalignant process. As late as the 1950s, some pathologists and clinicians argued that CIS was not the precursor to cervical cancer, but the common finding of CIS adjacent to cervical cancer, and the nearly identical incidence of both lesions eventually sealed this link [22, 23]. Although many acknowledged the difficulty in differentiating severe dysplasia from CIS, women with CIS continued to be treated by hysterectomy, whereas women with severe dysplasia were more often treated by cold knife conization.

In 1956, Koss and Durfee [24] described cells with ballooned cytoplasm, labeling them koilocytes from the Greek word for "empty space," and noted the similarity to descriptions of Reagan's mild dysplasia. In 1976, Meisels and Fortin [25] linked koilocytotic atypia with HPV.

The most profound change in cervical histologic terminology came in 1969 when Richart proposed that cervical carcinogenesis was a continuum of disease ranging from mild dysplasia to cervical cancer [26, 27]. Because of this morphologic spectrum, he coined the term *cervical intraepithelial neoplasia* (CIN) to emphasize its association as a precursor to cancer. Mild dysplasia was now termed CIN 1; moderate dysplasia, CIN 2; and severe dysplasia, CIN 3. Richart found "an absence of objective evidence" to support the arbitrary division of CIN into 2 diseases—dysplasia and CIS—and therefore basing therapy on such a distinction was not valid. Because all grades of CIN were thought to be on a continuum to cancer, treatment of all, based on the size and location of the lesion, became common practice. Treating even minor HPV-induced abnormalities quickly threatened to overburden the capacity of hospital-based surgical treatment of cervical precancer. In response, in-office ablative treatment methods—first, cryotherapy and later, CO_2 laser ablation—were developed. However, tradition and lingering misunderstanding of the precancerous nature of CIS resulted in a slow demise of the term and the use of hysterectomy as primary treatment for women with CIS continued.

By the late 1980s, the biology of HPV and cervical oncogenesis was increasingly understood. In addition, the subjectivity of the differentiation between CIN 2 and CIN 3 became apparent. This led to increasing recognition that a 2-tiered system of low- and high-grade intraepithelial lesions was more biologically relevant and histologically reproducible than the 3-tiered CIN 1, CIN 2, and CIN 3 terminology [28–30]. The creation of the 1988 TBS cytology terminology supported a similar low-grade and high-grade division [31]. However, the promotion of a 2-tiered terminology for histology in the 1990s lacked official support by any professional organizations and was never widely adopted. The 2001 and 2006 ASCCP Consensus Guidelines for the clinical management of cervical histological abnormalities use a 2-tiered terminology for cervix, except in adolescents and young women with CIN 2 and CIN 3 [32, 33]. This exception in the ASCCP Consensus Guidelines perpetuated the clinical reliance on a 3-tiered terminology for cervical histology for managing adolescents and young women.

Two important changes in the management of intraepithelial neoplasia began in the 1990s: expectant management of CIN 1 and in-office excision of high-grade precancer (CIN 2, 3) using the loop electrosurgical excision procedure (LEEP). Unlike prior transitions that paralleled changes in terminology, these were largely driven by a better understanding of the transience of most CIN 1 lesions and to improved excisional technology with LEEP that could be performed safely in an office setting (see Figure 2).

In the new millennium, there has been renewed debate about adopting a 2-tiered low-grade and high-grade terminology for all LAT HPV-associated intraepithelial lesions [34–36]. The primary concern regarding adopting a 2-tiered system for the cervical histology is that guidelines for management of CIN 2, 3 in adolescents and young women promoted expectant management of CIN 2 with the option to follow lesions reported as CIN 2, 3 but not CIN 3 [33, 37, 38]. The counter arguments advanced for adopting a 2-tiered system include that it better reflects the known biology of HPV-associated disease, that diagnostic variability is reduced, and that management based on further divisions in terminology does improve patient outcomes [35]. The CAP-ASCCP LAST Consensus Conference addresses these recent concerns.

Table 3. Summary of Recommendations

Recommendation	Comment
SQUAMOUS INTRAEPITHELIAL LESIONS, WG2	
1. A unified histopathologic nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the LAT.	
2. A 2-tiered nomenclature is recommended for noninvasive HPV-associated squamous proliferations of the LAT, which may be further qualified with the appropriate –IN terminology.	–IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location, the appropriate complete term should be used. Thus, for an –IN 3 lesion: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3
3. The recommended terminology for HPV-associated squamous lesions of the LAT is LSIL and HSIL, which may be further classified by the applicable –IN subcategorization.	
SUPERFICIALLY INVASIVE SQUAMOUS CELL CARCINOMA, WG3	
1. The term *superficially invasive squamous cell carcinoma* (*SISCCA*) is recommended for minimally invasive SCC of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy.	Note: Lymph-vascular invasion (LVI) and pattern of invasion are not part of the definition of SISCCA, with the exception of penile carcinoma.
2. For cases of invasive squamous carcinoma *with positive biopsy/resection margins*, the pathology report should state whether: The examined invasive tumor exceeds the dimensions for a SISCCA (defined below) OR The examined invasive tumor component is less than or equal to the dimensions for a SISCCA and conclude that the tumor is "*At least a superficially invasive squamous carcinoma*."	
3. In cases of SISCCA, the following parameters should be included in the pathology report: The presence or absence of LVI. The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma).	
4. CERVIX: SISCCA of the cervix is defined as an invasive squamous carcinoma that: Is not a grossly visible lesion, AND Has an invasive depth of $\leq$3 mm from the basement membrane of the point of origin, AND Has a horizontal spread of $\leq$7 mm in maximal extent, AND Has been completely excised.	
5. VAGINA: No recommendation is offered for early invasive squamous carcinoma of the vagina.	Owing to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina.
6. ANAL CANAL: The *suggested* definition of superficially invasive squamous cell carcinoma (SISCCA) of the anal canal is an invasive squamous carcinoma that: Has an invasive depth of $\leq$3 mm from the basement membrane of the point of origin, AND Has a horizontal spread of $\leq$7 mm in maximal extent, AND Has been completely excised.	
7. VULVA: Vulvar SISCCA is defined as an AJCC T1a (FIGO IA) vulvar cancer. No change in the current definition of T1a vulvar cancer is recommended.	Current AJCC definition of T1a vulvar carcinoma: Tumor $\leq$2 cm in size, confined to the vulva or perineum AND Stromal invasion $\leq$1 mm Note: The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
8. PENIS: Penile SISCCA is defined as an AJCC T1a. No change in the current definition of T1a penile cancer is recommended.	Current AJCC definition of T1a penile carcinoma: Tumor that invades only the subepithelial connective tissue, AND No LVI AND Is not poorly differentiated (i.e., grade 3–4)
9. SCROTUM: No recommendation is offered for early invasive squamous carcinoma of the scrotum.	Owing to the rarity of primary SCC of the scrotum, there is insufficient literature to make a recommendation regarding the current AJCC staging of early scrotal cancers.

Table 3 Continued

Recommendation	Comment
10. PERIANUS: The *suggested* definition for SISCCA of the perianus is an invasive squamous carcinoma that: Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND Has a horizontal spread of ≤7 mm in maximal extent, AND Has been completely excised.	
BIOMARKERS IN HPV-ASSOCIATED LOWER ANOGENITAL SQUAMOUS LESIONS, WG4	
1. p16 IHC is *recommended* when the H&E morphologic differential diagnosis is between precancer (–IN 2 or –IN 3) and a mimic of precancer (e.g., processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting).	Strong and diffuse block-positive p16 results support a categorization of precancerous disease.
2. If the pathologist is entertaining an H&E morphologic interpretation of –IN 2 (under the old terminology, which is a biologically equivocal lesion falling between the morphologic changes of HPV infection [low-grade lesion] and precancer), p16 IHC is *recommended* to help clarify the situation. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or non–block-positive staining strongly favors an interpretation of low-grade disease or a non–HPV-associated pathology.	
3. p16 is *recommended* for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (–IN 2 or –IN 3).	
4. WG4 *recommends against* the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN 1, and –IN 3.	
a. SPECIAL CIRCUMSTANCE: p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤ –IN 1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV-16+, or AGC (NOS).	Any identified p16-positive area must meet H&E morphologic criteria for a high-grade lesion to be reinterpreted as such.

Cervix: Early Invasive Lesions.—*Microinvasive* carcinoma is defined as a lesion that is predominantly intraepithelial with a focus of cells invading below the basement membrane into the superficial stroma. The histologic criteria for microinvasive carcinoma, particularly as related to the depth, length, and breadth of the invasive component, has varied greatly over the years, as has the importance of lymph-vascular invasion (LVI), confluence, and tumor volume. Therefore, this term and its definition have remained controversial.

In 1947, Mestwerdt gave the first definition of *microcarcinoma* as a carcinoma with invasion no more than 5 mm in depth [39]. Several other terms have been used, including *microinvasive carcinoma*, *early invasive carcinoma*, *very small carcinoma*, *early invasive preclinical carcinoma*, *pin-point invasion*, and *stage IA cervical carcinoma*. Between 1961 and 1985, the International Federation of Gynecology and Obstetrics (FIGO) changed the definition of stage IA microinvasive carcinoma 6 times, with treatment varying from conization alone, to the opposite extreme of radical hysterectomy with pelvic lymphadenectomy [39]. Concern continues to be expressed about marked interobserver variability in diagnosing microinvasion, with many cases of intraepithelial gland involvement being overinterpreted and the depth of invasion measured by different methods with variable measurement cutoffs.

Vaginal Preinvasive Lesions.—The first description of a vaginal intraepithelial lesion was made at the Mayo Clinic in 1933 more than a century after vaginal cancer was first described by Cruveilhie. For several decades, the lesion was termed vaginal CIS and was felt to be very rare, an impression that continued with Woodruff's [40] 1981 review of all literature on vaginal CIS in which he could find only 300 cases. However, increasing use of cytology and colposcopy soon demonstrated that vaginal HPV-induced squamous lesions were very common, particularly those of lower grades than CIS. By the 1980s, the terminology of vaginal intraepithelial neoplasia (VaIN) came into common use, with VaIN 1 equating to mild dysplasia; VaIN 2, to moderate dysplasia; and VaIN 3, to severe dysplasia/CIS [41].

Anal Preinvasive Lesions.—Early descriptions of anal preinvasive and invasive disease did not separate anal canal from perianus. These were primarily cutaneous lesions variously described as Bowen disease and CIS. It was not until 1962 that the need to separate perianal from anal tumors based on the different biology and behavior of these diseases was proposed [42]. In 1971, Oriel and Whimster [43] suggested the possible viral origin of Bowen disease in a report of CIS adjacent to anal warts. The association of HPV with anal precancer and cancer became plausible after documentation of HPV-16 in cervical cancer. Subsequent

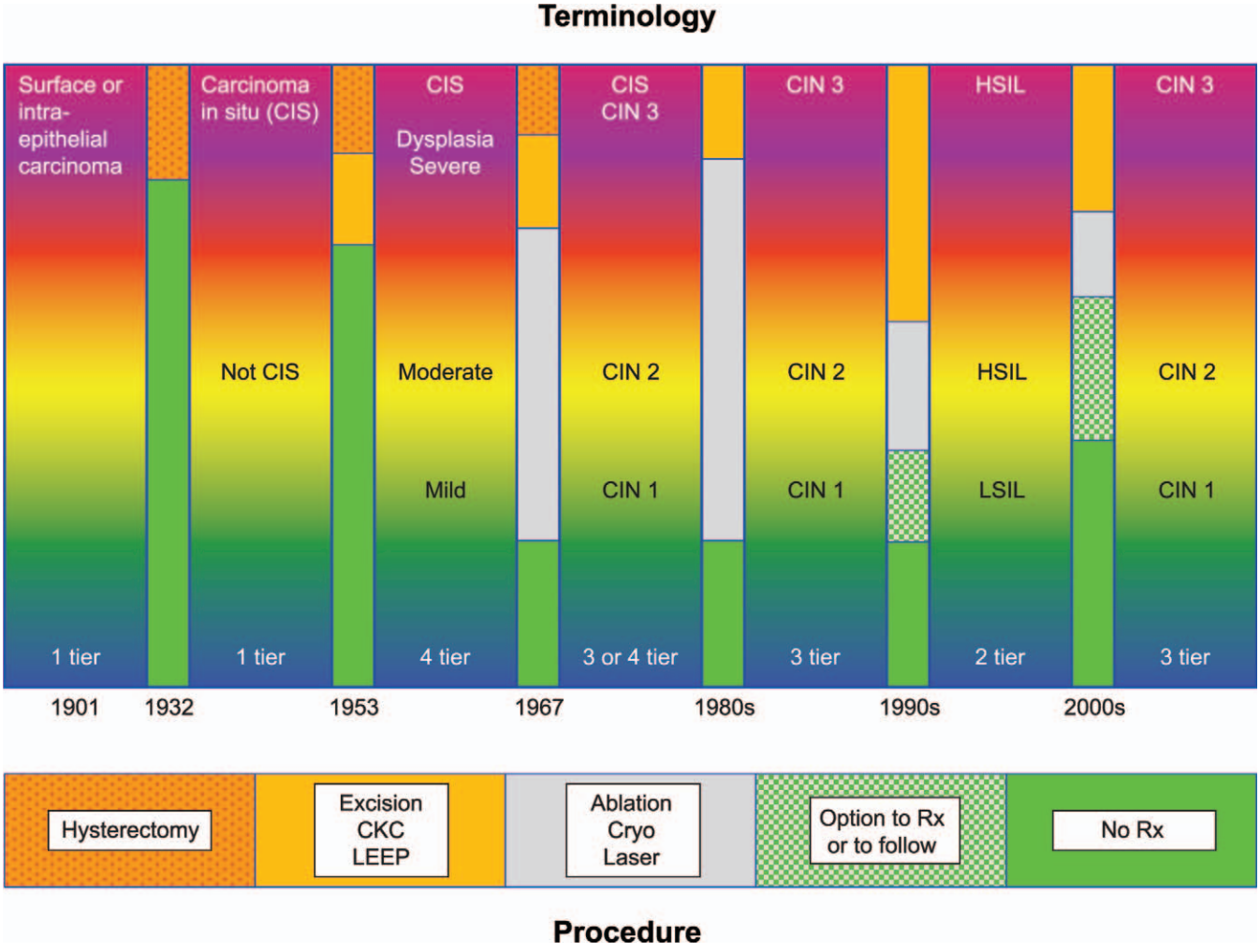

Figure 2. Changes to the terminology and number of tiers used to describe cervical precancer over time with corresponding management options (procedure). See text for additional details. CKC, cold knife conization; Cryo, cryotherapy; RX, treatment. Modified with permission. Courtesy of J. Thomas Cox.

documentation of oncogenic HPV types in both preinvasive and invasive anal cancer confirmed this association, as acknowledged by the International Agency for Research on Cancer in 1995 [44, 45].

In 1981, Fenger and Bichel [46] published the first study of *dysplastic* changes in the anal canal. In 1986, Fenger and Nielsen [47] described the presence of dysplasia and CIS adjacent to most anal canal carcinomas, showing that anal lesions shared the common HPV-associated oncogenic pathway seen in the cervix and other areas of the LAT. In the same year, they introduced the terminology of *intraepithelial neoplasia in the anal canal* (*AIN*). Analogous to CIN, AIN was divided into 3 grades: AIN 1, AIN 2, and AIN 3.

In the mid-1990s, the International Agency for Research on Cancer monograph on the evaluation of carcinogenic risks to humans supported the association of HPV with AIN and anal cancer [45]. In 1996, Northfelt et al [48] introduced the term *anal squamous intraepithelial lesion* as an alternative to AIN, with low-grade anal squamous intraepithelial lesion corresponding to AIN 1 and high-grade anal squamous intraepithelial lesion comparable to AIN 2 or 3. In 2000, the CAP published the cancer protocol for the examination of specimens from patients with carcinoma of the perianus and anal canal exposing the controversies regarding tumor location and anatomic terminology [49]. This controversy in the terms used to describe tumor location was further explored by Wendell-Smith in 2000 [50]. The surgical definition of the anal canal, proposed by the American Joint Committee on Cancer (AJCC), is the most widely accepted [51, 52]. By its definition, the anal canal extends from the apex of the anal sphincter complex to the palpable intersphincteric groove at the distal edge of the internal sphincter muscle.

Cutaneous Terminology

Cutaneous HPV-associated precancers on the vulva, perianus, and penis were all initially named after the 2 clinicians who first described them. In 1911, a dermatologist, Louis Queyrat, described lesions of the glans penis that were subsequently named *erythroplasia of Queyrat*. In 1912, JT Bowen described lesions on the shaft of the penis, buttocks, and thighs that were given the eponym *Bowen disease* [53]. As numerous descriptions of similar lesions on the vulva and the perianus began to appear in the literature, *Bowen disease* became the term applied to cutaneous precancers throughout the LAT.

Vulvar Preinvasive Lesions.—The histological description of Bowen disease was a full-thickness intraepithelial lesion, later termed *carcinoma in situ* by Woodruff and Hildebrandt in 1958 [54]. However, it soon became clear that cutaneous intraepithelial lesions were of 2 types and perhaps of 2 different etiologies. In 1961, Abell and Gosling [55] described 2 distinct histopathologic types as *intraepithelial carcinoma of Bowen's type* and *intraepithelial carcinoma simplex type*. The natural history of these vulvar squamous intraepithelial lesions was not well understood. There was a general consensus that all of these intraepithelial lesions were "premalignant" and required therapy. The 1972 report by Friedrich [56] of a pregnant woman with multifocal papular lesions of the vulva that histologically resembled CIS and resolved spontaneously postpartum questioned the consensus that these lesions required extensive treatment. Friedrich suggested the term *reversible vulva atypia*, but in 1978, Wade, Kopf, and Ackerman coined the term *Bowenoid papulosis* because these lesions looked histologically like Bowen disease but were clinically different in both appearance and in natural history [57].

The divergence in terminology between dermatopathologists and gynecologic pathologists for cutaneous areas of the LAT continued in 1976 with the report from the International Society for the Study of Vulvovaginal Disease (ISSVD) on "New Nomenclature for Vulvar Disease" [58]. The ISSVD recommended the continued use of the term *squamous cell carcinoma in situ*. It provided a classification of atypical changes of the vulvar epithelium less atypical than CIS under the rubric of "hyperplastic dystrophy with atypia." These were subclassified as mild, moderate, or severe atypia depending on the extent of the intraepithelial changes. Terms that were not recommended "because of the confusion associated with the use" included *Bowen disease*, *erythroplasia of Queyrat*, *carcinoma simplex*, and *leukoplakic vulvitis*. In 1982, the term *vulvar intraepithelial neoplasia* (VIN) was first introduced by Crum et al [59], paralleling the CIN nomenclature. The term, *VIN*, eventually gained great acceptance and adoption of similar terminology for the description of penile (PeIN) and perianal (PAIN) HPV-associated intraepithelial neoplasia followed. In 1986, the ISSVD accepted VIN as a general category of intraepithelial neoplasia with the grades of VIN 1, 2, and 3 [60]. The ISSVD added that *condylomatous dysplasia* was not a preferred term.

In 1994, the World Health Organization published a second edition of *Histological Typing of Female Genital Tract Tumours* addressing vulvar tumor terminology [61]. In this work, the term *squamous intraepithelial lesion* was introduced as an encompassing term, including lesions classified as dysplasia and CIS. The term *VIN* (including VIN 1, 2, and 3) was included as an alternate to the dysplasia/CIS terminology.

The intraepithelial neoplasia (–IN) term did not completely dominate LAT cutaneous terminology, and numerous names were proposed that reflected increasing knowledge of the HPV-associated etiology of these lesions. In 1994, Gross et al [62] demonstrated that typical condylomata acuminata and flat condyloma-like lesions were due to HPV-6 or –11, whereas papular and pigmented lesions with severe atypia, referred to as Bowenoid papulosis, were due to HPV-16.

In 2004, the ISSVD proposed a modified terminology for VIN as 2 distinct processes: the "usual type" encompassed high-grade VIN lesions (VIN 2 and 3) and were caused by HPV and the "differentiated type" was not caused by HPV [63]. The classification did not include grading of VIN lesions. Cases formerly interpreted as VIN 1 were designated as a nonneoplastic disorder or as condyloma acuminatum. In the 2010 American Registry of Pathology Fascicle 13, Kurman et al [64] proposed resurrecting the terms *VIN 1* and *VIN 2/3* and further subclassifying these as warty, basaloid, mixed warty-basaloid, pagetoid, and differentiated (simplex) VIN.

This lengthy history of vulvar terminology was paralleled by changes in the management of the disease. Intraepithelial lesions of the vulva were initially all considered to be premalignant and aggressive therapy, usually surgical, was recommended. As late as the mid-1960s, full or deep vulvectomy was the standard treatment [65]. By the late 1970s, less aggressive therapies with vulvar sparing techniques became more common [66]. In addition, treatment based on other factors, such as patient age and the size and extent of the lesion, was implemented.

In the 2011 ACOG-ASCCP Committee Opinion, VIN 1 lesions are considered condyloma and should be managed accordingly [67]. The preferred treatment recommended for high-grade VIN lesions is local excision, with 0.5- to 1.0-cm margins, but modified "…to avoid injury to the clitoris, urethra, anus, or other critical structures." When invasion is suspected, wide local excision is recommended. Laser ablation is considered an acceptable treatment if cancer is not suspected. Topical imiquimod 5% is also an acceptable nonsurgical treatment of HPV-associated VIN 2, 3 [67].

Perianal Preinvasive Lesions.—The demarcation between the perianus and adjacent perineum in both sexes, and the adjacent vulva in women, is not anatomically clear. The terminology of perianal HPV-associated precancer has paralleled the terminology of vulvar lesions. Common terminology for perianal preinvasive lesions includes Bowen disease, CIS, and PAIN grades 1, 2, and 3.

Penile/Scrotal Preinvasive Lesions.—Scrotal cancer was the first cancer determined to have an environmental cause (soot). In 1775, Sir Percival Pott described scrotal cancer as a rare cancer overall but very common in young chimney sweeps. In 1891, Tarnovsky first described a squamous intraepithelial lesion of the penis. Twenty years later, Queyrat and Bowen identified similar penile lesions [53]. As with terminology in other areas of the LAT, full-thickness intraepithelial lesions on the penis or scrotum were variously described as *Bowen disease* if on the shaft of the penis or scrotum, *erythroplasia of Queyrat* if on the glans penis, or *CIS* in any of these areas [57, 68]. Bowen disease was described clinically as typically raised, white, and scaly, whereas erythroplasia of Queyrat was usually a macular-papular, red to violet, velvety lesion. In 1982, the terminology of PeIN was introduced, akin to CIN and other HPV-associated intraepithelial lesions.

In 1992, Della Torre et al [69] reported that HPV-related warty and basaloid types of PeIN were more prevalent than the non-HPV related differentiated type of PeIN. As with squamous carcinoma of the vulva, 2 etiologic pathways to penile cancer were proposed: one HPV related and the other non-HPV related. More recently, the terms *low-grade* (*LSIL*) and *high-grade squamous intraepithelial lesion* (*HSIL*) have been proposed for squamous lesions of the penis [70]. In the 2011 Armed Forces Institute of Pathology Fascicle, the PeIN terminology is used and further subclassified as differenti-

ated or simplex PeIN and undifferentiated PeIN as *warty*, *basaloid*, *mixed warty-basaloid*, with other descriptions including *small cell*, *spindle* (*clear*) *cell*, *pagetoid*, and *pleomorphic* types. It also recognized a mixed differentiated and undifferentiated histology [71]. In this classification, Bowenoid papulosis is considered as a separate lesion and is not included as a PeIN lesion.

As summarized in this historical overview, the disparate terminologies for squamous lesions of the anogenital tract and their clinical management have morphed over time. The next step in this evolutionary process is a common nomenclature reflecting the morphologic and biologic similarities of these lesions and our current understanding of HPV-associated disease.

SQUAMOUS INTRAEPITHELIAL LESIONS—WG2

Work group 2 was in charge of determining whether the current knowledge of HPV-associated biology could be harmonized with histopathologic terminology across all lower anogenital body sites and, if so, to develop appropriate terminology. The ultimate goal of a unified and scientifically based terminology is to optimize clinical management by improving communication between pathologists and clinicians.

Work group 2 reviewed 1,909 articles from the published literature. After exclusions, 186 articles were included for data extraction and analysis. Recent textbooks and professional society documents were also reviewed. The recommendations were based on this comprehensive literature review, expert opinion, and open comment period responses. The current state of clinical management for noninvasive cervical disease is based on guidelines from the ASCCP and ACOG, which use a 2-tiered terminology for cervix, except in adolescents and young women where a 3-tiered scheme is used [33, 72]. The recent ASCCP/ACOG guidelines for treating HPV-related vulvar disease are based on ISSVD nomenclature with 2 tiers—condyloma and VIN [73, 74]. At present, there are no formal guidelines for the management of vaginal, anal, perianal, or penile noninvasive disease. As described previously, there is considerable overlap in the terminology between the body sites, with multiple variations of cytologic, gynecologic, dermatologic, and dermatopathologic terms used in an ad hoc fashion. This situation leads to potential confusion about the meaning of individual terms and complicates the development of appropriate management guidelines. The following recommendations were developed based on the common biology of HPV-associated squamous disease at these sites.

WG2 Recommendation No. 1

A unified histopathologic nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the LAT.

Rationale for Recommendation No. 1.—The comprehensive literature review and expert opinion support the biologic and morphologic equivalence of HPV-associated squamous proliferations across the LAT. Given this equivalence, a unified histopathologic nomenclature is recommended for all HPV-associated preinvasive intraepithelial squamous lesions in the LAT. Biomarker characteristics, as noted by WG4, are also consistent across LAT sites, lending further support to this recommendation.

WG2 Recommendation No. 2

A 2-tiered nomenclature is recommended for noninvasive HPV-associated squamous proliferations of the LAT, which may be further qualified with the appropriate –IN terminology. (–IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location, the appropriate complete term should be used. Thus, for an –IN 3 lesion: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3.)

Rationale for Recommendation No. 2.—Current understanding of HPV biology does not support a 3-tiered system of mild, moderate, severe dysplasia/CIS or –IN 1, 2, 3. Rather, as stated in the introduction, there is support for a dichotomous separation of morphologic designations that reflect transient active HPV replication and persistent HPV-associated precancer. On the basis of the comprehensive literature review by WG4, no biomarker data supported a 3-tiered system (see below). Instead, data are consistent with a 2-tiered system with low-grade lesions that are generally self-limited HPV infection and high-grade lesions that have the potential to progress to invasive carcinoma. The equivocal nature of the diagnosis of –IN 2, an intermediate category that has no biologic correlate, is thought to represent a mixture of low-grade and precancerous disease that cannot be reliably distinguished based on hematoxylin and eosin (H&E) morphology [10, 75]. The –IN 2 category is not a reproducible histologic category among pathologists. Studies of diagnostic concordance demonstrate considerable interobserver variability reflected in very low κ statistics [10]. As might be expected from this mixture of high- and low-grade lesions, the risk of progression for lesions classified as –IN 2 is intermediate between –IN 1 and –IN 3. In addition, a substantial proportion of CIN 2 is found to represent CIN 3 on follow-up [6]. The recommendation for a 2-tiered system also harmonizes LAT terminology with other published systems, including those of recent textbooks and professional societies [64, 73, 74, 76, 77].

As expected, classification agreement with lower variability between observers can be improved in a 2-tiered versus a 3-tiered system [10, 28, 78–87]. Improved agreement among pathologists leads to a more consistent and reproducible diagnosis, which may lead to more valid clinical outcome data. Further methods for more precise classification of identified lesions using biomarkers are discussed in the recommendations from WG4. There is evidence to show that using certain biomarkers significantly increases interobserver agreement [88–91].

Considerable discussion occurred at the LAST consensus meeting and during the open comment period regarding the utility of maintaining an intermediate or equivocal category (i.e., –IN 2). The most frequently raised rationale for retaining this category was that current management guidelines for the cervix recommend conservative management of this intermediate category in young reproductive-aged women. Hence, there was concern for overtreatment should the –IN 2 category be merged into a high-grade tier. Given this concern, it was decided that qualifying the 2-tiered diagnosis with the relevant –IN category in parentheses is appropriate. This qualified 2-tiered stratification is similar to the recommendation for the initial, transitional TBS terminology from 1989 and 1991 that proposed a 2-tiered cytologic squamous intraepithelial lesion classification

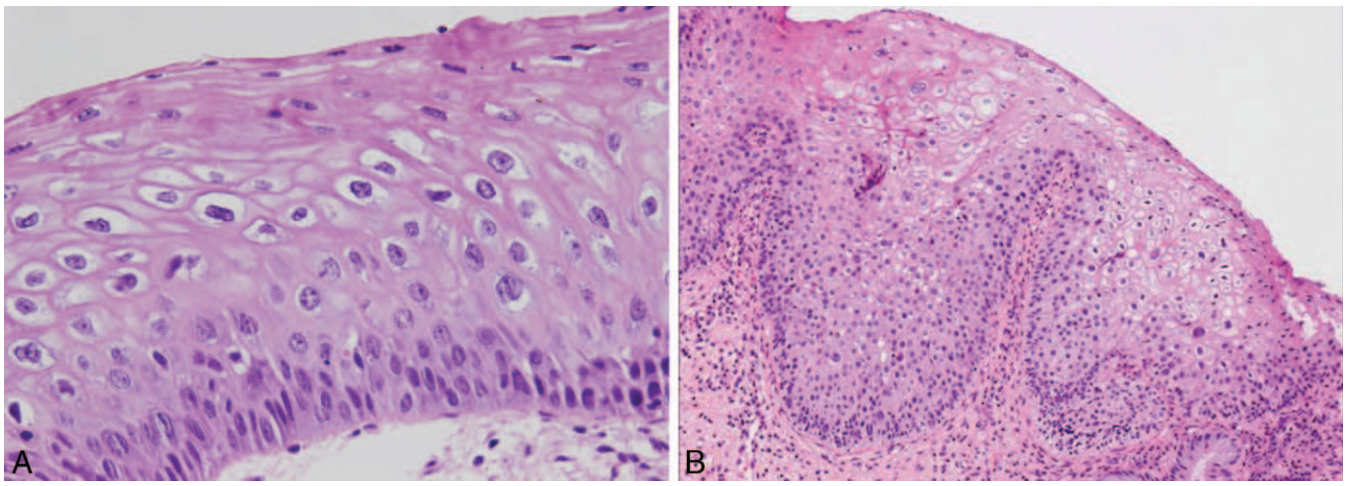

Figure 3. A, Vagina: LSIL (VaIN 1). B, Cervix: LSIL (CIN 1). In both images, the nuclei in the lower one third of the epithelium are enlarged with variable size and increased nuclear-to-cytoplasmic ratios. Cells in the upper layers show changes associated with HPV infection including nuclear size variability, multinucleation or binucleation, and cytoplasmic koilocytic change. Abnormal mitoses and marked nuclear atypia are not present. A, High power, H&E. B, Medium power, H&E.

with the option for further subclassification such as mild, moderate, or severe dysplasia (CIN 1, 2, or 3) [92].

WG2 Recommendation No. 3

The recommended terminology for HPV-associated squamous lesions of the LAT is *low-grade squamous intraepithelial lesion* (*LSIL*) and *high-grade squamous intraepithelial lesion* (*HSIL*), which may be further classified by the applicable –IN subcategorization.

Rationale for Recommendation No. 3.—This recommendation harmonizes the descriptive terminology for cytology and histopathology for biologically similar HPV-associated squamous lesions of the LAT. This terminology is also the one used for 2-tiered histologic systems in recent textbooks published in the field [64, 76, 77]. In addition, this terminology was the most widely supported by responses during the open comment period and at least a 67% supermajority of the participants at the consensus conference.

Concern was expressed that using the same terminology for cytology and histomorphology would not allow for distinction as to whether the diagnosis was associated with a cytologic or histologic specimen. On a written pathology report, the specimen type is clearly stated, so this confusion is minimized. However, in short-hand verbal communication, it may be important to designate reports as associated with cytology or histology specimens. The option of adding the specific –IN terminology with the basic 2-tiered classification would also help to identify these samples as histopathology.

The hallmark of SIL is an abnormal cellular proliferation with nuclear atypia that includes enlargement, pleomorphism, change in chromatin texture, and irregular nuclear borders. With increasing severity of SIL, the nuclear-to-cytoplasmic ratios increase, mitotic activity increases, and, in most cases, the cells appear more immature. It is important to note that nuclear changes are usually present throughout the full thickness of the epithelium, irrespective of the severity of the lesion. For that reason, cytologic sampling of the superficial layers can detect both low- and high-grade lesions. In general, it is the relative maturation or lack of maturation of the cytoplasm in the superficial layers, coupled with persistent mitotic activity, that defines the severity of the process.

Criteria that define the 2-tiered classification system:

LSIL:

- Proliferation of squamous or metaplastic cells with abnormal nuclear features including increased nuclear size, irregular nuclear membranes, and increased nuclear-to-cytoplasmic ratios. There is little cytoplasmic maturation in the lower third of the epithelium, but maturation begins in the middle third and is relatively normal in the upper third. Mitotic figures are limited to the lower one third of the epithelium (see Figure 3A).

And/or

- The presence of diagnostic cytopathic effect of HPV (koilocytosis) including multinucleation, nuclear enlargement, and pleomorphism accompanied by perinuclear halos without the features of a high-grade lesion (see Figure 3B).

HSIL:

- Proliferation of squamous or metaplastic squamous cells with abnormal nuclear features including increased nuclear size, irregular nuclear membranes, and increased nuclear-to-cytoplasmic ratios accompanied by mitotic figures. There is little or no cytoplasmic differentiation in the middle third and superficial thirds of the epithelium. Mitotic figures are not confined to the lower third of the epithelium and may be found in the middle and/or superficial thirds of the epithelium (see Figure 4).

It is important to NOT overcall LSIL as HSIL. Low-grade SIL is a common finding, especially on cervical biopsies. These are typically self-limited HPV infections that will resolve spontaneously.

Special circumstances:

Abnormal mitosis or significant nuclear atypia (see Figure 5): Abnormal mitoses and substantial nuclear atypia are more commonly seen in high-grade lesions. Some consider lesions with the overall morphology of LSIL, with either marked nuclear atypia in the lower third of the epithelium or atypical mitoses at any level, to be consistent with HSIL. As noted in WG4's recommendations, positive p16

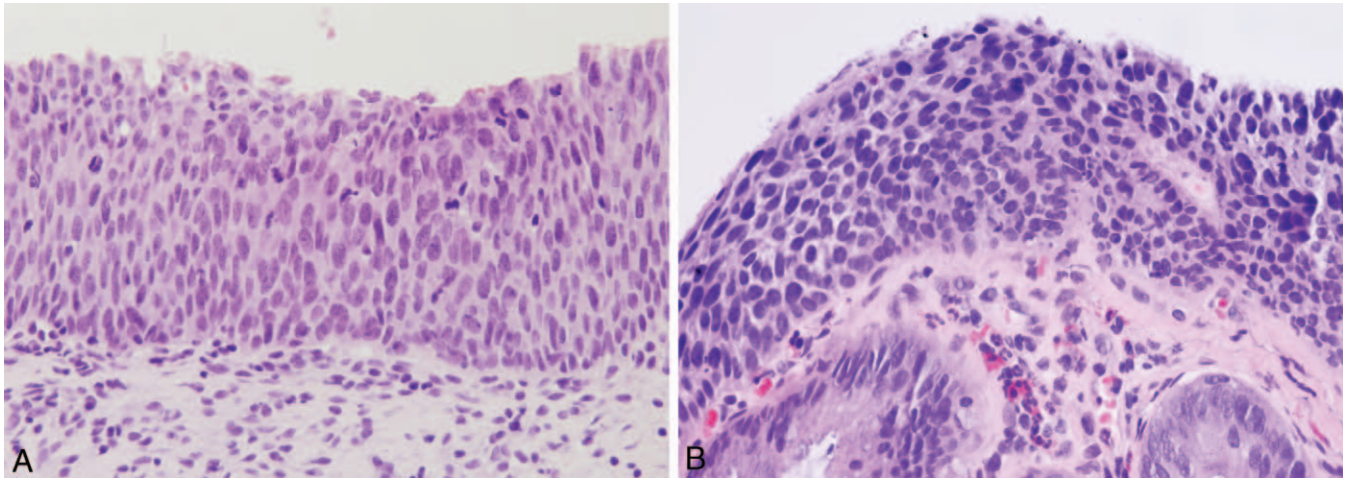

Figure 4. A, Cervix: HSIL (CIN 3). B, Anal: HSIL (AIN 3). These mucosal lesions have a full-thickness proliferation of abnormal immature or parabasal-like cells. There is loss of nuclear polarity, anisonucleosis, and increased nuclear-to-cytoplasmic ratios. Mitoses are seen in the upper two thirds of the epithelium. A and B, High power, H&E.

staining in this circumstance supports the diagnosis of HSIL.

Thin SIL (historically called thin dysplasia; see Figure 6): Morphologically, these are immature intraepithelial lesions less than 10 cells thick. If a lesion is unequivocally SIL with significant immature abnormal basal proliferation or mitosis above the basal cells, it is designated as HSIL. If there is doubt about the nature of the proliferation (e.g., immature metaplasia versus SIL) then p16 staining can be used as per WG4 Recommendation No. 1.

Keratinizing SIL (see Figure 7): A markedly atypical keratinizing proliferation is high grade. These lesions are defined by an abnormal keratinizing layer on the surface. The epithelium has dyskeratotic cells with markedly atypical, often pleomorphic nuclei. There is an abnormal proliferation of basal-type cells, but these often have more eosinophilic cytoplasm than is seen in mucosal high-grade lesions. These changes are most often seen in cutaneous sites with keratinizing epithelium such as vulva or perianus, although these changes may occasionally be seen in a mucosal epithelium such as cervix and vagina.

Dysplasia extending into the endocervical glands (see Figure 8): In general, grading of lesions extending into the endocervical glands can be performed as with surface lesions. If the abnormal basal proliferation fills the gland with no or minimal evidence of maturation, this should be classified as high grade. However, it is important to be aware of the possibility of tangential sectioning of epithelial basal layers that may make accurate grading difficult or impossible.

Condyloma acuminatum (see Figure 9): Condyloma acuminatum is, by definition, a papillary proliferation with low-grade cytopathic features of HPV infection. The majority are caused by low-risk HPV types 6 and 11. Lesions within this spectrum are designated as LSIL, with the additional optional designation of condyloma in parentheses. Condylomas are common in external anogenital areas and less frequent in the cervix and vagina.

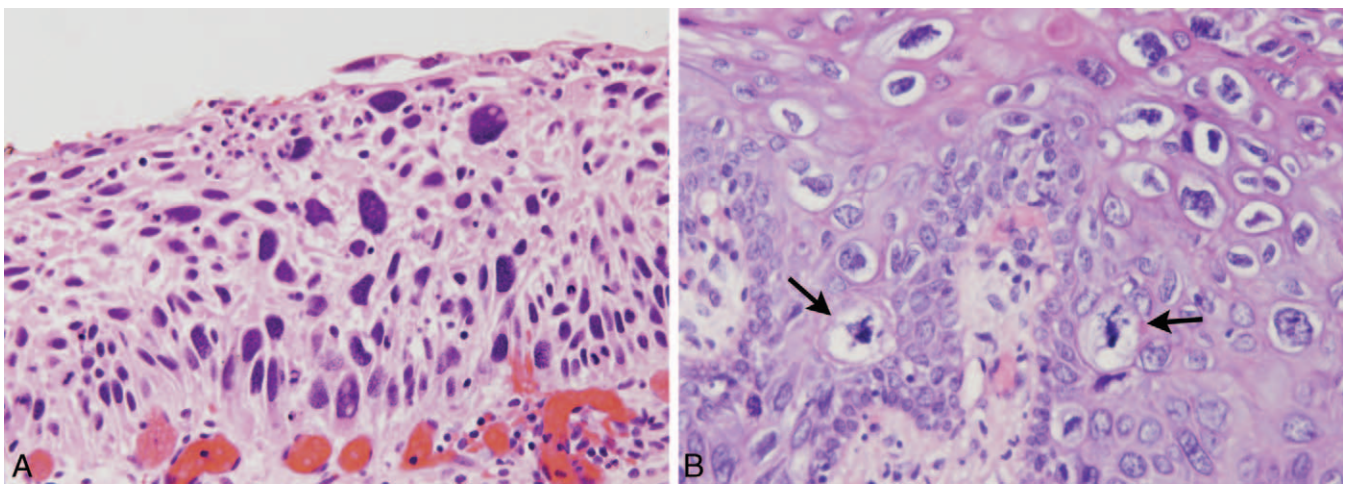

Figure 5. A and B, Cervical HSIL (CIN 2). A, Marked nuclear atypia is seen extending throughout the full thickness of the epithelium. Unlike classic –IN 3, these cells have more abundant cytoplasm. However, this degree of nuclear change is considered to be high grade. B, In this biopsy, there are abnormal mitoses (arrows) that are in the lower one third of the epithelium. The overlying cells show maturation and koilocytic change. The presence of these abnormal mitoses suggests HSIL and, in the presence of block-positive p16 staining, the diagnosis is HSIL (CIN 2). A and B, High power, H&E.

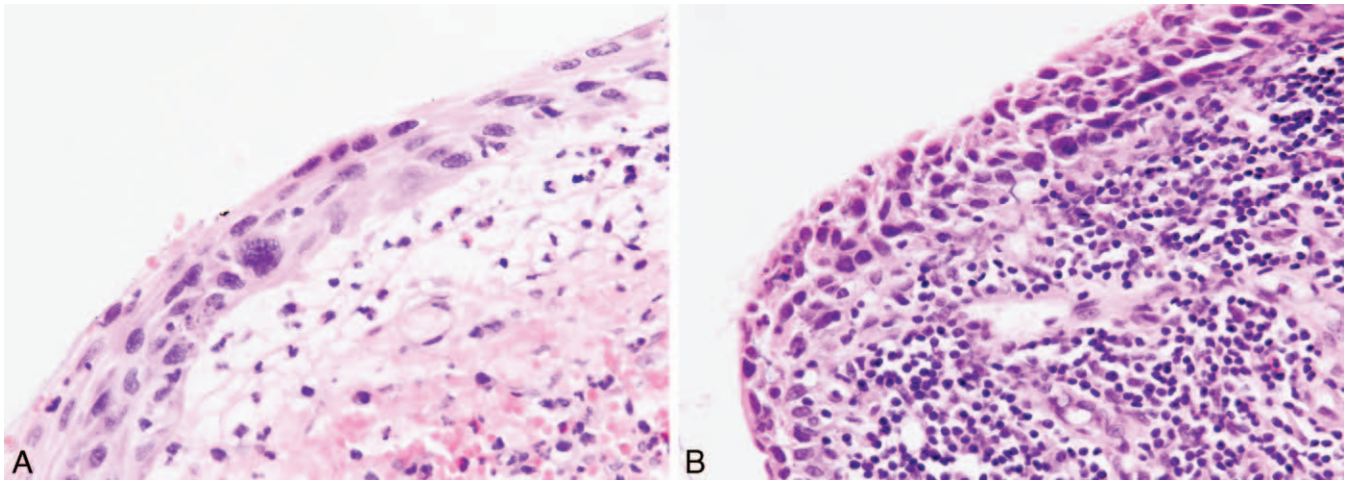

Figure 6. A and B, Cervix: HSIL (CIN 3). Both A and B demonstrate a thin SIL. The epithelium is less than 10 cells in thickness but shows marked nuclear atypia with anisonucleosis, mitotic activity above the basal layer, and loss of nuclear polarity consistent with a high-grade lesion. A and B, High power, H&E.

Bowenoid papulosis (see Figure 10): The clinical morphology of Bowenoid papulosis consists of small cutaneous papules that have high-grade histomorphology indistinguishable from –IN 3. In small or partial biopsies, an unequivocal diagnosis of Bowenoid papulosis is not possible based solely on microscopic findings. In the appropriate clinical setting of a patient with small, cutaneous anogenital papules, a note stating that the differential diagnosis includes Bowenoid papulosis may be warranted. If the lesion is excised and its small size can be identified, it can be diagnosed as HSIL with an additional designation of Bowenoid papulosis in parentheses. Bowenoid papulosis may have a lower risk of progression to cancer than cutaneous HSIL found in larger plaques (Bowen disease).

Use of LAST Terminology in a Pathology Report

The recommended terminology for squamous intraepithelial lesions should be used as with any other diagnostic terms in a routine surgical pathology report. In general, when an –IN qualifier is used in parentheses, the lesion grade should be based on the H&E histomorphology of the lesion. However, if a biomarker is used to evaluate the specimen, as specifically recommended by WG4, the results may override the original H&E interpretation. For example, if a putative –IN 2 lesion is negative for p16, the lesion represents either LSIL or a non–HPV-associated mimic, and should be reported as such (see Figures 16–18).

SUPERFICIALLY INVASIVE SQUAMOUS CELL CARCINOMA—WG3

Work group 3's charge was to review data across LAT sites to recommend specific terminology for minimally invasive squamous cell carcinoma (SCC), especially where minimal invasion is not well defined (i.e., anus). If possible, unification of terminology across sites was favored. Such terminology should be designed to provide clear and relevant communication between pathologists and clini-

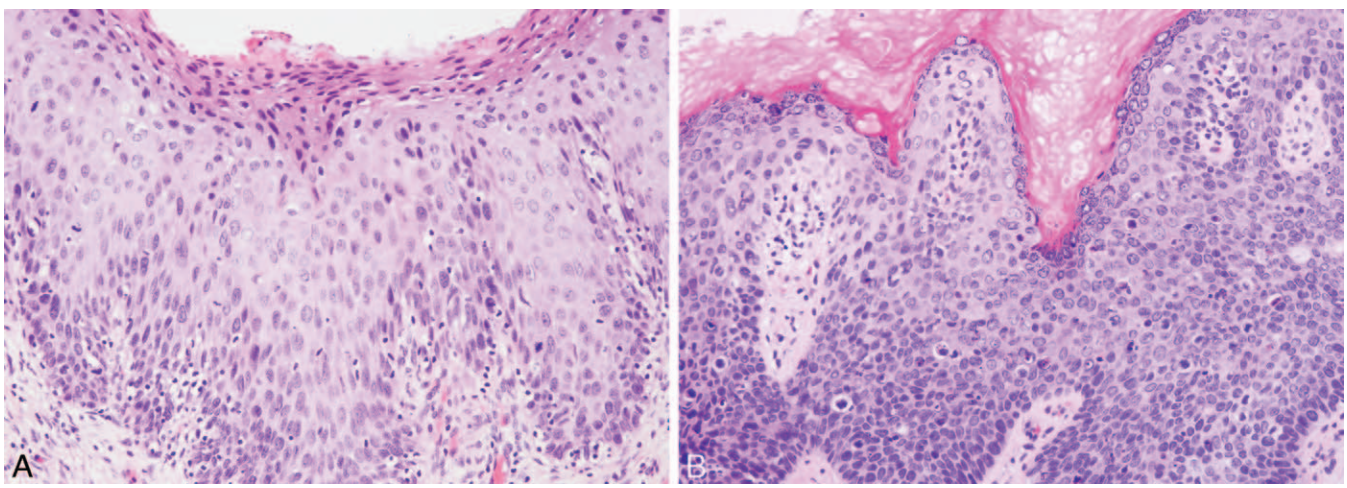

Figure 7. A, Cervix: HSIL (CIN 3). B, Perianus: HSIL (PAIN 3). High-grade keratinizing SIL often shows more cellular maturation in the middle layers of the epithelium as is seen in A. In both panels, there is an abnormal keratinizing surface, and mitoses are seen throughout the epithelium. Although keratinizing dysplastic change is most commonly seen in cutaneous anogenital sites, (B) they may be seen in the mucosal areas such as the cervix or anal canal. A and B, High power, H&E.

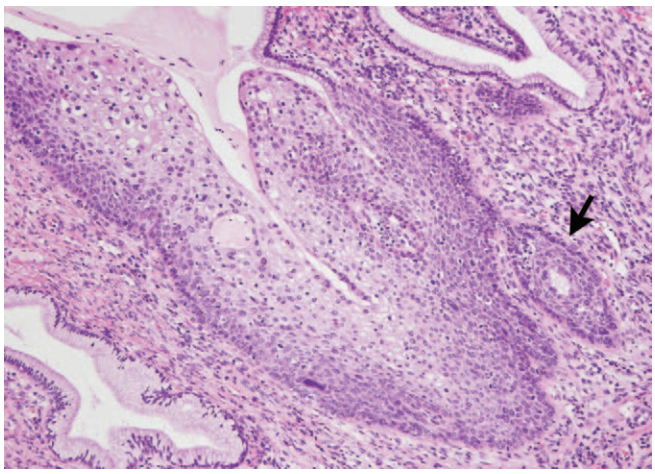

Figure 8. Cervical LSIL (CIN 1). Low-grade squamous intraepithelial lesion extends into an endocervical gland neck. When the full thickness of the abnormal epithelium is seen, the interpretation is straightforward. In areas with tangential sectioning (arrow), care must be taken not to overcall HSIL. Medium power, H&E.

cians, with a specific focus on reconciling histopathologic diagnoses with current clinical management. Work group 3 identified 1863 articles in its comprehensive literature search and extracted data from 194. Most articles dealt with cervical disease, but some articles did address vulvar, penile, anal, and perianal diseases. This literature review was supplemented with background information, the current *AJCC Cancer Staging Manual* (*7th edition*) and errata, and other current pathology textbook resources [52]. The recommendations are based on this comprehensive literature review, expert opinion, open comment period responses, and consensus conference discussion.

The literature review highlighted a widespread but inconsistent use of "microinvasive" terminology. There are a variety of definitions, per site and between sites. Different sites use different defining parameters. There are outstanding methodological issues such as multifocality and precision in measurement. The use of some potential prognostic parameters, for example, LVI, varies among systems and sites. There is lack of clarity in reporting margin involvement by invasive carcinoma or intraepithelial neoplasia. There is no current definition identified for minimally invasive cancers of the anal canal and perianus. Cancer of the perianus is staged as skin cancer, not as anal cancer or vulvar cancer, and the vulvar and perianal regions anatomically overlap in women. The central conclusion of the literature review was that adopting a category of superficially invasive squamous cell carcinoma (SISCCA) based on clinical outcome for these sites would have several potential benefits: clear identification of groups that might be amenable to conservative treatment (e.g., cervix), permit comparison of results for management of identical stage disease across body sites, and eliminate confusion in defining early invasive disease across body sites.

Superficially invasive squamous cell carcinoma is defined based largely on depth and width of invasion. The diagnostic criteria proposed for SISCCA recognize that the risks for metastasis differ across body sites. In addition, biopsy reports should include consistent terminology for lesions that have been completely excised and those that have positive margins.

Reports on minimally invasive squamous carcinomas could merely state the diagnosis and list all objective findings of potential prognostic importance, such as depth and width of invasion and any LVI, rather than define a category of SISCCA for invasive carcinomas that might be amenable to local excisional (conservative) treatment only. However, defining the features of a SISCCA category for each LAT site would have 3 major advantages. First, although a listing of prognostic parameters alone might be sufficient for the oncologic subspecialist's management of patients, it is not optimal reporting for all health professionals managing LAT neoplasia who may only occasionally deal with SISCCA. The role of the modern pathologist is to integrate objective parameters into a definitive diagnostic report based on evidence-based outcomes. Using this approach, the surgical pathology report delivers synthesized information relevant to clinical management rather than just data points. A clearly defined category of SISCCA identifies those patients who can be potentially managed by local treatment only. Second, a well-defined category of SISCCA will permit comparative

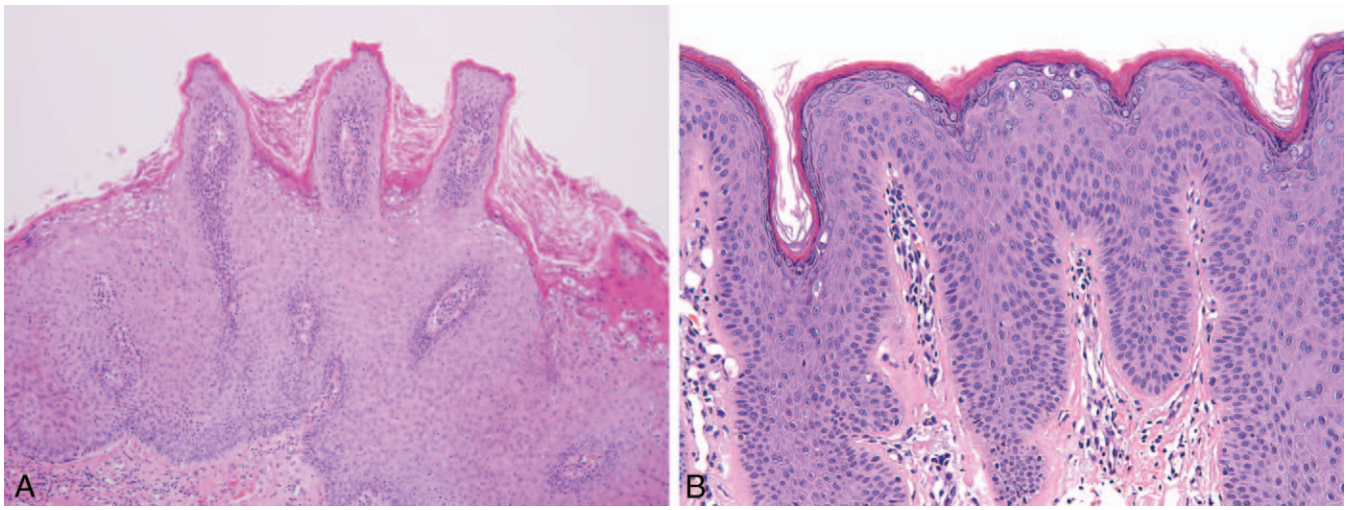

Figure 9. A, Perianus: LSIL (condyloma). B, Vulva: LSIL (condyloma). Low-grade lesions with a papillary growth pattern may be designated as condylomas in the proper clinical setting. These lesions should not demonstrate high-grade features. A, Low power, H&E. B, Medium power, H&E.

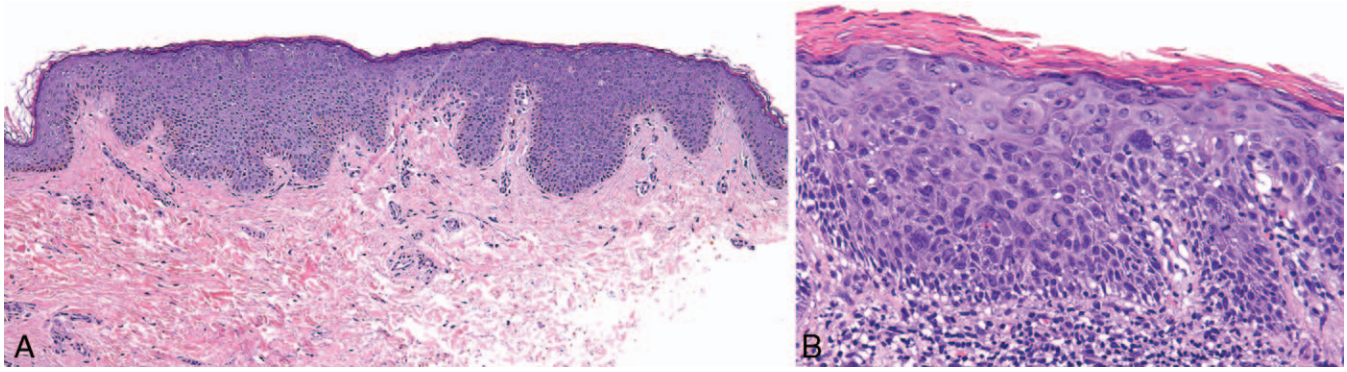

Figure 10. A, Vulva: HSIL (Bowenoid papulosis). B, Penis: HSIL (PeIN 3). In A, the entire extent of the high-grade lesion can be seen, and given the small size and location, Bowenoid papulosis can be included in parentheses in the diagnoses. In B, only a portion of the lesion can be seen and, although Bowenoid papulosis may be suggested in a comment, it should not be part of the diagnostic line. A, Low power, H&E. B, High power, H&E.

research in the management of identical groups of patients, which is not assured if only prognostic parameters are listed. Third, defining SISCCA would eliminate confusion in dealing with the parameters of early invasive disease that exists in some anogenital sites, such as the cervix.

The first 3 recommendations from WG3 are general and are to be applied across all LAT sites. These are followed by an additional 7 site-specific recommendations that include measurement recommendations where these have been shown to have prognostic significance. A subsequent paper with detailed methods of measurement is planned for future publication.

WG3 Recommendation No. 1

The term *superficially invasive squamous cell carcinoma* (SISCCA) is recommended for minimally invasive squamous cell carcinoma of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy. Note: Lymph-vascular invasion (LVI) and pattern of invasion are not part of the definition of SISCCA, with the exception of penile carcinoma.

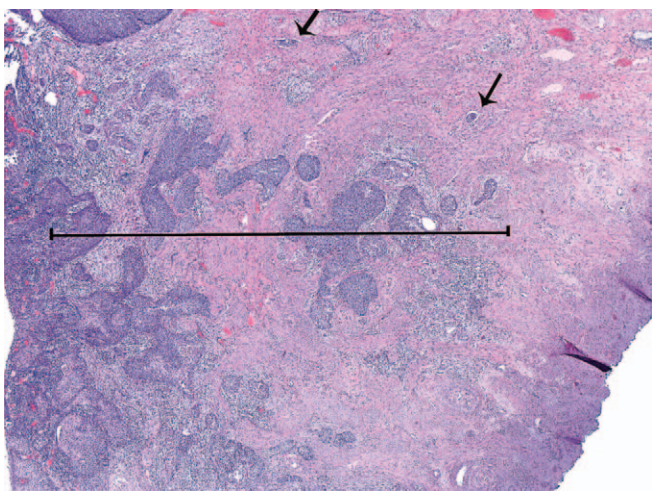

Figure 11. Cervical SISCCA with less than 3 mm (line); LVI is present (arrows). It was completely excised. Low power, H&E. Reprinted with permission from *Journal of Lower Genital Tract Disease* (2011;15:146–57). Copyright 2011, American Society for Colposcopy and Cervical Pathology.

Explanatory Notes: Recommendation No. 1.—Resection margin status is best determined from a single marked or inked surgical excisional biopsy. In the cervix, for example, this will usually mean a LEEP or cone specimen. Punch biopsies may identify invasive carcinoma, but their size is usually suboptimal to definitively identify SISCCA. In the setting of multiple specimens from the same lesion, the final diagnosis must be based on the consideration of all the findings. For example, if a 3-mm punch cervical biopsy shows invasive squamous carcinoma 2 mm in depth and a subsequent LEEP specimen shows only a healing biopsy site without residual carcinoma, then SISCCA is present.

WG3 Recommendation No. 2

For cases of invasive squamous carcinoma with positive biopsy/resection margins, the pathology report should state whether:

The examined invasive tumor exceeds the dimensions for a SISCCA (defined below)

OR

The examined invasive tumor component is less than or equal to the dimensions for a SISCCA and conclude that the tumor is "*at least a superficially invasive squamous carcinoma*."

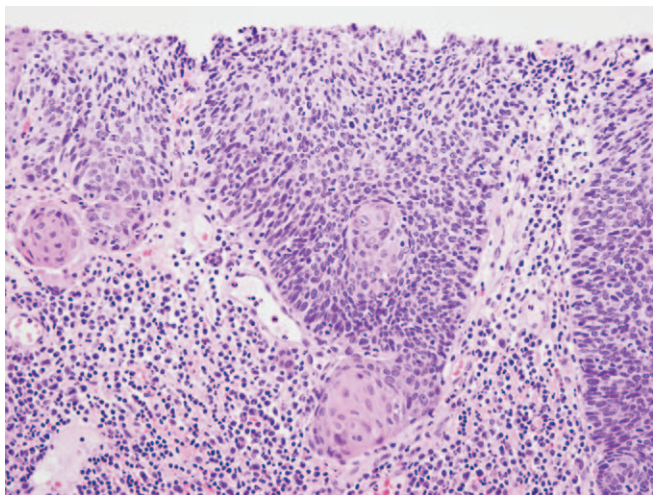

Figure 12. Superficially invasive squamous cell carcinoma of the anal canal with a nest of malignant squamous cells invading into the stroma. Note overlying HSIL. Medium power, H&E.

Explanatory Notes: Recommendation No. 2.—Anogenital tract biopsies may show invasive squamous carcinoma with invasive disease at the margins. In this clinical situation, it is important to clearly indicate whether the current specimen qualifies for SISCCA (if no more invasive disease is identified) or whether more advanced disease is already evident.

In this recommendation, positive biopsy or resection margins refers to invasive carcinoma at the surgical resection margin. The presence of HSIL at the surgical margins does not negate the diagnosis of SISCCA; however, its presence should be reported.

WG3 Recommendation No. 3

In cases of SISCCA, the following parameters should be included in the pathology report:

The presence or absence of LVI.

The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma).

Explanatory Notes: Recommendation No. 3.—Lymph-vascular invasion and tumor multifocality may play a role in the management of LAT squamous carcinomas but are not usually criteria in the diagnosis of SISCCA. However, these 2 parameters should also be reported.

Lymph-vascular invasion is most reliably defined when the following features are identified in an H&E histologic section: a tumor island is present within a space, the space has an apparent endothelial lining, the tumor is adherent to the lining, the space is not due to retraction artifact, and the finding is beyond the invasive front. Frequently, however, LVI is only identified within the invasive tumor front and the latter criterion cannot be met. Immunohistochemical (IHC) staining for vascular and lymphatic endothelium may be used to confirm the presence of LVI. The absence of IHC staining, however, does not exclude the presence of LVI because a variety of preanalytic and technical factors can lead to negative IHC staining of the endothelium.

Site-Specific Recommendations

After establishing the primary general recommendations for SISCCA, the current terminology systems and evidence for each specific anogenital site were reviewed, and recommendations were adopted.

Cervix.—It is thought that all SCCs of the cervix are attributable to HPV [93]. There are abundant data that early invasive squamous carcinoma (SCC) of the cervix can safely be treated conservatively. Historically, a variety of terms, including *microinvasive carcinoma*, have been used to label this group. Criteria for defining patients amenable to conservative management have changed over the years.

Initially, invasive squamous carcinomas as deep as 5 mm, regardless of LVI, were considered to be amenable to conservative therapy, but evidence accumulated that metastatic lymph node disease and/or local recurrence occurred in a small, but significant proportion of these patients [94–97]. Consequently, more restrictive definitions of minimally invasive squamous carcinoma were proposed.

Currently, 2 principal systems are used: the first, developed by the Society of Gynecologic Oncologists (SGO), is more commonly used in the United States and the second, developed by FIGO, is used in other parts of the world. Staging of minimally invasive squamous carcinoma differs between these 2 systems, making comparisons difficult.

In 1973, SGO defined microinvasive cervical carcinoma as any lesion in which neoplastic cells invade the stroma, in 1 or more sites, to a depth of 3 mm or less below the base of the epithelium, without lymphatic or blood vessel involvement [98, 99]. The margins of the specimen must be clear of the lesion [76]. The SGO definition does not comment on the width of the lesion. Clinical studies and expert opinion have generally concluded that "microinvasive" SCC can be managed conservatively by cervical conization, LEEP excision, or simple hysterectomy, although more restrictive depth criteria of 2 mm or even 1 mm have been proposed or used [98, 100–113].

In the last 40 years, accumulated evidence indicates that there are significant deficiencies in the SGO criteria for "microinvasive" disease. No lateral or horizontal criteria are used in the SGO definition of "microinvasive" carcinoma, although tumor volume has been shown to be a major predictor of lymph nodal metastases [114, 115]. Occasional cases have been reported with extensive lateral spread and tumor volume, but with less than 3 mm depth of invasion that still meets the criteria for SGO "microinvasive" carcinomas [116]. The 2009 revised CAP protocol for cervical carcinoma introduced a 7-mm maximal lateral extent for "microinvasive" carcinoma [117]. Moreover, the prognostic significance of LVI in minimally invasive carcinomas remains unclear [105]. The presence of LVI strongly correlates with the depth of invasion and tumor volume, and this correlation is a major confounding variable [110, 111, 118]. Clinical studies have shown LVI to be an inconsistent predictor of lymph node metastases in cases of invasive carcinoma 3 mm or less in depth [105, 119–123]. Consequently, it is unclear whether LVI should remain an unequivocal exclusion criterion to preclude conservative management among cases in which the depth of invasion is 3 mm or less. Although the SGO definition of "microinvasion" requires that the lesion be entirely excised, it is unclear whether this requires the margin to be free of invasive squamous carcinoma, HSIL (CIN 3), or any SIL (CIN). Finally, perpetuation of the use of the SGO microinvasive carcinoma concept may continue to impair the international comparability of cervical carcinoma management.

The AJCC (TNM) and FIGO staging classifications are concordant albeit with minor nomenclature discrepancies. For example, AJCC T1a is labeled as FIGO IA. Large cervical carcinomas are staged clinically, but early-stage carcinomas are defined by pathologic examination of a biopsy specimen. FIGO stage I is a carcinoma strictly confined to the cervix (extension to the corpus is disregarded) [124]. Any grossly or clinically identified carcinoma is staged as IB. Colposcopic suspicion or identification of an invasive carcinoma alone does not lead to a diagnosis of stage IB. Stage IA carcinoma is present when the invasive disease is only identified microscopically, and stromal invasion is limited to 5 mm or less and to a lateral or horizontal width of 7 mm or less [125]. The depth of invasion is measured from the base of the epithelium of the presumptive point of origin, whether squamous or glandular. Vascular space involvement, either venous or lymphatic, does not alter the staging. Stage IA1 lesions, a subset of IA, has a depth of invasion of 3 mm or less, whereas stage IA2 carcinomas have invasion of greater than 3 mm. These 2 subsets of disease reflect an increasing risk of metastatic lymph node disease secondary to increasing tumor volume.

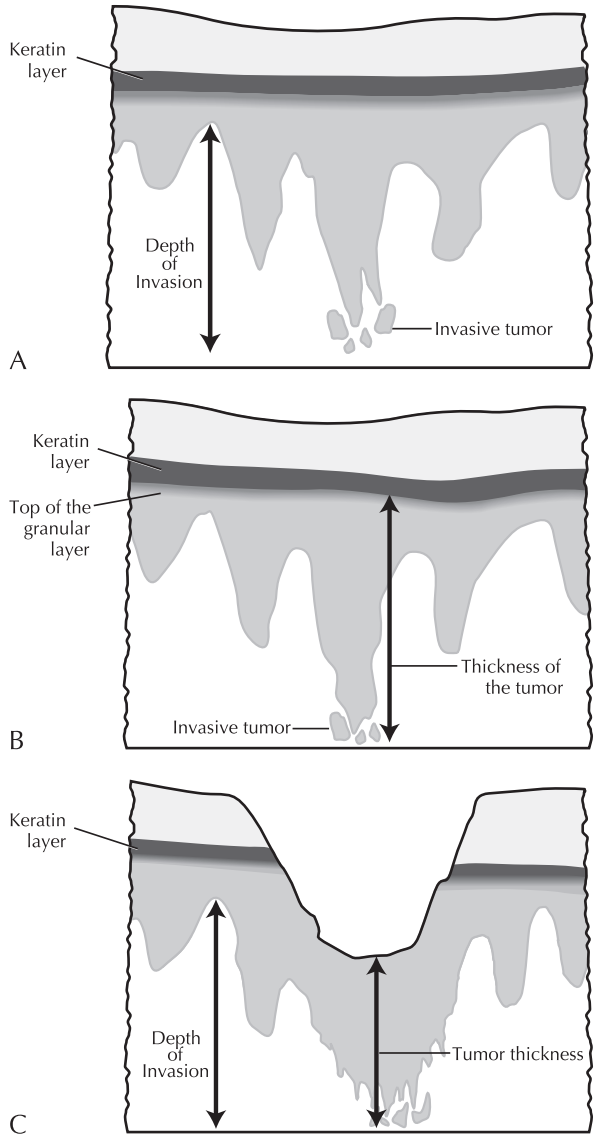

Figure 13. Cutaneous anogenital SISCCA: measurement of the depth of invasion. A, The depth of invasion is measured from the epithelial-dermal junction of the adjacent-most superficial dermal papillae to the deepest point of invasion. This measurement is applicable whether the surface epithelium is ulcerated or keratinized. This is the AJCC-recommended method of measuring vulvar squamous cell carcinomas in determining whether a tumor is stage T1a or T1b. B, Measurement for the thickness of the tumor when the epithelial surface is intact. If the tumor is keratinized, the thickness of the tumor is measured from the granular cell layer to the deepest point of invasion. For squamous cell carcinomas, the convention is to measure from the bottom of the granular cell layer. If the epithelium is not keratinized, the thickness of the tumor is measured from the surface of the tumor to the deepest point of invasion. C, Measurement for tumor thickness when the tumor is ulcerated. The tumor thickness is measured from the surface of the ulcerated tumor to the deepest point of invasion. For SCC, the depth of invasion is a more accurate measurement of the true depth of the tumor, as measured from the epithelial dermal junction of the adjacent dermal papillae to the deepest point of invasion. Reprinted with permission. Figure © E.J. Wilkinson, 2007 From *AJCC Cancer Staging Manual*, 6th ed. New York, NY: Lippincott, Williams & Wilkins; 2002.

Since the adoption of FIGO IA staging methods more than 15 years ago, evidence has accumulated and confirmed the clinical utility of the FIGO IA1 and IA2 subsets. The proportion of patients with lymph node metastases in FIGO IA1 or invasive carcinomas 3 mm or less in depth is negligible, and many authors have concluded that local excision is adequate management [97, 121, 126–133]. Nevertheless, some have adopted the presence of LVI, or "extensive" LVI, as an exclusion criterion for conservative management [105, 110, 111, 134]. In contrast, there is an increased prevalence of both lymph node metastases and recurrence after local excision in FIGO IA2, and many studies conclude that local excision alone is inadequate for this group of patients [39, 103, 118, 126, 128, 130, 134–138].

In summary, the comprehensive literature review and expert opinion supports that a unifying terminology for invasive squamous carcinoma of the cervix be based on the widely adopted FIGO system and that cervical SISCCA is equivalent to a FIGO IA1.

WG3 Recommendation No. 4.—Cervix.—Superficially invasive squamous cell carcinoma of the cervix is defined as an invasive squamous carcinoma that:

Is not a grossly visible lesion, AND
Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
Has a horizontal spread of ≤7 mm in maximal extent, AND
Has been completely excised.

Rationale for Recommendation No. 4.—Patients with SISCCA of the cervix may have SIL (CIN) at margins of excision (see Figure 11). The diagnosis of SISCCA is not excluded based on this parameter. Persistent or recurrent cervical disease may occur in women with negative margins or those involved by SIL, and both groups remain at risk for persistent or recurrent SIL [98]. Women with involved margins are at increased risk for both the presence of multifocal invasive squamous carcinoma and persistent SIL [96, 137, 139–143]. Clinical follow-up or immediate reexcision may be chosen in the management of women with SIL at the surgical margins.

Vagina.—Vaginal cancers are rare. Approximately 40% to 60% of SCCs of the vagina are attributable to HPV [93]. In addition, vaginal squamous carcinomas are, in general, not amenable to local resection. FIGO uses clinical staging for cancer of the vagina. All available data before the first definitive treatment should be used, including the results of biopsy or fine needle aspiration of regional lymph nodes. Pathologic staging of vaginal cancer focuses on examination of the resected specimen, including pelvic and retroperitoneal lymph nodes. The current AJCC definition of a T1 (FIGO stage I) tumor is one confined to the vagina. T1 tumors are not further subdivided. Scant literature on the behavior of minimally invasive squamous carcinoma is available [144–146]. On the basis of the lack of evidence on early vaginal carcinoma and the general absence of a local resection option, no recommendation could be made to define SISCCA of the vagina.

WG3 Recommendation No. 5—Vagina.—No recommendation is offered for early invasive squamous carcinoma of the vagina. Owing to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina.

Rationale for Recommendation No. 5.—The literature review yielded no data to recommend changes to the current staging for vaginal SCC. It is staged clinically and uses all available data including biopsy results and regional lymph

node fine needle aspiration to determine definitive treatment. Squamous cell carcinoma confined to the vagina is an AJCC T1 tumor (FIGO stage I). T1 tumors are not further subdivided.

Anal Canal.—Approximately 90% to 93% of anal canal SCC is attributable to HPV [93]. Historically, abdominoperineal resection was the primary management for anal canal cancer [52, 147, 148]. In the 1980s, primary surgical therapy was supplanted by combined modality therapy with radiation and chemotherapy. Combined modality therapy has achieved superior survival rates and reduced recurrence rates while preserving the anal sphincter [149]. Surgical therapy was reserved for those with poor performance status, those who declined a colostomy, and those with small, well-differentiated tumors [150]. Local surgical excision can provide excellent outcomes for patients with tumors that are small (<1 cm) and do not infiltrate the sphincter [150, 151]. The significance for the diagnosis of "microinvasive squamous cell carcinoma" in the anal canal is undetermined [152].

WG3 Recommendation No. 6.—Anal Canal.—The *suggested* definition of superficially invasive squamous cell carcinoma (SISCCA) of the anal canal is an invasive squamous carcinoma that:

Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
Has a horizontal spread of ≤7 mm in maximal extent, AND
Has been completely excised.

Rationale for Recommendation No. 6.—The current AJCC definition of a T1 anal tumor is 2 cm or less in greatest dimension (see Figure 12) [52, 147, 148]. T1 tumors of the anal canal are not subdivided further. Combined modality therapy is the current primary therapy and standard of care for anal SCC but also has associated morbidity [153]. Historically, patients with small cancers excised with clean margins have had good outcomes [150, 151]. As more early invasive anal cancers are diagnosed (owing to increased awareness and screening), highlighting minimally invasive cancers that are potentially amenable to conservative sphincter-sparing surgical therapy with lower morbidity than combined modality therapy is imperative. The suggested definition of anal canal SISCCA, albeit arbitrary, is similar to that for the cervix. It will allow capturing of consistent, prospective data for this potentially important category. In addition, it is our opinion that the conservative management of a patient with anal SISCCA should include an evaluation by an expert experienced with high-resolution anoscopy and anal canal cancer.

Vulva.—Approximately 40% to 50% of SCCs of the vulva are attributable to HPV [93]. Current staging for SCCA of the vulva is the same regardless of the etiology. The AJCC definition of a T1a (FIGO IA) vulvar squamous carcinoma is a lesion 2 cm or less in size, confined to the vulva or perineum, and with stromal invasion of 1 mm or less. T1b (FIGO IB) lesions are those more than 2.0 cm in size or any size with stromal invasion of more than 1.0 mm. FIGO adds that stage I lesions are node-negative.

WG3 Recommendation No. 7—Vulva.—Vulvar SISCCA is defined as an AJCC T1a (FIGO IA) vulvar cancer. No change in the current definition of T1a vulvar cancer is recommended. The current AJCC definition of T1a vulvar carcinoma is:

Tumor 2 cm or less size, confined to the vulva or perineum AND Stromal invasion of 1 mm or less.

Note: The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent-most superficial dermal papilla to the deepest point of invasion.

Rationale for Recommendation No. 7.—The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent-most superficial dermal papilla to the deepest point of invasion (see Figure 13). Measurement of depth can be problematic in the vulva (e.g., in an ulcerated lesion). Measurement is less likely to be an issue on excisional than on punch biopsy specimens. The current prognostic literature uses depth as the most important measurement. Prospective collection of thickness data may provide prognostication in the future. On the basis of the literature review, no changes to the current AJCC definition are suggested.

The purpose of defining a separate category of superficially invasive lesions is that these lesions have an extremely low risk of lymph node metastases and hence may be treated less aggressively than larger tumors [154]. Vulvar stage IA lesions can be managed by wide local tumor excision without inguinofemoral node dissection [155, 156]. Lymph node dissection can then be performed if final pathology shows a lesion exceeding "superficially invasive" criteria. For the vulva, the definition is well established and in use by the AJCC, as well as CAP and ISSVD.

Penis.—Cancers of the penis are rare in the United States. Approximately 40% of SCCs of the penis are attributable to HPV [93]. The AJCC definition of a T1a penile squamous carcinoma is a tumor that invades subepithelial connective tissue without LVI and is not poorly differentiated (i.e., not grade 3–4). If LVI is identified or the tumor is poorly differentiated, the lesion is classified as T1b. Both parameters are independent predictors of inguinal lymph node involvement in patients with SCC of the penis and should prompt more aggressive care. For the penis, AJCC does not provide a specific measurement but limits the definition to invasion of no more than the subepithelial connective tissue. Measurement of depth of invasion for penile cases will provide data for future studies as to whether the measurement of depth of invasion is significant.

There are fewer studies available on SISCCA of the penis than of the vulva. The current AJCC TNM staging defines stage T1 penile cancer as a tumor that invades the subepithelial connective tissue without LVI and is not poorly differentiated. Specific measurements of depth of invasion are not included in the definition [157]. Some authors stratify T1 tumors by grade into low-, intermediate-, and high-risk categories, recommending lymphadenectomy for high-risk (T1G3) lesions, surveillance for low-risk (T1G1) lesions, and consideration of lymphadenectomy for intermediate-risk (T1G2) lesions, potentially including growth pattern and presence of LVI as points of consideration in the decision [158].

WG3 Recommendation No. 8—Penis.—Penile SISCCA is defined as an AJCC T1a. No change in the current definition of T1a penile cancer is recommended.

Current AJCC definition of T1a penile carcinoma:
Tumor that invades only the subepithelial connective tissue, AND No LVI
AND Is not poorly differentiated (i.e., grade 3–4).

Rationale for Recommendation No. 8.—On the basis of the literature review, no changes to the current AJCC definition are suggested.

Scrotum.—Squamous cell carcinoma of the scrotum is now very rare. Although some are HPV-associated, historically its development is linked to occupational exposure in chimney sweeps [159]. The current AJCC staging system for scrotal cancer is as per cutaneous SCC. There are no subdivisions of T1 skin cancers, defined as 2 cm or less with fewer than 2 high-risk features (>2 mm thickness, Clark level ≥ IV, perineural invasion, poorly differentiated, or undifferentiated).

WG3 Recommendation No. 9—Scrotum.—No recommendation is offered for early invasive squamous carcinoma of the scrotum.

Owing to the rarity of primary SCC of the scrotum, there is insufficient literature to make a recommendation regarding the current AJCC staging of early scrotal cancers.

Rationale for Recommendation No. 9.—On the basis of the literature review, no changes to the current AJCC definition are suggested.

Perianus.—The proportion of SCC of the perianus attributable to HPV are different between women and men, with 80% of female and 29% of male perianal cancers associated with HPV [160]. The perianus is currently defined as the region extending 5 cm from the anal opening or verge as visualized by gentle retraction on the buttocks [161]. This region overlaps anatomically with the vulvar perineum. In women, the perineum should be considered part of the vulva for staging and management purposes [52]. The distinction between anal canal and perianal malignancies is important because anal canal lesions have different natural histories [148].

WG3 Recommendation No. 10—Perianus.—The *suggested* definition for SISCCA of the perianus is an invasive squamous carcinoma that:
Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND
Has a horizontal spread of ≤7 mm in maximal extent, AND
Has been completely excised.

Rationale for Recommendation No. 10.—In the current AJCC staging system, perianal cancers are staged as cutaneous SCC. T1 skin cancers are defined as those measuring 2 cm or less with fewer than 2 high-risk features (>2 mm thickness, Clark level ≥IV, perineural invasion, poorly differentiated, or undifferentiated). There are no subdivisions of T1 skin cancers [49, 52]. Historically, anal canal and perianal cancers have often been grouped together in studies of anal cancer. The suggested measurements of depth and horizontal spread for anal canal and perianal SISCCA are the same. Similar to the situation for the anal canal, defining a minimally invasive cancer of the perianus will allow for meaningful and consistent prospective data collection.

WG3 Outstanding Issues

The major outstanding issue for SISCCA is the methodology for measurement. Specific details on methodology for measurements of depth, definitions of horizontal/lateral extent, and measurements in the presence of multifocality of carcinoma are planned for a future publication.

BIOMARKERS IN HPV-ASSOCIATED LOWER ANOGENITAL SQUAMOUS LESIONS—WG4

Work group 4 was tasked with evaluating the use of molecular markers in conjunction with H&E morphology for the assessment of specimens from the LAT. In doing so, 2,291 articles were identified from the literature search. Using prespecified criteria and following a systematic title/abstract and full-text review process, this number was culled to 72 from which complete data extraction was performed. Fifty-three of these articles dealt with the biomarker p16. Most articles focused on cervical disease; however, some articles did address lesions in vulvar, penile, and anal sites. Of the selected literature, prospective studies and those having histologic adjudication as a criterion standard were given more emphasis.

The literature and expert review process was directed toward evaluating and selecting the best science for the best possible patient care, regardless of costs. In this regard, WG4 was highly cognizant of the interplay between medicine and industry in the published literature. Just as the utility of HPV testing for cervical cytology screening and triage was critically tied to the performance characteristics of HPV DNA tests, similar concepts must be applied for biomarker-based tests [162]. On the basis of these considerations, the clinical utility of p16 immunohistochemistry as proposed by WG4 is directly related to the performance characteristics of a particular clone described in the literature and, in some cases, to specific immunohistochemistry (IHC) kits as reported in the literature. These tests have defined characteristic staining patterns in consensus adjudicated diagnostic categories. For example, the test kits used in peer-reviewed publication show that more than 99% of histologic CIN 3 are p16-positive [163]. In contrast, less than 5% of histologically negative biopsies are p16-positive, and many of such cases, in retrospect, contain small missed lesional areas of high-grade disease [163, 164]. Clinical use of alternative clones, kits, or systems requires equivalent data to ensure similar clinical performance. Similar concepts would apply to any other potential biomarker (e.g., ProEx C [Becton Dickinson, Franklin Lakes, NJ] or Ki-67) with similarly developed criteria, albeit with some marker-specific nuances. Use of test kits with different test characteristics raises the possibility of causing harm by overcalling or undercalling severity of lesions.

Work group 4's recommendations, and the evidence used to support them, were evaluated by an independent reviewer with experience in the development of evidence-based guidelines (Evan R. Myers, MD, MPH, Department of Obstetrics and Gynecology, Duke University) before the consensus conference; articles excluded during the initial search and review phase were not reviewed again. On the basis of the reviewer's overall assessment of the quality of the evidence for test characteristics and observer variability, WG4's recommendations were framed using "recommend" if the recommendations are unlikely to change based on further evidence and "suggest" if the recommendation is

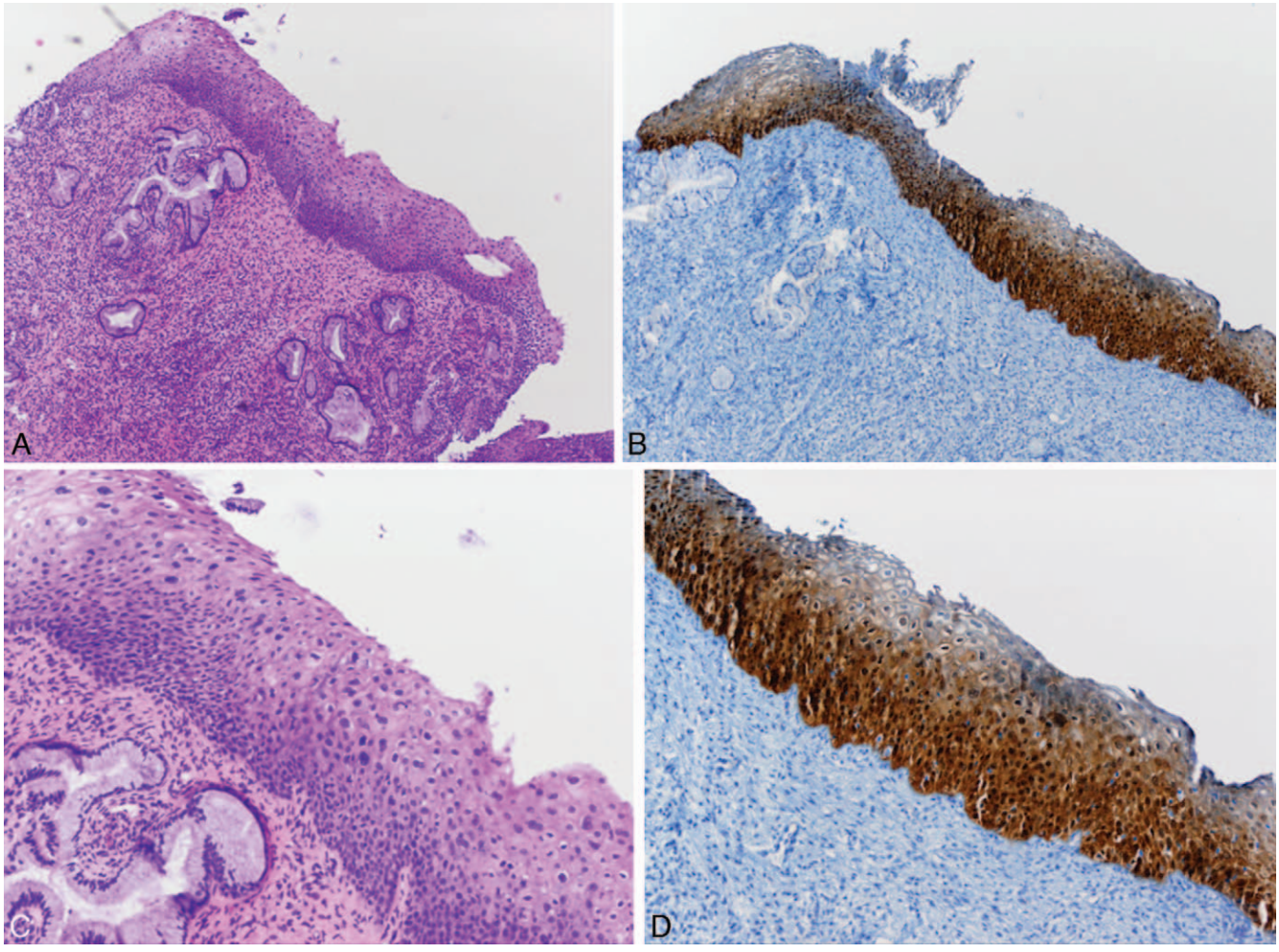

Figure 14. A cervical biopsy with SIL showing partial maturation; some might question the lesion grade (? CIN 2). A and C, H&E morphology at low and medium power with atypical parabasal-like cells extending into the middle third of the epithelium (C). B and D, Corresponding p16 IHC stains with diffuse strong staining meeting the definition of p16 strong diffuse block-positive described in the text. Therefore, this case is best interpreted as HSIL.

most likely correct but could be better supported by additional data.

Work group 4 was tasked with evaluating which, if any, biomarkers (broadly defined as any molecular or immunochemical assay) would be useful in better defining HPV-associated lesions of the LAT and would reduce interobserver variability in diagnosis. On the basis of this, recommendations were made regarding their optimal use. Key to WG4's recommendation decisions was the need to discourage and prevent inappropriate use or overuse of any biomarker(s).

After completion of the initial tier of literature review, WG4 evaluated data associated with the following biomarkers: p16, Ki-67 (Mib1), ProEx C, L1, HPV 16/18 mRNA, telomerase/TERC, and HPV genotyping.

On the basis of final literature review and data extractions, we concluded that only p16, a biomarker that is recognized in the context of HPV biology to reflect the activation of E6/E7–driven cell proliferation, had sufficient evidence on which to make recommendations regarding use in LAT squamous lesions. ProEx C and Ki-67 (Mib1) had similar trending data, but the literature was insufficient to make an independent recommendation for use, alone or in combination. Individual institutions might opt to use these other markers in cases with equivocal p16 IHC staining or as an adjunct, given that both have cleaner nuclear staining. However, the accumulated evidence was insufficient to make an independent recommendation for use of any additional biomarker, alone or in combination.

Although only a few studies that focused on body sites other than cervix were available, all showed results similar to cervix. Given the underlying similarities in HPV-associated biology in all LAT sites, we concluded that the recommendations below are applicable across all LAT sites. It should be noted, however, that these data and recommendations do not apply to non–HPV-associated precancerous lesions, such as simplex or differentiated VIN.

WG4 Recommendation No. 1

p16 IHC is *recommended* when the H&E morphologic differential diagnosis is between precancer (–IN 2 or –IN 3) and a mimic of precancer (e.g., processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangen-

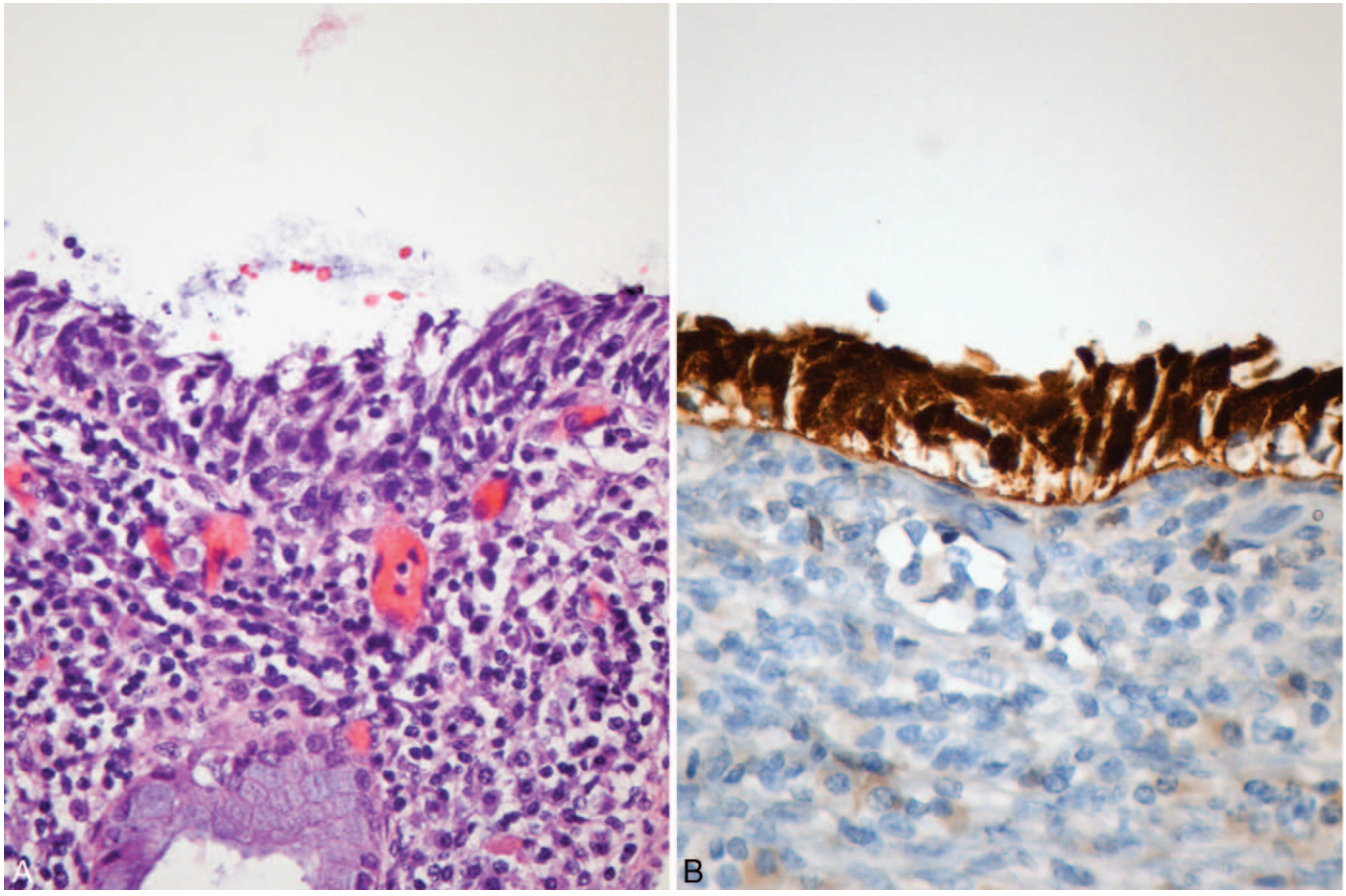

Figure 15. Some cases of HSIL, especially in the zone of immature metaplasia where the epithelium may be thin, can be diagnostically problematic. In this cervical biopsy (A), the differential diagnosis includes inflamed immature squamous metaplasia and HSIL. Strong diffuse block-positive p16 staining (B) strongly favors the interpretation of this biopsy as precancer (HSIL). A, High power, H&E. B, High power, p16.

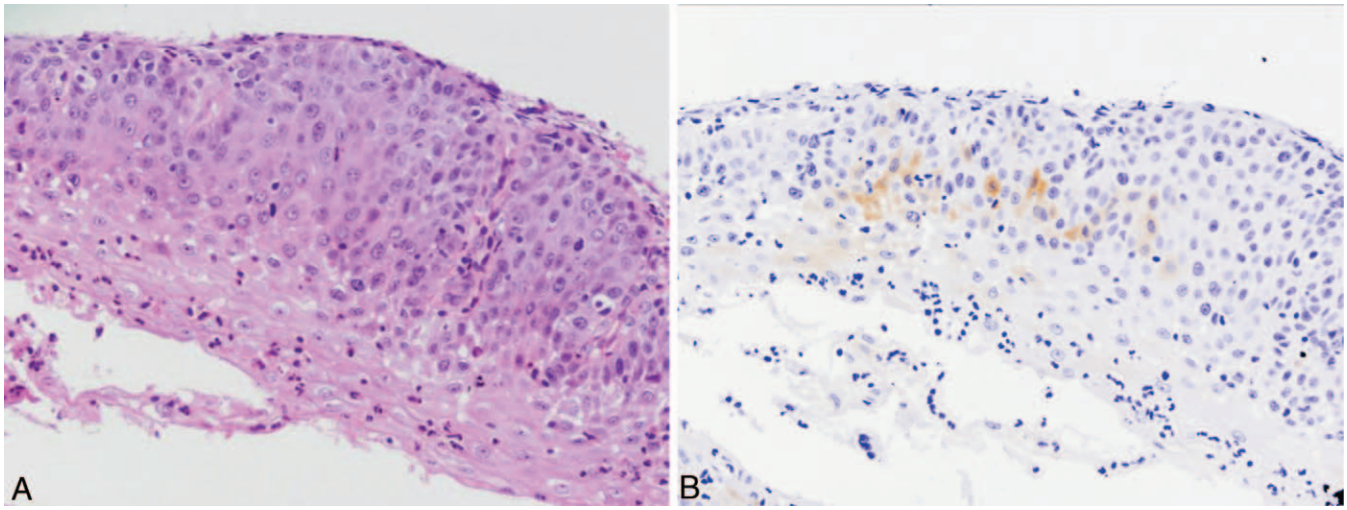

Figure 16. A, A cervical biopsy with a differential diagnosis on H&E of HSIL (CIN 2) versus reparative atypia owing to the relative lack of maturation and koilocytosis. B, The weak, patchy and irregular staining with p16 IHC (p16-negative) supports the interpretation of a reactive process rather than an HSIL. This pattern of blotchy or patchy p16 staining should be interpreted as negative (non–block-positive staining). A, Medium power, H&E. B, Medium power, p16.

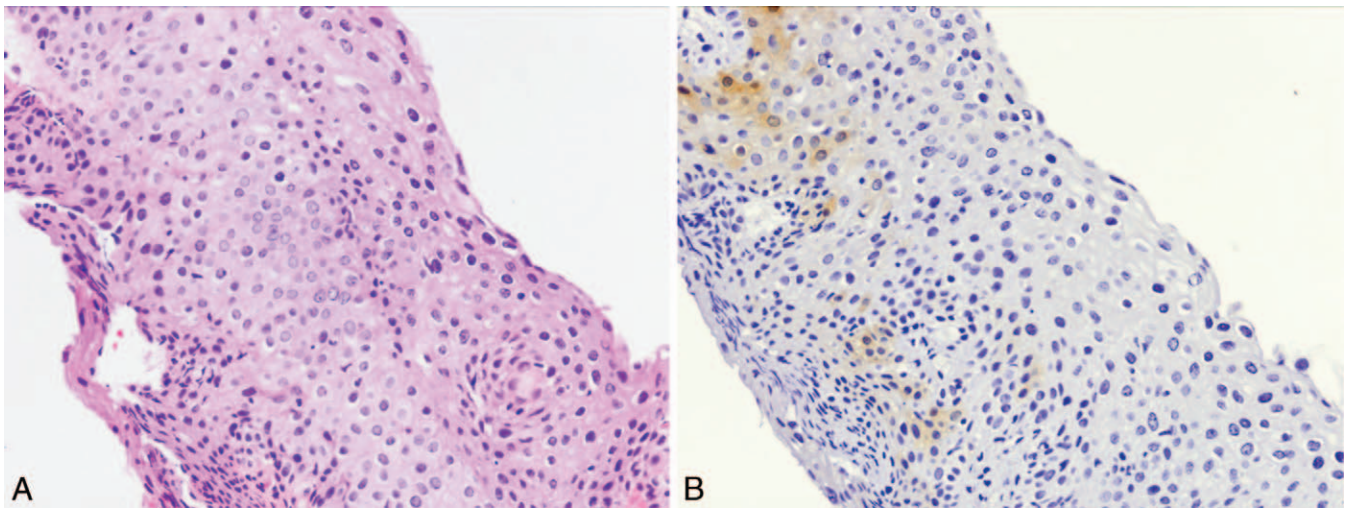

Figure 17. A, Cervical biopsy with unequivocal SIL that is tangentially cut, raising the differential diagnosis of LSIL versus HSIL. B, Immunohistochemical stain demonstrating weak, patchy p16 reactivity that starts above the basal layer, a pattern that should be interpreted as negative, which, in this case, supports the final combined interpretation as LSIL. A, High power, H&E. B, High power, p16.

tial cutting). Strong and diffuse block-positive p16 results support a categorization of precancerous disease.

Strong and diffuse block staining for p16 = p16-positive.—*In squamous epithelia, this is defined as continuous strong nuclear or nuclear plus cytoplasmic staining of the basal cell layer with extension upward involving at least one third of the epithelial thickness. The latter height restriction is somewhat arbitrary but adds specificity. Note that full-thickness staining or extension into the upper third or upper half is specifically not required to call a specimen positive (see Figures 14 and 15).*

Focal or patchy nuclear staining is nonspecific and can be seen with reactive squamous metaplasia, as well as low-grade disease (LSIL, –IN 1). All other staining patterns, described as cytoplasmic only, wispy, blob-like, puddled, scattered, single cells, and others, are defined as negative (see Figures 16–18).

Clearly, the concept of continuous block staining requires "adequate" tissue size and orientation and should correlate with the area of morphologic concern. Small fragments, tangential cuts, free-floating single cells, and others may lead to more subjective and variable interpretations, but in such cases, the minimum would be that all cells in question are strongly stained and morphologically are already under consideration in the differential diagnosis of a precancerous lesion (see Figure 19).

WG4 Recommendation No. 2

If the pathologist is entertaining an H&E morphologic interpretation of –IN 2 (under the old terminology), which is a biologically equivocal lesion falling between the morphologic changes of HPV infection (low-grade lesion) and precancer, p16 IHC is *recommended* to help clarify the diagnosis. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or non–block-positive staining strongly favors an interpretation of

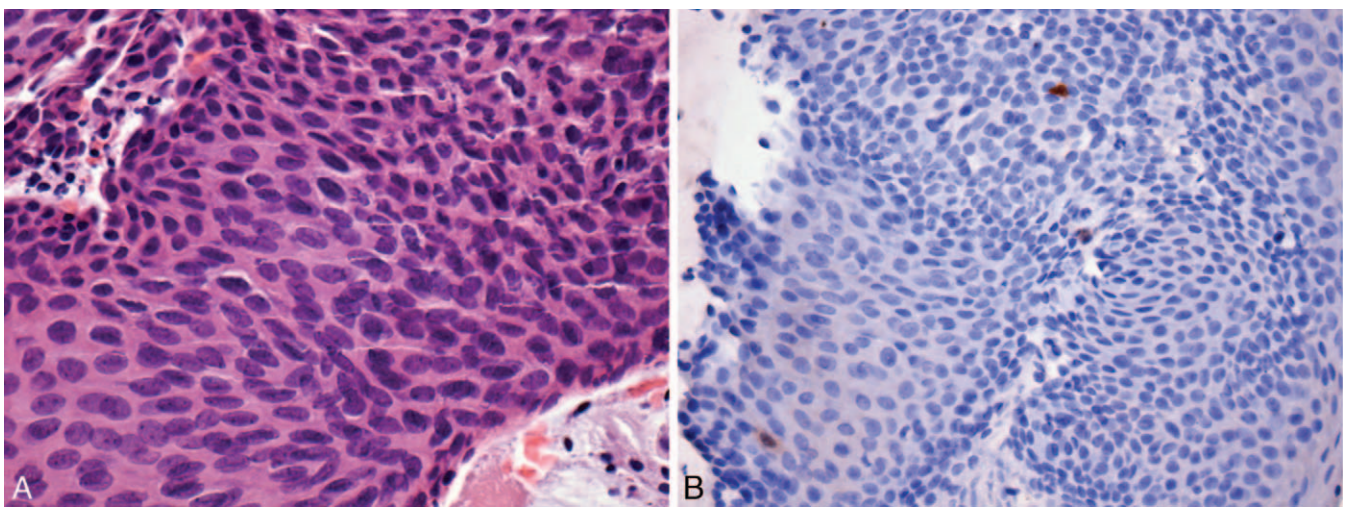

Figure 18. Some immature squamous metaplastic lesions can be hyperplastic rather than thin (A, contrast with Figure 15A). In this case, the cervical epithelium mimics bladder mucosa with somewhat elongate nuclei and some nuclear grooves (transitional metaplasia). Note the absence of mitotic figures and relative nuclear uniformity. B, The near total absence of p16 reactivity strongly supports the interpretation that this is a HSIL mimic rather than precancer. A, High power, H&E. B, High power, p16.

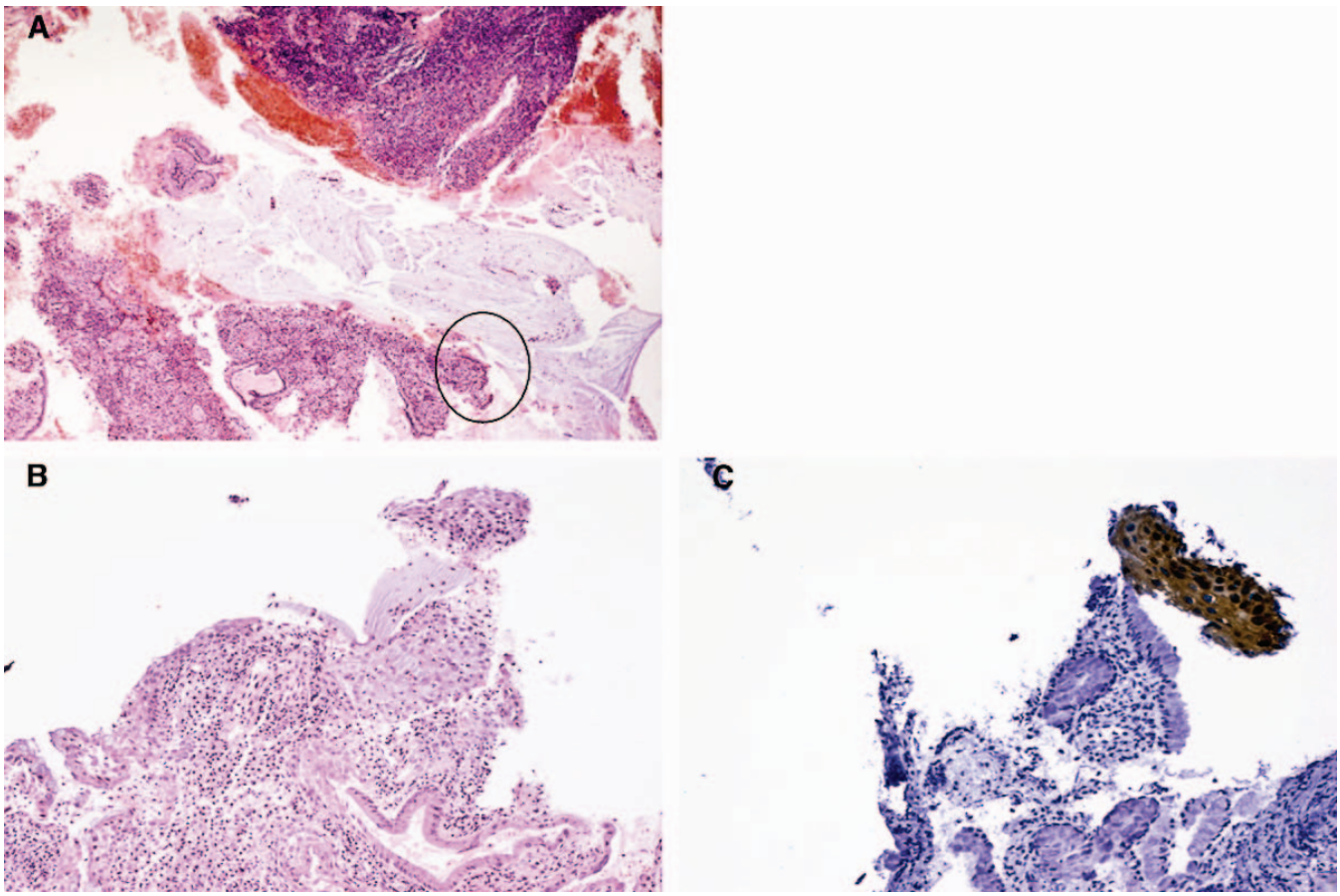

Figure 19. A, Low-power H&E of the colposcopic biopsy from a patient referred for an HSIL on her Pap test. The biopsy was initially read as negative, but because of the lack of correlation between the cytology and histology, a p16 stain was performed. The small fragment seen in C was reinterpreted as HSIL (B), based on strong diffuse block-positive p16 staining and abnormal underlying histologic appearance. The same small area is circled in A. A, Low power, H&E. B, High power, H&E. C, High power, p16.

low-grade disease or a non–HPV-associated pathology (see Figures 14 and 17).

Note: Unlike Recommendation No. 1, Recommendation No. 2 deals with a specimen that already has the morphology of SIL, not its benign mimics. p16 immunohistochemistry should be used to clarify a H&E diagnosis of –IN 2. If the pathologist's histologic diagnosis is unequivocal –IN 1, p16 immunohistochemistry is NOT recommended (see Recommendation No. 4). There is insufficient evidence to determine whether there is an actionable difference in patient management between p16-positive and p16-negative –IN 1. Hence, now, it is recommended that clinical management of –IN 1 be based on the H&E histologic diagnosis alone; p16 IHC is not indicated.

Note: p16 should not be used if the H&E morphologic differential diagnosis is between low-grade disease (–IN 1) and negative because –IN 1 can be p16-negative and p16 positivity is not a definition for –IN (of any level).

Rationale for Recommendation Nos. 1 and 2.—In the largest prospective, adjudicated study using p16, Galgano et al [163] showed that diffuse strong staining with p16 showed similar accuracy for high-grade disease when compared with an adjudicated histology result. Given that –IN 2 has been consistently proven to be a poorly reproducible diagnosis, p16 immunostaining improves the accuracy of single-pathologist interpretations of high-grade versus low-grade disease relative to adjudicated pathology panel interpretations, which are the best surrogate available for biologic accuracy. This is with the caveat that the pathologist is already entertaining an interpretation of –IN 2. Hence, adding a p16 result to the H&E morphologic assessment leads to a more accurate prediction of the risk of the patient for having a precancerous lesion. Additional studies have demonstrated a strong positive correlation between p16 block staining and precancerous disease [89, 164–168]. p16 immunostaining substantially reduces interobserver variability in the diagnosis of precancerous disease (see next paragraphs) [88–91, 163]. Studies also show that diffuse strong p16 staining is highly associated with a positive test result for HPV-16 (or other high-risk HPVs) [169–171].

WG4 Recommendation No. 3

p16 is *recommended* for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (–IN 2 or –IN 3).

Rationale for Recommendation No. 3.—A number of studies address the issue of interobserver variability in interpretation of LAT squamous lesions [88–91, 163]. These studies all show that there is substantial improvement in

correlation between observers when p16 immunostaining is used. Therefore, in association with Recommendation No. 1 above, the addition of p16 provides a more objective adjudication of the differential diagnosis than does H&E histologic assessment alone.

Quality of Evidence for WG4 Recommendation Nos. 1, 2, and 3.—Review of the 18 articles cited for Recommendations 1 to 3 found 2 studies directly comparing the performance of H&E alone versus H&E/p16 for cervical disease using consensus histology as the reference standard and 4 reporting test characteristics for H&E/p16–positive alone (see C2 for additional details, Supplemental Digital Content; http://links.lww.com/LGT/A6). For each of these studies, sensitivity, specificity, and 95% confidence intervals could be directly calculated from the data. In addition, 5 studies provided data on interobserver variability as measured by κ statistics, for H&E alone versus H&E/p16. The quality of the evidence for the test characteristics of H&E/p16, based on the studies identified through the review process, is moderate to high. Both of the direct comparisons showed statistically significant increases in sensitivity for a consensus diagnosis of CIN 2+ and increases in sensitivity for CIN 3+ (statistically significant in the study of Galgano et al [163], although not significant in that of Bergeron et al [90]). Specificity was decreased with the addition of p16; the absolute decrease was much larger in the study of Galgano et al than in that of Bergeron et al. In studies without a comparator, sensitivities were all 95% or higher at both thresholds. Factors contributing to the high quality of evidence included (1) consistency of results across multiple studies and settings, (2) precision of results, and (3) low risk of bias in the study designs. Factors decreasing the quality of evidence included (1) relative indirectness in terms of specific clinical outcomes—in particular, the association of CIN 2 lesions, even if based on consensus histology, with cancer; and (2) indirectness in terms of setting. The 2 studies involving direct comparisons were both performed in settings outside general US practice, either in Europe or in a single academic institution where institutional bias in terms of histologic thresholds may have lowered sensitivity and raised specificity for histology alone [90, 163].

The quality of the evidence for improved consistency of readings with p16 is high. All 5 studies measuring interobserver variability found significant or close-to-significant improvement in consistency of readings with the addition of p16 to H&E assessment alone. The clinical significance of this finding is supported by the data on sensitivity and specificity for individual pathologists presented in Galgano et al [163].

On the basis of the quality of the reviewed evidence, there is a high degree of certainty that use of p16 leads to improved sensitivity but decreased specificity compared with H&E alone, with substantially improved consistency between observers. This suggests that use of p16, in accordance with WG4 Recommendation Nos. 1 to 3, would result in improved clinical outcomes, but there is lack of direct evidence about the impact of implementing these recommendations in a general US population. This especially raises concern about the potential for overtreatment if the recommendations are not followed; this concern specifically led to the development of WG4 Recommendation No. 4.

WG4 Recommendation No. 4

WG4 *recommends against* the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN 1 and –IN 3.

Rationale for Recommendation No. 4.—At the consensus conference, there was considerable concern about the potential for overuse of p16 IHC by pathologists as an assessment tool for cases of morphologic –IN 1. Overuse in unequivocal cases of –IN 1 might lead some pathologists to inappropriately overinterpret such cases as high-grade (–IN 2), leading to the potential for overtreatment. As noted above, the natural history of p16-positive –IN 1 is not well known, and although some evidence exists to support it as a higher risk category, the evidence is insufficient at this time to alter clinical management from that based on the histologic assessment alone [172–174]. In addition, the natural history of p16-negative –IN 3 is uncertain, and hence, the use of p16 to downgrade an unequivocal example of –IN 3 is not recommended. p16 IHC should not be performed when these morphologic diagnoses are unequivocal. In these circumstances, p16 IHC should only be used when the differential diagnosis contains mimics of high-grade lesions (see WG4 Recommendation No. 1), when –IN 2 is in the differential diagnosis with a low-grade lesion (see WG4 Recommendation No. 2), or when there is a difference of opinion to be resolved in these areas (see WG4 Recommendation No. 3).

WG4 Recommendation No. 4a

Special Circumstance.—p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤–IN 1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV-16 +, or AGC (NOS).

Any identified p16-positive area must meet H&E morphologic criteria for a high-grade lesion to be reinterpreted as such.

Rationale for Recommendation 4a.—This recommendation addresses a special situation in which use of p16 IHC is recommended to maximize the sensitivity for detecting high-grade lesion foci that might have been missed on initial H&E examination of tissue biopsies in very specific high-risk situations (see Figure 19). Data using p16 IHC show that areas of small or equivocal high-grade disease have been identified on histologic specimens using p16 that were not initially recognized on H&E sections alone in a significant proportion of high-risk cases [175]. Specific high-risk situations are those in which the patient is at substantial risk for prevalent precancer (at least 30%), such as when preceding cervical cytology specimens have been interpreted as HSIL, ASC-H, ASC-US positive for HPV-16, or AGC [176–178]. In such circumstances, p16 block-positive areas identified are most likely to represent precancerous disease. However, p16-positive foci identified in such cases must, on review of H&E slides, also have morphologic features diagnostic of HSIL to make the diagnosis.

p16 IHC should NOT be used in circumstances other than those special high-risk situations as stipulated in this recommendation or other circumstances with equivalent or higher risk of precancer. In other lower-risk situations, the likelihood of false-positive results not indicative of high-grade disease is increased, which could lead to overtreatment. In the future, as the use of HPV genotyping becomes

Table 4. Estimated Percentage (%) of Total Cervical Biopsies for Which IHC Is Recommended [6, 10, 163, 178–180]		
LAST WG4 recommendation	**Comment**	**Estimated % of biopsies for IHC**
No. 1: HSIL vs mimics	CIN 3 accounts for <10% of biopsies and we estimate that approximately 10% of these may be problematic or have mimics	1
No. 2: Possible CIN 2	CIN 2 currently accounts for no more than 10% of biopsies	10
No. 3: Professional disagreement	An uncommon situation	1
No. 4: Cautions against use in LSIL (CIN 1)	LSIL (CIN 1) accounts for up to 40% of diagnoses for cervical biopsies. If an estimated 10% of those are problematic (i.e., the pathologist is considering LSIL versus HSIL [CIN 2]), the impact is low	4
No. 4a: High-risk colposcopic referral situations with H&E biopsies initially ≤LSIL	Most referrals for colposcopy are for Pap tests interpreted as LSIL or ASC-US and high-risk HPV-positive (not genotyped). Reported rates for these results are HSIL 1%, ASC-H 0.5%, AGC 0.5%, and ASC-US, HPV-16–positive at 1%	3
Total	Conservative estimate of overall utilization of IHC is <20% of all cervical biopsies	19

more common, additional high-risk situations, such as LSIL with HPV-16 positivity, may be considered as an additional high-risk category.

Quality of Evidence for WG4 Recommendation No. 4.—The quality of the evidence for superior sensitivity of H&E/p16 is high to moderate (see C2 for additional details, Supplemental Digital Content; http://links.lww.com/LGT/A6). In the clinical setting described above, where there is a higher pretest probability of precancer, the likelihood of a false-positive is reduced, and the importance of detecting true disease is increased. Therefore, the balance of benefit versus harm is toward the higher sensitivity but lower specificity of adding p16, and given the overall quality of the evidence, the use of "recommend" is warranted.

Additional Findings From WG4

On the basis of the evidence reviewed, we could make no recommendation for or against a 2-tiered or 3-tiered nomenclature system based on histologic evaluation alone. However, we noted that, although all the marker studies examined were neutral or supportive of a 2-tiered system/biology, no positive marker-based studies to support a distinct 3-tiered biology were identified. Because of the lack of evidence for a biologically defined intermediate category, p16, as noted above, is recommended to clarify any considered intermediate category (–IN 2) into either a low-grade or precancerous lesion (WG4 Recommendation No. 2). Therefore, use of p16 may effectively support the use of a 2-tiered classification system in this particular circumstance.

We concluded that there is insufficient evidence to prospectively determine high-grade versus low-grade disease based solely on a p16 result. In particular, the natural history of –IN 1 adjudicated by p16 is uncertain and critically needs further study. Hence, at present, no recommendation can be made for or against the use of p16 for this purpose. In addition, we concluded that there is insufficient evidence to prospectively make a determination of –IN 1 versus no –IN based solely on the use of p16. Strong and diffuse block-positive p16 staining, in the appropriate morphologic context, strongly supports a diagnosis of high-grade –IN. The majority (80%–90%) of –IN 2 and approximately 99% of –IN 3 cases are p16-positive. A positive p16 stain does not exclude CIN 1; at least 30% of adjudicated CIN 1 cases are p16-positive. At present, no recommendation could be made for or against the use of p16 for this purpose. Hence, p16 should not be used to initially assess biopsies that, on H&E alone, would otherwise be interpreted as morphologically negative or CIN 1.

We concluded that no recommendation could be made regarding any differences in –IN 1 management (based on the addition of a p16 stain) at this time. There are 3 studies that provide data regarding this question [172–174]. In these studies, the presence of strong and diffuse block-positive p16 immunostaining in CIN 1 was associated with increased "progression" or precancer outcomes on follow-up. Conversely, those cases testing negative for p16 were far more likely to "regress." However, this association was not absolute because there were cases having precancer outcomes that were p16-negative. Therefore, at this time, although p16-positive –IN 1 lesions may represent a subgroup of cases that are at higher risk of progression, no management recommendation can be made based solely on a p16 result.

We concluded that no recommendation could be made regarding any management differences in morphologically determined high-grade dysplasia (–IN 3) based solely on the addition of a p16 result. However, it was noted that most adjudicated CIN 3 lesions are p16-positive (>99%), which strongly argues against its utility in this diagnostic category [163].

We also concluded that the evidence does not support any combination of markers to substantially improve performance when compared with the use of p16 alone. A number of studies addressed the use of p16 in combination with Ki-67. The overall improvement of performance (sensitivity and specificity) was minimal when compared with the p16 result alone [163]. Hence, the routine addition of Ki-67 to p16 IHC is not recommended. Other studies detail the use of ProEx C, which performs in a similar manner to p16; however, currently, there is insufficient evidence to make an independent recommendation for use. In cases for which p16 IHC is inconclusive or technically inadequate, use of Ki-67 and/or ProEx C IHC may be considered.

Considerations on Practice Impact—Cervical Biopsies

The most common concern expressed during the open comment period and at the consensus conference was the

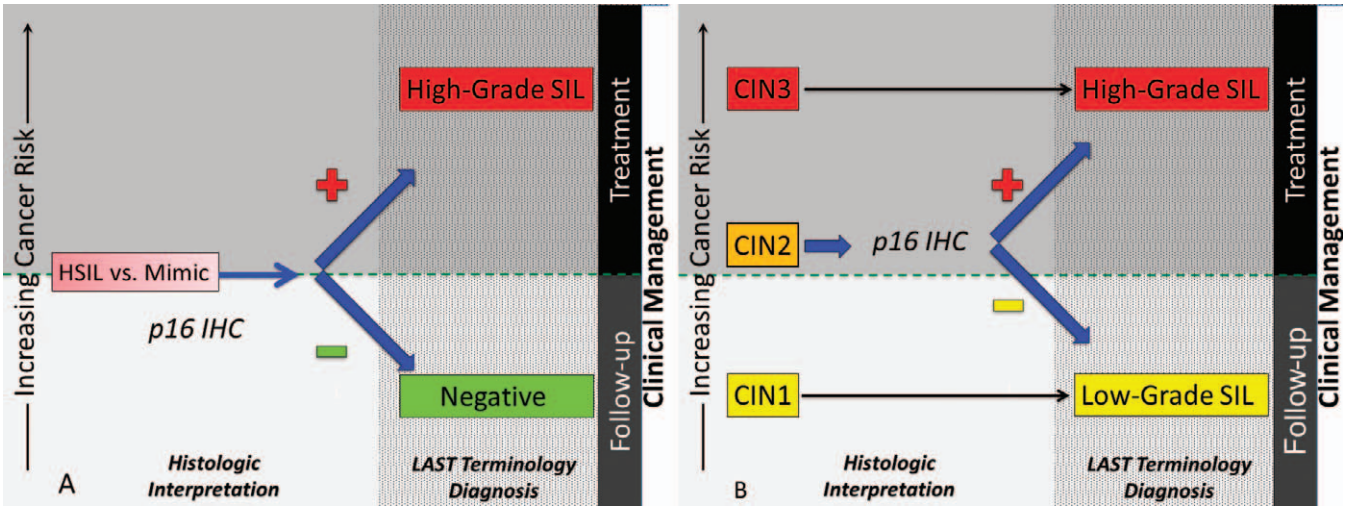

Figure 20. Pathologic diagnoses using p16 and potential clinical management options for cervical biopsies. A, Use of p16 to evaluate the differential diagnosis of HSIL versus a mimic, such as immature squamous metaplasia and atrophy. B, Use of p16 to evaluate morphologic CIN 2. The choice of clinical management for HSIL depends on the entire clinical scenario including patient's age, colposcopic findings, and biopsy diagnosis. Management options include excisional therapy (cold knife conization, LEEP), ablative therapy (cryotherapy, laser vaporization), and close observation, as during pregnancy. Modified with permission. Courtesy of Philip E. Castle.

impact of biomarker use, especially overutilization leading to potential overtreatment. As noted above, the recommended use of the biomarker p16 will result in both downgrading and upgrading of H&E diagnoses. The estimated magnitude of p16 IHC utilization when used according to WG4 recommendations is for fewer than 25% of all cervical biopsy specimens, and in these specimens, it will improve sensitivity and consistency of diagnoses (see Table 4). The statistics used to generate these estimates were based on published data from large surveys, population-based studies, and clinical trials and the conservative data available from several very large clinical studies [6, 10, 163, 178–180].

IMPLICATIONS AND IMPLEMENTATION OF STANDARDIZED TERMINOLOGY—WG5

The overall scope and purpose of WG5 was to address the potential implications of the LAST Project recommendations and to develop and initiate action plans for implementation of the recommendations.

Effective communication is absolutely necessary for widespread acceptance and adoption to occur. As with the Bethesda System terminology for gynecologic cytology, widespread communication of the benefits of changing and unifying terminology was necessary before adoption occurred. Likewise, we identified communities of interest for the LAST Project recommendations to include patients and patient advocacy groups; pathologists; treating physicians including gynecologists, primary care providers, dermatologists, gynecologic oncologists, infectious disease specialists, colorectal surgeons, urologists, and others; and nurse practitioners and other allied health professionals; government, regulatory, and nomenclature agencies including CMS, Joint Commission, AJCC, FIGO, SGO, World Health Organization, and others; public health, research, and surveillance organizations such as the Centers for Disease Control and Prevention, Surveillance Epidemiology and End Results (SEER), and tumor registries; educational, training, and testing organizations including specialty societies, training facilities, examination boards, publications and scientific literature; and payers and *Current Procedural Terminology* and *International Classification of Disease* coding organizations.

To communicate to these communities of interest, we recommended sustained organizational support to aid in the dissemination of the LAST recommendations. Specific actions include support for guideline publication; promote editorial commentaries for journals in related fields; present summary recommendations at scientific meetings; produce educational materials for professionals and patients; and develop a Web site that will include reference images, sample reports, and a self-test.

One of the major concerns raised by the clinical community regards management of cervical lesions in young women. The ASCCP will address specific issues related to its clinical management guidelines in the near future. A potential reconciliation of the LAST terminology and the 3-tiered CIN system with current clinical management is represented in Figure 20.

Many of these recommendations have already been initiated and will continue to be developed further. It is also imperative to have liaison with professional organizations to assess current practice regarding use of LAST terminology for squamous HPV-associated lesions and associated biomarker usage and to monitor adoption of the LAST recommendations.

CONCLUSIONS

The LAST Project was conceived to align terminology for HPV-associated squamous lesions of the LAT with current knowledge to improve communication between pathologists making diagnoses and clinicians using these diagnoses to optimally manage patients. In doing so, the project found ample justification to recommend a unified terminology across all LAT sites. For intraepithelial lesions, a 2-tiered terminology (LSIL and HSIL) reflects the biology of transient, productive HPV infections and persistent precancerous lesions. For superficially invasive squamous carcinomas of these sites, a uniform terminology and criteria for diagnosis brings order to similar entities. As a corollary to

the process, the use of biomarkers was addressed, to aid in the accurate and reproducible classification of intraepithelial lesions and strong recommendations for appropriate use were made. The LAST Project recommendations were made after a rigorous process that included comprehensive literature reviews with grading of evidence where appropriate, formulation of the recommendations by experts in the field, solicitation of public comment, and a final consensus conference with recommendation ballot that included representatives from professional societies, government agencies, and interested observers. The LAST Project recommendations reflect the participants' consensus judgment for best evidence-based pathology practice and nomenclature for HPV-associated squamous lesions of the LAT.

The work is not yet done. Integrating the LAST recommendations into the standard practice of pathologists and clinicians is an ongoing task. Plans to implement educational programs detailing the recommendations and their appropriate incorporation into practice are underway. Assessments of both the uptake and effects of the recommendations are being planned. All the members of the LAST Project anticipate the results of this implementation and its beneficial effects on providing optimal patient care.

CAP-ASCCP CONSENSUS STATEMENT

The CAP developed the Pathology and Laboratory Quality Center as a forum to create and maintain evidence-based practice guidelines and consensus statements. Practice guidelines and consensus statements reflect the best available evidence and expert consensus supported in practice. They are intended to assist physicians and patients in clinical decision making and to identify questions and settings for further research. With the rapid flow of scientific information, new evidence may emerge between the time a practice guideline or consensus statement is developed and when it is published or read. Guidelines and statements are not continually updated and may not reflect the most recent evidence. Guidelines and statements address only the topics specifically identified therein and are not applicable to other interventions, diseases, or stages of diseases. Furthermore, guidelines and statements cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge, to determine the best course of treatment for the patient. Accordingly, adherence to any practice guideline or consensus statement is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. CAP and ASCCP assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this statement or for any errors or omissions.

Acknowledgments

The authors thank the following: Dr Evan Myers for his modeling and evidence review contributions, Dr Herschel W. Lawson (ASCCP) and Dr Gene N. Herbek (CAP) for serving as the onsite meeting moderators, and Dr Dina R. Mody who served as the CAP Center Subcommittee representative to the overall project. The authors thank Ms Lisa Fatheree for her contributions in staffing the LAST Project Steering Committee and Work Groups 2 and 3 and oversight of the literature process; Ms Kathleen Poole for her contributions staffing Work Groups 1, 4, and 5 and oversight of the public bulletin board process; Mr Tony Smith for his contributions to the literature review process and article referencing work; Ms Sandi Larsen and Dr John Olsen for their oversight of the conference and conflict of interest process; and Ms Debbie McClain for her work in programming the public bulletin board and preparing the meeting jump drives. The authors also thank the following individuals who served to complete the technical peer-review of the article: Drs Philip E. Castle, David Chelmow, Timothy McCalmont, Christopher Otis, Joel Palefsky, Mary Schwartz, Paul Staats, Alan Waxman, Thomas Wright, and Richard Zaino.

Steering Committee: David C. Wilbur, MD (co-chair), Massachusetts General Hospital, Harvard Medical School, Boston, MA; Teresa M. Darragh, MD (co-chair), University of California – San Francisco, Mt Zion Medical Center, San Francisco, CA; Michael R. Henry, MD, Mayo Clinic, Rochester, MN; Timothy McCalmont, MD, University of California – San Francisco, San Francisco, CA; Ronald D. Luff, MD, Quest Diagnostics, Teterboro, NJ, Thomas Jefferson University, Philadelphia, PA; and Edward J. Wilkinson, MD, University of Florida College of Medicine, Gainesville, FL.

Work Group 1: J. Thomas Cox, MD (co-chair), University of California – Santa Barbara Student Health Service (retired), Santa Barbara, CA; Edward J. Wilkinson, MD (co-chair), University of Florida College of Medicine, Gainesville, FL; Dennis M. O'Connor, MD, CPALab, Louisville, KY; R. Kevin Reynolds, MD, University of Michigan Health System, Ann Arbor, MI; and M. Angelica Selim, MD, Duke University Medical School, Durham, NC. **Advisor:** James Scurry, MD, Mercy Hospital for Women, East Melbourne, Victoria, Australia.

Work Group 2 (Cervix/Vagina): Michael R. Henry, MD (co-chair), Mayo Medical Laboratories, Rochester, MN; David Chelmow, MD, Virginia Commonwealth University School of Medicine, Richmond, VA; Lydia P. Howell, MD, University of California-Davis Health System, Davis, CA; Brigitte Ronnett, MD, Johns Hopkins University School of Medicine, Baltimore, MD; and Alan G. Waxman, MD, MPH, University of New Mexico School of Medicine, Albuquerque, NM.

Work Group 2 (Vulva/Penis): Timothy McCalmont, MD (co-chair), University of California – San Francisco, San Francisco, CA; Hope K. Haefner, MD, University of Michigan Center for Vulvar Diseases, Ann Arbor, MI; Kieron S. Leslie, MD, University of California – San Francisco, San Francisco, CA; Christopher Shea, MD, The University of Chicago Medicine, Chicago, IL; and Paul N. Staats, MD, University of Maryland Medical School, Baltimore, MD.

Work Group 2 (Anus/Perianus): Joel M. Palefsky, MD, CM (co-chair), University of California – San Francisco, San Francisco, CA; Leona Council, MD, University of Alabama – Birmingham, Birmingham, AL; Alice Lytwyn, MD, MSc, McMaster University Medical Centre, Hamilton, Ontario, Canada; and Barbara Winkler, MD, Mount Kisco Medical Group, Mount Kisco, NY. **Advisor:** Jennifer Roberts, MD, Douglass Hanley Moir Pathology, Sydney, NSW, Australia.

Work Group 3 (Cervix/Vagina): Terence J. Colgan, MD (co-chair), Mount Sinai Hospital, Toronto, Ontario, Canada; Levi Downs, MD, University of Minnesota Medical School, Minneapolis, MN; Rodolfo Laucirica, MD, Baylor College of Medicine, Ben Taub General Hospital, Houston, TX; and Richard J. Zaino, MD, Hershey Medical Center, Penn State University Hershey, PA.

Work Group 3 (Vulva/Penis): Debra S. Heller, MD (co-chair), UMDNJ-New Jersey Medical School, Newark, NJ; Jill Allbritton, MD, Miraca Life Sciences, Baltimore, MD; Olga Ioffe, MD, University of Maryland School of Medicine, Baltimore, MD; and Nancy Joste, MD, University of New Mexico Health Sciences Center, Albuquerque, NM.

Work Group 3 (Anus/Perianus): Teresa M. Darragh, MD (co-chair), University of California – San Francisco, Mt Zion Medical Center, San Francisco, CA; J. Michael Berry, MD, University of California – San Francisco, San Francisco, CA; Oscar Lin, MD,

Memorial-Sloan Kettering Cancer Center, New York, NY; and Mark Welton, MD, Stanford Hospital and Clinics, Stanford School of Medicine, Stanford, CA. **Advisor:** Christopher N. Otis, MD, Tufts University School of Medicine, Springfield, MA.

Work Group 4: David C. Wilbur, MD (co-chair), Massachusetts General Hospital, Harvard Medical School, Boston, MA; Mark H. Stoler, MD (co-chair), University of Virginia Health System, Charlottesville, VA; Joel S. Bentz, MD, Laboratory Medicine Consultants/Aurora Diagnostics, Las Vegas, NV; Christina S. Kong, MD, Stanford Hospital and Clinics, Stanford, CA; Bradley Quade, MD, PhD, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and Mary R. Schwartz, MD, The Methodist Hospital, Houston, TX. **Advisor:** Sarah M. Bean, MD, Duke University Medical School, Durham, NC.

Work Group 5: Ronald D. Luff, MD (co-chair), Quest Diagnostics, Teterboro, NJ, Thomas Jefferson University, Philadelphia, PA; Ritu Nayar, MD (co-chair), Northwestern University Feinberg School of Medicine, Chicago, IL; Philip E. Castle, PhD, MPH, ASCP, Washington, DC; Maire Duggan, MD, University of Calgary, Calgary, Alberta, Canada; Francisco A. R. Garcia, MD, MPH, Center of Excellence in Women's Health, University of Arizona, Tucson, AZ; Ann T. Moriarty, MD, AmeriPath, Indianapolis, IN; and G. Chip Niedt, MD, Columbia University, New York, NY. **Advisors:** Alicia Carter, MD, Laboratory Corporation of America Holdings, Atlantic Division, Burlington, NC; Marc Goodman, MD, University of Hawaii Medical School, Honolulu, HI; Margaret Neal, MD, Ketchum, Wood & Burgert Pathology Associates, Tallahassee, FL; Vijaya Reddy, MD, Rush University Medical Center, Chicago, IL; Stanley Robboy, MD, CAP President, Duke University Medical System, Durham, NC; Mona Saraiya, MD, Centers for Disease Control and Prevention, Atlanta, GA; Steven Silverberg, MD, University of Maryland Medical System, Baltimore, MD; Susan Spires, MD, University of Kentucky Chandler Medical Center, Lexington, KY.

References

1. Doorbar J. Papillomavirus life cycle organization and biomarker selection. *Dis Markers* 2007;23:297–313.
2. Doorbar J. The papillomavirus life cycle. *J Clin Virol* 2005;32(suppl 1):S7–15.
3. Stoler MH. The pathology of cervical neoplasia. In: Rohan TE, Shah KV, eds. *Cervical Cancer: From Etiology to Prevention*. New York, NY: Springer; 2004: 3–60.
4. Stoler MH. Human papillomaviruses and cervical neoplasia: a model for carcinogenesis. *Int J Gynecol Pathol* 2000;19:16–28.
5. Solomon D, Davey D, Kurman R, Moriarty A, O'connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002;287:2114–9.
6. Stoler MH, Vichnin MD, Ferenczy A, Ferris DG, Perez G, Paavonen J, et al. The accuracy of colposcopic biopsy: analyses from the placebo arm of the Gardasil clinical trials. *Int J Cancer* 2011;128:1354–62.
7. Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, et al. Number of cervical biopsies and sensitivity of colposcopy. *Obstet Gynecol* 2006; 108:264–72.
8. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. *Am J Obstet Gynecol* 2004;191:430–4.
9. Pretorius RG, Belinson JL, Burchette RJ, Hu S, Zhang X, Qiao YL. Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. *J Low Genit Tract Dis* 2011;15:180–8.
10. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL triage study. *JAMA* 2001;285:1500–5.
11. Mccredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 2008;9:425–34.
12. Mccredie MR, Paul C, Sharples KJ, Baranyai J, Medley G, Skegg DC, et al. Consequences in women of participating in a study of the natural history of cervical intraepithelial neoplasia 3. *Aust N Z J Obstet Gynaecol* 2010;50:363–70.
13. Jones RW. Vulvar intraepithelial neoplasia and squamous cell carcinoma of the vulva in young women. *J Reprod Med* 2001;46:408.
14. Jones RW. Vulval intraepithelial neoplasia: current perspectives. *Eur J Gynaecol Oncol* 2001;22:393–402.
15. Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol* 2012;13:487–500.
16. Williams J. *On Cancer of the Uterus: Being the Harveian Lectures for 1886*. London, UK: H. K. Lewis; 1888.
17. Cullen TS. *Cancer of the Uterus: Its Pathology, Symptomatology, Diagnosis, and Treatment*. New York, NY: Appleton; 1900.
18. Rubin IC. The pathological diagnosis of incipient carcinoma of the cervix. *Am J Obstet Gynecol* 1910;62:668–76.
19. Broders AC. Carcinoma in situ contrasted with benign penetrating epithelium. *JAMA* 1932;99:1670–4.
20. Reagan JW, Hicks DJ. A study of in situ and squamous-cell cancer of the uterine cervix. *Cancer* 1953;6:1200–14.
21. Reagan JW, Seidemann IL, Saracusa Y. The cellular morphology of carcinoma in situ and dysplasia or atypical hyperplasia of the uterine cervix. *Cancer* 1953;6:224–34.
22. Mckelvey JL. Carcinoma in situ of the cervix: a general consideration. *Am J Obstet Gynecol* 1952;64:816–32.
23. Hoffman J, Farell DM, Hahn GA. Review of 4,152 biopsies of the cervix with relation to carcinoma in situ. *JAMA* 1953;151:535–40.
24. Koss LG, Durfee GR. Unusual patterns of squamous epithelium of the uterine cervix: cytologic and pathologic study of koilocytotic atypia. *Ann N Y Acad Sci* 1956;63:1245–61.
25. Meisels A, Fortin R. Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. *Acta Cytol* 1976;20:505–9.
26. Richart RM, Barron BA. A follow-up study of patients with cervical dysplasia. *Am J Obstet Gynecol* 1969;105:386–93.
27. Koss LG. Dysplasia. A real concept or a misnomer? *Obstet Gynecol* 1978; 51:374–9.
28. Robertson AJ, Anderson JM, Beck JS, Burnett RA, Howatson SR, Lee FD, et al. Observer variability in histopathological reporting of cervical biopsy specimens. *J Clin Pathol* 1989;42:231–8.
29. Ismail SM, Colclough AB, Dinnen JS, Eakins D, Evans DM, Gradwell E, et al. Reporting cervical intra-epithelial neoplasia (CIN): intra- and interpathologist variation and factors associated with disagreement. *Histopathology* 1990;16: 371–6.
30. Richart RM. A modified terminology for cervical intraepithelial neoplasia. *Obstet Gynecol* 1990;75:131–3.
31. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. National Cancer Institute Workshop. *JAMA* 1989;262:931–4.
32. Wright TC Jr, Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003;189:295–304.
33. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol* 2007;197:340–5.
34. Heatley MK. How should we grade CIN? *Histopathology* 2002;40:377–90.
35. Crum CP. Symposium Part 1. Should the Bethesda System terminology be used in diagnostic surgical pathology?: Point. *Int J Gynecol Pathol* 2003;22:5–12.
36. Schneider V. Symposium Part 2. Should the Bethesda System terminology be used in diagnostic surgical pathology?: Counterpoint. *Int J Gynecol Pathol* 2003;22:13–7.
37. Herbert A, Arbyn M, Bergeron C. Why CIN3 and CIN2 should be distinguished on histological reports. *Cytopathology* 2008;19:63–4.
38. Boonlikit S, Srisantiroj N. Is there any clinical advantage in separating CIN2 from CIN3 in the current two-tiered cytological classification? *Asian Pac J Cancer Prev* 2009;10:115–8.
39. Bellino R, Wierdis T, Arisio R, Re A, Tessarolo M, Leo L, et al. Microinvasive carcinoma of the uterine cervix. Diagnostic and therapeutic dilemma. *Eur J Gynaecol Oncol* 1994;15:380–5.
40. Woodruff JD. Carcinoma in situ of the vagina. *Clin Obstet Gynecol* 1981; 24:485–501.
41. Mccartney AJ. Surgery of intraepithelial neoplasia, CIN, VaIN, and VIN. *Baillieres Clin Obstet Gynaecol* 1987;1:447–84.
42. Turell R. Epidermoid squamous cell cancer of the perianus and anal canal. *Surg Clin North Am* 1962;42:1235–41.
43. Oriel JD, Whimster IW. Carcinoma in situ associated with virus-containing anal warts. *Br J Dermatol* 1971;84:71–3.
44. Durst M, Gissmann L, Ikenberg H, ZurHausen H. A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proc Natl Acad Sci U S A* 1983;80:3812–5.
45. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Human Papillomaviruses*. Lyon, France: International Agency for Research on Cancer; 1995.
46. Fenger C, Bichel P. Flow cytometric DNA analysis of anal canal epithelium and ano-rectal tumours. *Acta Pathol Microbiol Scand A* 1981;89: 351–5.
47. Fenger C, Nielsen VT. Intraepithelial neoplasia in the anal canal. The appearance and relation to genital neoplasia. *Acta Pathol Microbiol Scand A* 1986;94:343–9.
48. Northfelt DW, Swift PS, Palefsky JM. Anal neoplasia. Pathogenesis, diagnosis, and management. *Hematol Oncol Clin North Am* 1996;10:1177–87.

49. Rickert RR, Compton CC. Protocol for the examination of specimens from patients with carcinomas of the anus and anal canal: a basis for checklists. Cancer Committee of the College of American Pathologists. *Arch Pathol Lab Med* 2000;124:21–5.

50. Wendell-Smith CP. Anorectal nomenclature: fundamental terminology. *Dis Colon Rectum* 2000;43:1349–58.

51. Bilimoria KY, Bentrem DJ, Rock CE, Stewart AK, Ko CY, Halverson A. Outcomes and prognostic factors for squamous-cell carcinoma of the anal canal: analysis of patients from the National Cancer Data Base. *Dis Colon Rectum* 2009; 52:624–31.

52. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

53. Bowen JT. Precancerous dermatoses: a study of two cases of chronic atypical epithelial proliferation. *J Cutan Dis Syph* 1912;30:241–55.

54. Woodruff JD, Hildebrandt EE. Carcinoma in situ of the vulva. *Obstet Gynecol* 1958;12:414–24.

55. Abell MR, Gosling JR. Intraepithelial and infiltrative carcinoma of vulva: Bowen's type. *Cancer* 1961;14:318–29.

56. Friedrich EG Jr. Reversible vulvar atypia. A case report. *Obstet Gynecol* 1972;39:173–81.

57. Wade TR, Kopf AW, Ackerman AB. Bowenoid papulosis of the penis. *Cancer*. 1978;42:1890–1903.

58. Friedrich EG Jr. New nomenclature for vulvar disease: report of the committee on terminology. *Obstet Gynecol* 1976;47:122–4.

59. Crum CP, Fu YS, Levine RU, Richart RM, Townsend DE, Fenoglio CM. Intraepithelial squamous lesions of the vulva: biologic and histologic criteria for the distinction of condylomas from vulvar intraepithelial neoplasia. *Am J Obstet Gynecol* 1982;144:77–83.

60. Wilkinson EJ, Kneale B, Lynch PJ. Report of the ISSVD terminology committee. *J Reprod Med* 1986;31:973–4.

61. Scully RE, Poulsen HE. *Histological Typing of Female Genital Tract Tumours*. 2nd ed. Berlin, Germany: Springer-Verlag; 1994.

62. Gross G, Ikenberg H, Gissmann L, Hagedorn M. Papillomavirus infection of the anogenital region: correlation between histology, clinical picture, and virus type. Proposal of a new nomenclature. *J Invest Dermatol* 1985;85:147–52.

63. Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD vulvar oncology subcommittee. *J Reprod Med* 2005;50:807–10.

64. Kurman RJ, Ronnett J, Sherman ME, Wilkinson EJ. *Atlas of Tumor Pathology: Tumors of the Cervix, Vagina, and Vulva*. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; 2010.

65. Barclay DL, Collins CG. Intraepithelial cancer of the vulva. *Am J Obstet Gynecol* 1963;86:95–106.

66. Kaufman RH. Intraepithelial carcinoma of the vulva. *Obstet Gynecol Annu* 1977;6:317–39.

67. Committee on Gynecologic Practice of American College Obstetricians and Gynecologists. ACOG Committee Opinion No. 509: management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011;118:1192–4.

68. Sulzberger MB, Satenstein DL. Erythroplasia of Queyrat. *AMA Arch Derm Syphilol* 1933;28:798–806.

69. Della Torre G, Donghi R, Longoni A, Pilotti S, Pasquini G, De Palo G, et al. HPV DNA in intraepithelial neoplasia and carcinoma of the vulva and penis. *Diagn Mol Pathol* 1992;1:25–30.

70. Cubilla AL, Reuter V, Velazquez E, Piris A, Saito S, Young RH. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. *Int J Surg Pathol* 2001;9:111–20.

71. Epstein J, Cubilla AL. *Tumors of the Prostate Gland, Seminal Vesicles, Penis, and Scrotum*. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; 2011.

72. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 99: Management of abnormal cervical cytology and histology. *Obstet Gynecol* 2008;112:1419–44.

73. Heller DS. Report of a new ISSVD classification of VIN. *J Low Genit Tract Dis* 2007;11:46–7.

74. Scurry J, Wilkinson EJ. Review of terminology of precursors of vulvar squamous cell carcinoma. *J Low Genit Tract Dis* 2006;10:161–9.

75. Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *Am J Clin Pathol* 2007;127:805–15.

76. Witkiewicz AK, Wright TC, Ferenczy A, Ronnett BM, Kurman RJ. Carcinoma and other tumors of the cervix. In: Kurman RJ, Ellenson LH, Ronnett BM, eds. *Blaustein's Pathology of the Female Genital Tract*. 6th ed. New York, NY: Springer; 2011.

77. Crum CP, Lee KR. *Diagnostic Gynecologic and Obstetric Pathology*. Philadelphia, PA: Saunders; 2005.

78. Tabbara S, Saleh AD, Andersen WA, Barber SR, Taylor PT, Crum CP. The Bethesda classification for squamous intraepithelial lesions: histologic, cytologic, and viral correlates. *Obstet Gynecol* 1992;79:338–46.

79. Genest DR, Stein L, Cibas E, Sheets E, Zitz JC, Crum CP. A binary (Bethesda) system for classifying cervical cancer precursors: criteria, reproducibility, and viral correlates. *Hum Pathol* 1993;24:730–6.

80. Mccluggage WG, Walsh MY, Thornton CM, Hamilton PW, Date A, Caughley LM, et al. Inter- and intra-observer variation in the histopathological reporting of cervical squamous intraepithelial lesions using a modified Bethesda grading system. *Br J Obstet Gynaecol* 1998;105:206–10.

81. Mccluggage WG, Bharucha H, Caughley LM, Date A, Hamilton PW, Thornton CM, et al. Interobserver variation in the reporting of cervical colposcopic biopsy specimens: comparison of grading systems. *J Clin Pathol* 1996;49:833–5.

82. Creagh T, Bridger JE, Kupek E, Fish DE, Martin-Bates E, Wilkins MJ. Pathologist variation in reporting cervical borderline epithelial abnormalities and cervical intraepithelial neoplasia. *J Clin Pathol*. 1995;48:59–60.

83. Lie AK, Skjeldestad FE, Hagen B, Haugen OA. Occurrence of human papillomavirus infection in cervical intraepithelial neoplasia. A retrospective histopathological study of 317 cases treated by laser conization. *APMIS* 1995; 103:693–8.

84. De Vet HC, Knipschild PG, Schouten HJ, Koudstaal J, Kwee WS, Willebrand D, et al. Interobserver variation in histopathological grading of cervical dysplasia. *J Clin Epidemiol* 1990;43:1395–8.

85. Kato I, Santamaria M, De Ruiz PA, Aristizabal N, Bosch FX, De Sanjose S, et al. Inter-observer variation in cytological and histological diagnoses of cervical neoplasia and its epidemiologic implication. *J Clin Epidemiol* 1995;48:1167–74.

86. Preti M, Mezzetti M, Robertson C, Sideri M. Inter-observer variation in histopathological diagnosis and grading of vulvar intraepithelial neoplasia: results of an European collaborative study. *Br J Obstet Gynaecol* 2000;107:594–9.

87. Lytwyn A, Salit IE, Raboud J, Chapman W, Darragh T, Winkler B, et al. Interobserver agreement in the interpretation of anal intraepithelial neoplasia. *Cancer* 2005;103:1447–56.

88. Dijkstra MG, Heideman DA, De Roy SC, Rozendaal L, Berkhof J, Van Krimpen K, et al. p16(INK4a) immunostaining as an alternative to histology review for reliable grading of cervical intraepithelial lesions. *J Clin Pathol* 2010; 63:972–7.

89. Klaes R, Benner A, Friedrich T, Ridder R, Herrington S, Jenkins D, et al. $p16^{INK4a}$ immunohistochemistry improves interobserver agreement in the diagnosis of cervical intraepithelial neoplasia. *Am J Surg Pathol* 2002;26:1389–99.

90. Bergeron C, Ordi J, Schmidt D, Trunk MJ, Keller T, Ridder R. Conjunctive $p16^{INK4a}$ testing significantly increases accuracy in diagnosing high-grade cervical intraepithelial neoplasia. *Am J Clin Pathol* 2010;133:395–406.

91. Horn LC, Reichert A, Oster A, Arndal SF, Trunk MJ, Ridder R, et al. Immunostaining for $p16^{INK4a}$ used as a conjunctive tool improves interobserver agreement of the histologic diagnosis of cervical intraepithelial neoplasia. *Am J Surg Pathol* 2008;32:502–12.

92. The revised Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda workshop. *J Reprod Med* 1992;37:383–6.

93. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. *Vaccine* 2006;24(suppl 3):S11–25.

94. Roche WD, Norris HJ. Microinvasive carcinoma of the cervix. The significance of lymphatic invasion and confluent patterns of stromal growth. *Cancer* 1975;36:180–6.

95. Chitale AR, Bhuvaneshwari AP, Khilnani P, Purandare VN. Pathology of microinvasive (stage 1 A) carcinoma of uterine cervix. *Indian J Cancer* 1977;14: 189–94.

96. Gurgel MS, Bedone AJ, Andrade LA, Panetta K. Microinvasive carcinoma of the uterine cervix: histological findings on cone specimens related to residual neoplasia on hysterectomy. *Gynecol Oncol* 1997;65:437–40.

97. Creasman WT, Fetter BF, Clarke-Pearson DL, Kaufmann L, Parker RT. Management of stage IA carcinoma of the cervix. *Am J Obstet Gynecol* 1985; 153:164–72.

98. Greer BE, Figge DC, Tamimi HK, Cain JM, Lee RB. Stage IA2 squamous carcinoma of the cervix: difficult diagnosis and therapeutic dilemma. *Am J Obstet Gynecol* 1990;162:1406–9; discussion 1409–11.

99. Zheng W, Robboy SJ. Cervical squamous cell carcinoma. In: Robboy SJ, Mutter GL, Prat J, Bentley R, Russell P, eds. *Robboy's Pathology of the Female Reproductive Tract*. 2nd ed. Philadelphia, PA: Churchill Livingstone/Elsevier; 2008:227–48.

100. Andersen ES, Husth M, Joergensen A, Nielsen K. Laser conization for microinvasive carcinoma of the cervix. Short-term results. *Int J Gynecol Cancer* 1993;3:183–5.

101. Simon NL, Gore H, Shingleton HM, Soong SJ, Orr JW Jr, Hatch KD. Study of superficially invasive carcinoma of the cervix. *Obstet Gynecol* 1986;68:19–24.

102. Hopkins MP, Morley GW. Microinvasive squamous cell carcinoma of the cervix. *J Reprod Med* 1994;39:671–3.

103. Raspagliesi F, Ditto A, Solima E, Quattrone P, Fontanelli R, Zanaboni F, et al. Microinvasive squamous cell cervical carcinoma. *Crit Rev Oncol Hematol* 2003;48:251–61.

104. Seski JC, Abell MR, Morley GW. Microinvasive squamous carcinoma of the cervix: definition, histologic analysis, late results of treatment. *Obstet Gynecol* 1977;50:410–4.

105. Ostor AG, Rome RM. Micro-invasive squamous cell carcinoma of the cervix: a clinico-pathologic study of 200 cases with long-term follow-up. *Int J Gynecol Cancer* 1994;4:257–64.

106. Sevin BU. Management of microinvasive cervical cancers. *Semin Surg Oncol* 1999;16:228–31.

107. Ayhan A, Tuncer ZS, Koseoglu F, Yuce K, Kucukali T. Microinvasive carcinoma of the cervix: an analysis of 31 patients. *Eur J Gynaecol Oncol* 1997; 18:127–9.

108. Hasumi K, Sakamoto A, Sugano H. Microinvasive carcinoma of the uterine cervix. *Cancer* 1980;45:928–31.
109. Trelford JD, Tesluk H, Franti CE, Bradfield G, Ordorica E, Deer D. 20 year follow-up on microinvasive squamous carcinoma of the cervix. *Eur J Gynaecol Oncol* 1992;13:155–9.
110. Copeland LJ, Silva EG, Gershenson DM, Morris M, Young DC, Wharton JT. Superficially invasive squamous cell carcinoma of the cervix. *Gynecol Oncol* 1992;45:307–12.
111. Benedet JL, Anderson GH. Stage IA carcinoma of the cervix revisited. *Obstet Gynecol* 1996;87:1052–9.
112. Sedlis A, Sall S, Tsukada Y, Park R, Mangan C, Shingleton H, et al. Microinvasive carcinoma of the uterine cervix: a clinical-pathologic study. *Am J Obstet Gynecol* 1979;133:64–74.
113. Averette HE, Nelson JH, Ng AB, Hoskins WJ, Boyce JG, Ford JH. Diagnosis and management of microinvasive (stage IA) carcinoma of the uterine cervix. *Cancer* 1976;38:414–25.
114. Burghardt E. Microinvasive carcinoma in gynaecological pathology. *Clin Obstet Gynaecol* 1984;11:239–57.
115. Burghardt E, Girardi F, Lahousen M, Pickel H, Tamussino K. Microinvasive carcinoma of the uterine cervix (International Federation of Gynecology and Obstetrics stage IA). *Cancer* 1991;67:1037–45.
116. Witkiewicz A, Lee KR, Brodsky G, Cviko A, Brodsky J, Crum CP. Superficial (early) endocervical adenocarcinoma in situ: a study of 12 cases and comparison to conventional AIS. *Am J Surg Pathol* 2005;29:1609–14.
117. Kalof KN, Dadmanesh F, Longacre TA, Nucci MR, Oliva E, Cooper K. Protocol for the examination of specimens from patients with carcinoma of the uterine cervix. Available at: http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/Cervix_11protocol.pdf. Accessed April 10, 2012.
118. Ostor AG, Mulvany N. The pathology of cervical neoplasia. *Curr Opin Obstet Gynecol* 1996;8:69–73.
119. Benedet JL. Cervical cancer staging systems: the endless debate. *Gynecol Oncol* 1997;65:6–7.
120. Ostor AG. Studies on 200 cases of early squamous cell carcinoma of the cervix. *Int J Gynecol Pathol* 1993;12:193–207.
121. Lee SW, Kim Y-M, Son W-S, You H-J, Kim D-Y, Kim J-H, et al. The efficacy of conservative management after conization in patients with stage IA1 microinvasive cervical carcinoma. *Acta Obstet Gynecol Scand* 2009;88:209–15.
122. Leman MH, Benson WL, Kurman RJ, Park RC. Microinvasive carcinoma of the cervix. *Obstet Gynecol* 1976;48:571–8.
123. Robert ME, Fu YS. Squamous cell carcinoma of the uterine cervix—a review with emphasis on prognostic factors and unusual variants. *Semin Diagn Pathol* 1990;7:173–89.
124. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Cancer* 2009;105:103–4.
125. Pecorelli S, Odicino F. Cervical cancer staging. *Cancer J* 2003;9:390–4.
126. Yamaguchi H, Ueda M, Kanemura M, Izuma S, Nishiyama K, Tanaka Y, et al. Clinical efficacy of conservative laser therapy for early-stage cervical cancer. *Int J Gynecol Cancer* 2007;17:455–9.
127. Andersen ES, Nielsen K, Pedersen B. Combination laser conization as treatment of microinvasive carcinoma of the uterine cervix. *Eur J Gynaecol Oncol* 1998;19:352–5.
128. Elliott P, Coppleson M, Russell P, Liouros P, Carter J, Macleod C, et al. Early invasive (FIGO stage IA) carcinoma of the cervix: a clinico-pathologic study of 476 cases. *Int J Gynecol Cancer* 2000;10:42–52.
129. Kolstad P. Follow-up study of 232 patients with stage IA1 and 411 patients with stage IA2 squamous cell carcinoma of the cervix (microinvasive carcinoma). *Gynecol Oncol* 1989;33:265–72.
130. Creasman WT, Weed JC. Microinvasive cancer vs occult cancer. *Int J Radiat Oncol Biol Phys* 1979;5:1871–2.
131. Schink JC, Lurain JR. Microinvasive cervix cancer. *Int J Gynaecol Obstet* 1991;36:5–11.
132. Duncan ID, Walker J. Microinvasive squamous carcinoma of cervix in the Tayside region of Scotland. *Br J Obstet Gynaecol* 1977;84:67–70.
133. Orlandi C, Costa S, Terzano P, Martinelli GN, Comerci G, Guerra B, et al. Presurgical assessment and therapy of microinvasive carcinoma of the cervix. *Gynecol Oncol* 1995;59:255–60.
134. Mota F. Microinvasive squamous carcinoma of the cervix: treatment modalities. *Acta Obstet Gynecol Scand* 2003;82:505–9.
135. Buckley SL, Tritz DM, Van Le L, Higgins R, Sevin BU, Ueland FR, et al. Lymph node metastases and prognosis in patients with stage IA2 cervical cancer. *Gynecol Oncol* 1996;63:4–9.
136. Van Nagell JR, Greenwell N, Powell DF, Donaldson ES, Hanson MB, Gay EC. Microinvasive carcinoma of the cervix. *Am J Obstet Gynecol* 1983;145:981–91.
137. Costa S, Marra E, Martinelli GN, Santini D, Casadio P, Formelli G, et al. Outcome of conservatively treated microinvasive squamous cell carcinoma of the uterine cervix during a 10-year follow-up. *Int J Gynecol Cancer* 2009;19:33–8.
138. Kodama J, Mizutani Y, Hongo A, Yoshinouchi M, Kudo T, Okuda H. Optimal surgery and diagnostic approach of stage IA2 squamous cell carcinoma of the cervix. *Eur J Obstet Gynecol Reprod Biol* 2002;101:192–5.
139. Kim WY, Chang S-J, Chang K-H, Yoo S-C, Ryu H-S. Conservative management of stage IA1 squamous cell carcinoma of the cervix with positive resection margins after conization. *Int J Gynaecol Obstet* 2010;109:110–2.
140. Marana HR, De Andrade JM, Matthes AC, Spina LA, Carrara HH, Bighetti S. Microinvasive carcinoma of the cervix. Analysis of prognostic factors. *Eur J Gynaecol Oncol* 2001;22:64–6.
141. Lin H, Chang HY, Huang CC, Changchien CC. Prediction of disease persistence after conization for microinvasive cervical carcinoma and cervical intraepithelial neoplasia grade 3. *Int J Gynecol Cancer* 2004;14:311–6.
142. Phongnarisorn C, Srisomboon J, Khunamornpong S, Siriaungkul S, Suprasert P, Charoenkwan K, et al. The risk of residual neoplasia in women with microinvasive squamous cervical carcinoma and positive cone margins. *Int J Gynecol Cancer* 2006;16:655–9.
143. Jones WB, Mercer GO, Lewis JL, Rubin SC, Hoskins WJ. Early invasive carcinoma of the cervix. *Gynecol Oncol* 1993;51:26–32.
144. Peters WA, Kumar NB, Morley GW. Microinvasive carcinoma of the vagina: a distinct clinical entity? *Am J Obstet Gynecol* 1985;153:505–7.
145. Dini MM, Park JM. Microinvasive squamous cell carcinoma of the vagina. *J Natl Med Assoc* 1984;76:709–11.
146. Wilkinson EJ. Pathology of the vagina. *Curr Opin Obstet Gynecol* 1991;3:553–60.
147. Shia J. An update on tumors of the anal canal. *Arch Pathol Lab Med* 2010;134:1601–11.
148. Salmo E, Haboubi N. Anal cancer: pathology, staging and evidence-based minimum data set. *Colorectal Dis* 2011;13(suppl 1):11–20.
149. Nigro ND. An evaluation of combined therapy for squamous cell cancer of the anal canal. *Dis Colon Rectum* 1984;27:763–6.
150. Martin FT, Kavanagh D, Waldron R. Squamous cell carcinoma of the anal canal. *Surgeon* 2009;7:232–7.
151. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer* 1999;85:1686–93.
152. Longacre TA, Kong CS, Welton ML. Diagnostic problems in anal pathology. *Adv Anat Pathol* 2008;15:263–78.
153. Roohipour R, Patil S, Goodman KA, Minsky BD, Wong WD, Guillem JG, et al. Squamous-cell carcinoma of the anal canal: predictors of treatment outcome. *Dis Colon Rectum* 2008;51:147–53.
154. Tantipalakorn C, Robertson G, Marsden DE, Gebski V, Hacker NF. Outcome and patterns of recurrence for International Federation of Gynecology and Obstetrics (FIGO) stages I and II squamous cell vulvar cancer. *Obstet Gynecol* 2009;113:895–901.
155. Faught W, Jeffrey J, Bryson P, Dawson L, Helewa M, Kwon J, et al. Management of squamous cell cancer of the vulva. *J Obstet Gynaecol Can* 2006;28:640–51.
156. Preti M, Rouzier R, Mariani L, Wilkinson EJ. Superficially invasive carcinoma of the vulva: diagnosis and treatment. *Clin Obstet Gynecol* 2005;48:862–8.
157. Maiche AG, Pyrhonen S. Clinical staging of cancer of the penis: By size? By localization? Or by depth of infiltration? *Eur Urol* 1990;18:16–22.
158. Pizzocaro G, Algaba F, Horenblas S, Solsona E, Tana S, Van Der Poel H, et al. EAU Penile Cancer Guidelines 2009. *Eur Urol* 2010;57:1002–12.
159. Lowe FC. Squamous-cell carcinoma of the scrotum. *Urol Clin North Am* 1992;19:397–405.
160. Frisch M, Fenger C, Van Den Brule AJ, Sorensen P, Meijer CJ, Walboomers JM, et al. Variants of squamous cell carcinoma of the anal canal and perianal skin and their relation to human papillomaviruses. *Cancer Res* 1999;59:753–7.
161. Welton ML, Sharkey FE, Kahlenberg MS. The etiology and epidemiology of anal cancer. *Surg Oncol Clin N Am* 2004;13:263–75.
162. Stoler MH. Toward objective cervical cancer screening: maybe the eyes do have it. *Am J Clin Pathol* 2010;134:5–6.
163. Galgano MT, Castle PE, Atkins KA, Brix WK, Nassau SR, Stoler MH. Using biomarkers as objective standards in the diagnosis of cervical biopsies. *Am J Surg Pathol* 2010;34:1077–87.
164. Santos M, Landolfi S, Olivella A, Lloveras B, Klaustermeier J, Suarez H, et al. p16 overexpression identifies HPV-positive vulvar squamous cell carcinomas. *Am J Surg Pathol* 2006;30:1347–56.
165. Klaes R, Friedrich T, Spitkovsky D, Ridder R, Rudy W, Petry U, et al. Overexpression of p16(INK4a) as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. *Int J Cancer* 2001;92:276–84.
166. Tringler B, Gup CJ, Singh M, Groshong S, Shroyer AL, Heinz DE, et al. Evaluation of $p16^{INK4a}$ and pRb expression in cervical squamous and glandular neoplasia. *Hum Pathol* 2004;35:689–96.
167. Branca M, Giorgi C, Santini D, Di Bonito L, Ciotti M, Costa S, et al. Survivin as a marker of cervical intraepithelial neoplasia and high-risk human papillomavirus and a predictor of virus clearance and prognosis in cervical cancer. *Am J Clin Pathol* 2005;124:113–21.
168. Bernard JE, Butler MO, Sandweiss L, Weidner N. Anal intraepithelial neoplasia: correlation of grade with $p16^{INK4a}$ immunohistochemistry and HPV in situ hybridization. *Appl Immunohistochem Mol Morphol* 2008;16:215–20.
169. Riethdorf S, Neffen EF, Cviko A, Loning T, Crum CP, Riethdorf L. $p16^{INK4a}$ expression as biomarker for HPV 16–related vulvar neoplasias. *Hum Pathol* 2004;35:1477–83.
170. Benevolo M, Terrenato I, Mottolese M, Marandino F, Muti P, Carosi M, et al. Comparative evaluation of nm23 and p16 expression as biomarkers of high-risk human papillomavirus infection and cervical intraepithelial neoplasia 2(+) lesions of the uterine cervix. *Histopathology* 2010;57:580–6.

171. Benevolo M, Mottolese M, Marandino F, Vocaturo G, Sindico R, Piperno G, et al. Immunohistochemical expression of p16(INK4a) is predictive of HR-HPV infection in cervical low-grade lesions. *Mod Pathol* 2006;19:384–91.

172. Negri G, Vittadello F, Romano F, Kasal A, Rivasi F, Girlando S, et al. $p16^{INK4a}$ expression and progression risk of low-grade intraepithelial neoplasia of the cervix uteri. *Virchows Arch* 2004;445:616–20.

173. Ozaki S, Zen Y, Inoue M. Biomarker expression in cervical intraepithelial neoplasia: potential progression predictive factors for low-grade lesions. *Hum Pathol* 2011;42:1007–12.

174. Del Pino M, Garcia S, Fuste V, Alonso I, Fuste P, Torne A, et al. Value of p16(INK4a) as a marker of progression/regression in cervical intraepithelial neoplasia grade 1. *Am J Obstet Gynecol* 2009;201:488.e1–7.

175. Ordi J, Garcia S, Del Pino M, Landolfi S, Alonso I, Quinto L, et al. $p16^{INK4a}$ immunostaining identifies occult CIN lesions in HPV-positive women. *Int J Gynecol Pathol* 2009;28:90–7.

176. Katki HA, Wacholder S, Solomon D, Castle PE, Schiffman M. Risk estimation for the next generation of prevention programmes for cervical cancer. *Lancet Oncol* 2009;10:1022–3.

177. Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol* 2011;12:663–72.

178. Stoler MH, Wright TC Jr, Sharma A, Apple R, Gutekunst K, Wright TL. High-risk human papillomavirus testing in women with ASC-US cytology: results from the ATHENA HPV study. *Am J Clin Pathol* 2011;135:468–75.

179. Wright TC Jr, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. *Am J Obstet Gynecol* 2012;206:46.e1–11.

180. College of American Pathologists. CAP laboratory accreditation checklists. Available at: http://www.cap.org/apps/cap.portal. Accessed April 11, 2012.

ORIGINAL ARTICLE

Validation of Companion Diagnostic for Detection of Mutations in Codons 12 and 13 of the *KRAS* Gene in Patients with Metastatic Colorectal Cancer: Analysis of the NCIC CTG CO.17 Trial 820
Christopher T. Harbison, PhD; Christine E. Horak, PhD; Jean-Marie Ledeine, PhD; Pralay Mukhopadhyay, PhD; Daniel P. Malone; Chris O'Callaghan, DVM, PhD; Derek J. Jonker, MD; Christos S. Karapetis, MD; Shirin Khambata-Ford, PhD; Nancy Gustafson, PhD; Ovidiu C. Trifan, PhD; Shao-Chun Chang, MD, PhD; Paul Ravetto; George A. Green IV, PhD

SPECIAL ARTICLE

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology 828
Neal I. Lindeman, MD; Philip T. Cagle, MD; Mary Beth Beasley, MD; Dhananjay Arun Chitale, MD; Sanja Dacic, MD, PhD; Giuseppe Giaccone, MD, PhD; Robert Brian Jenkins, MD, PhD; David J. Kwiatkowski, MD, PhD; Juan-Sebastian Saldivar, MD; Jeremy Squire, PhD; Erik Thunnissen, MD, PhD; Marc Ladanyi, MD

CASE REPORT

Limiting the Extent of a Delayed Hemolytic Transfusion Reaction With Automated Red Blood Cell Exchange 861
Christopher A. Tormey, MD; Gary Stack, MD, PhD

RESIDENT SHORT REVIEW

Histiocytic/Dendritic Cell Transformation of B-Cell Neoplasms: Pathologic Evidence of Lineage Conversion in Differentiated Hematolymphoid Malignancies. 865
Maggie M. Stoecker, MD; Endi Wang, MD, PhD

INSTRUCTIONS FOR AUTHORS

(See January 2013 issue, page 139. Also available at www.archivesofpathology.org.)

Erratum

A word was omitted from an article that appeared in the October 2012 issue of the *Archives* (Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al, for members of the LAST Project Work Groups. 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. *Arch Pathol Lab Med*. 2012;136(10):1266-1297). On page 1291 of the article, a sentence appears that currently states, "A positive p16 stain does exclude CIN 1; at least 30% of adjudicated CIN 1 cases are p16-positive." This sentence should have read as, "A positive p16 stain does not exclude CIN 1; at least 30% of adjudicated CIN 1 cases are p-16 positive."