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Revised Terminology for Cervical Histopathology and Its Implications for Management of High-Grade Squamous Intraepithelial Lesions of the Cervix

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Abstract

In March 2012, the College of American Pathologists and American Society for Colposcopy and Cervical Pathology, in collaboration with 35 stakeholder organizations, convened a consensus conference called the Lower Anogenital Squamous Terminology (LAST) Project. The recommendations of this project include using a uniform, two-tiered terminology to describe the histology of human papillomavirus-associated squamous disease across all anogenital tract tissues: vulva, vagina, cervix, penis, perianus, and anus. The recommended terminology is “low-grade” or “high-grade squamous intraepithelial lesion (SIL).” This terminology is familiar to clinicians, because it parallels the terminology of the Bethesda System cytologic reports. Biopsy results using SIL terminology may be further qualified using “intraepithelial neoplasia” (IN) terminology in parentheses. Laboratory p16 tissue immunostaining is recommended to better classify histopathology lesions that morphologically would earlier have been diagnosed as IN 2. p16 is also recommended for differentiating between high-grade squamous intraepithelial lesions and benign mimics. The LAST Project recommendations potentially affect the application of current guidelines for managing cervical squamous intraepithelial lesions. The authors offer interim guidance for managing cervical lesions diagnosed using this new terminology with special attention paid to managing young women with cervical high-grade squamous intraepithelial lesions on biopsy. Clinicians should be aware of the LAST Project recommendations, which include important changes from prior terminology.

In March 2012 the College of American Pathologists and American Society for Colposcopy and Cervical Pathology jointly sponsored the LAST Project. This conference was charged with recommending an updated terminology for histopathology of human papillomavirus (HPV)-associated squamous lesions of the lower anogenital tract. The project participants,

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including pathologists and clinicians representing the College of American Pathologists, the American Society for Colposcopy and Cervical Pathology, and representatives of 35 stakeholder organizations conducted an extensive evidence review and made recommendations to harmonize terminology across all lower anogenital sites and use terms consistent with current understanding of HPV-associated premalignant and superficially invasive disease. The LAST Project recommendations were recently published.[1] The revisions are intended to improve patient treatment by standardizing language and improving communication among and between pathologists and clinicians. The new terminology has important implications for managing women with preinvasive cervical squamous lesions, especially young women with high-grade disease. Because the recommendations were approved by the College of American Pathologists, the American Society for Colposcopy and Cervical Pathology, and 35 stakeholder organizations, future wide use is expected, and it is important that clinicians understand the changes. This document summarizes the recommendations from the LAST Project related to preneoplastic cervical disease and offers guidance for managing women whose results use the new terminology, particularly young women with high-grade lesions.

Background

Harmonization Across Body Sites

A historical review of terminology used for HPV-associated squamous lesions across all anogenital sites made it apparent that most of our knowledge of the natural history of HPV-associated conditions is related to the cervix with over 99% of cancers being caused by HPV.[2] Histopathologic similarities were found for vaginal and vulvar disease in women and penile disease in men with 40% of cancer at each site attributable to HPV.[3] Less is known about the natural history of HPV infections in these tissues than in the cervix. Human papillomavirus disease of the anal canal and perianus has recently received attention, and natural history studies show similarities to cervical disease in vulnerable groups such as immunocompromised persons. Anal cancers remain rarer than cervical cancer in the general population, underscoring gaps in our knowledge about HPV progression in noncervical sites.[4]

Current nomenclature reflects a bewildering array of terms, most originating before the pathophysiology of HPV-associated squamous neoplasia was understood. These terms developed over time from the differing perspectives of gynecologists, dermatologists, pathologists, urologists, colorectal surgeons, and others. Cervical cytology, for example, uses the two-tiered (low-grade squamous intraepithelial lesion [LSIL] and high-grade squamous intra-epithelial lesion [HSIL]) Bethesda System. For cervical histopathology, the three-tiered cervical intraepithelial neoplasia (CIN) classification (CIN 1, 2, and 3) is typically used. For histopathology of the vulva, the International Society for the Study of Vulvovaginal Disease recommends a single grade of VIN.[5] Although the American College of Obstetricians and Gynecologists[6] has adopted the International Society for the Study of Vulvovaginal Disease terminology, many pathologists continue to use either older VIN 1–3 terminology or a modified lexicon of high-grade and low-grade VIN. Given our current

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understanding of HPV infection and associated disease, these disparate terms create confusion and support harmonization of terms within and across anogenital sites.

Limitations of Current Cervical Histopathologic Nomenclature

We currently understand the natural history of HPV infection and disease to include two phases: an infectious, or productive phase and persistent infection. The infectious phase results in cellular changes, including basal cell proliferation resulting from E6 and E7 gene product expression and other cytopathic changes (eg, perinuclear halos) caused by E4 expression.[6] Cervical infections are manifested as low-grade lesions: LSIL cytology and CIN 1 histopathology. Because these lesions can be quite small and cytology is relatively insensitive, not all productive lesions are identified. Productive infections may also develop and spontaneously resolve between screening opportunities and so are undetected. Persistent high-risk HPV infection imparts risk for developing “true” precancerous lesions with considerable potential for progression if left untreated.[7,8] Persistent infections with the development of precancer are manifested by HSIL on cytology and CIN 3 on histology.

The current three-tiered intraepithelial neoplasia (-IN) classification used for histopathology of HPV-associated squamous lesions (-IN 1, -IN 2, -IN 3), is problematic for several reasons. Although both -IN 2 and -IN 3 are considered high-grade lesions, the diagnosis of the intermediate category of -IN 2 has much poorer reproducibility among pathologists than -IN 3.[8–10] In the Atypical Squamous Cells of Uncertain Significance–LSIL Triage Study, quality control reviewers agreed with community pathologists' diagnoses of CIN 2 in only 43% of cases.[11] In the National Cancer Institutes Guanacaste cohort, two expert reviewers agreed with community pathologists' diagnoses of CIN 2 in only 13% and 31% of specimens. In contrast, they agreed on 84% and 81% of community diagnoses of CIN 3.[12]

It remains unclear whether “-IN 2” is a distinct biological entity with specific clinical meaning. Many experts question whether CIN 2 exists as a distinct clinical entity.[11,12] and consider it analogous to an equivocal cytology report of atypical squamous cells. Atypical squamous cell is a mix of cells from which a final interpretation cannot be made based on cytologic criteria alone. The aggregate of biopsies reported as CIN 2 is a heterogeneous mix that includes some that could arguably be called CIN 1 and some that other pathologists would call CIN 3.[8] Observational studies show that CIN 2 has an intermediate risk of progression, between CIN 1 and CIN 3.[13] Many believe that this intermediate risk reflects averaging of the individual CIN 1 and CIN 3 risks rather than a true risk related to a CIN 2 diagnosis.[1] LAST Project participants generally agreed that the diagnosis of CIN 2 cannot be reliably differentiated by histopathologic criteria alone.[1,9,14]

Use of Biomarkers

One of the LAST Project work groups investigated the availability of specific biomarkers or other methodologies that could be used to resolve the uncertainty and poor reproducibility of -IN 2 much as high-risk HPV testing is used for atypical squamous cells of uncertain significance cytology triage. An extensive literature review pointed to the use of $p16^{INK4a}$ immunohistochemical stain (p16). Recent studies show that adding p16 immunostaining significantly improves the reliability of diagnosing high-grade CIN compared with

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hematoxylin and eosin morphology alone, especially when p16 is used as an adjunct to a diagnosis of CIN 2.[1,9,14] Overexpression of p16 occurs in squamous cells when the cell cycle regulator, retinoblastoma protein (pRB) is inactivated, as it is by the E7 oncoprotein of high-risk HPV, which helps drive the HPV-mediated neoplastic transformation.[7,9] Positive p16 immunostaining of squamous cells throughout the thickness of the epithelium correlates well with consensus diagnoses of HSIL.[9] p16 is already widely used by pathologists as an adjunct to cervical histopathology. Based on the evidence review, the workgroup reaffirmed that evidence was insufficient to determine whether use of any biomarker could replace histopathology as the primary diagnostic tool, but adding p16 in specific problematic diagnostic situations gives a more reliable and consistent histopathologic interpretation.[1,9,14]

Recommendations

These important observations resulted in a number of changes in recommendations for reporting HPV-associated squamous histopathology of lower anogenital tract sites, including the cervix. The group recommended using terms familiar to clinicians and decided on a two-tiered system similar to that used for reporting cervical cytology. Lesions will be categorized as high grade or low grade followed by the phrase “squamous intraepithelial lesion.” Acronyms like the Bethesda System (LSIL and HSIL) will be used.[1] During transition to the new terminology, and at the clinician's request, the diagnosis may be further supplemented with current “(-IN)” terminology for each lower anogenital site. If the -IN qualifier is used, it will be reported in parentheses after the main diagnosis. For example, a cervical biopsy previously reported as “CIN 2” will now be reported as “HSIL” or “HSIL (CIN 2)”. A prior “CIN 3” now would be reported as “HSIL” or as “HSIL (CIN 3).” Because the LAST Project terminology parallels cytology reporting, health care providers must ensure that the report received refers to either a cytologic or histopathologic specimen. Use of similar terminology was not intended to alter the role of cytology as a screening test or to imply that cytology can substitute for histologic diagnosis. Of note, a number of anatomic pathology laboratories and major pathology textbooks already use a two-tiered histopathology system for cervical lesions.[15–18]

The LAST Project recommendations include very specific guidelines for laboratory use of p16 immunostaining, and they recommend against the use of a panel of diagnostic immunostains in most situations. Most important, p16 is recommended to confirm a diagnosis of a high-grade lesion when entertaining a diagnosis of -IN 2 based on hematoxylin and eosin morphology. If a “CIN 2” specimen is p16-positive, it will be classified as “HSIL”; if p16 is negative, it will be classified as “LSIL.” Pathology reports already note when p16 or other immunostains are used. By using p16 immunostaining to clarify a diagnosis of CIN 2, some biopsy specimens previously called CIN 2 by hematoxylin and eosin stain alone will be p16-negative and will be downgraded to LSIL. This will result in increased specificity of diagnosing HSIL. Some pathologists already may be using p16 staining on cases confusingly reported as “CIN 1–2.” If p16-positive, these biopsies would now be classified as HSIL. p16 use is appropriate here within the LAST Project recommendations if the morphologic differential diagnosis truly includes a precancerous lesion. Many clinicians currently manage “CIN 1–2” as a high-grade lesion; use of p16 will allow lesions testing as p16-negative to be managed as low-grade lesions

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(LSIL). An additional recommendation is to use p16 to facilitate diagnosis when a potential high-grade lesion cannot be morphologically differentiated from a benign mimic such as reactive squamous metaplasia, atrophy, reparative epithelial changes, or tangential sectioning.

Considerable concern for the potential overuse of p16 was raised among LAST Project participants. The recommendations explicitly recommend against using p16 with biopsies that morphologically would be considered CIN 1 or CIN 3. The long-term natural history of CIN 1 and CIN 3 lesions whose morphologic diagnosis is modified by a p16 test is unknown. Three recent studies suggest that p16-positive CIN 1 has increased risk of progression to CIN 3 compared with p16-negative CIN 1.[19–21] Natural history of such lesion diagnoses, defined by p16, is an area needing further investigation; the significance and appropriate management of p16-negative CIN 3 and p16-positive CIN 1 are currently unknown.

Treatment of Women With a Histology Diagnosis of Low-Grade Squamous Intraepithelial Lesion

In general, the management recommended in the 2006 American Society for Colposcopy and Cervical Pathology Consensus Guidelines is already based on a two-tiered system of diagnosis. The authors state, “the histological classification incorporated into these guidelines is a 2-tiered system that applies the terms CIN 1 to low-grade lesions and CIN 2, 3 to high-grade precursors.”[22]

Under the LAST Project terminology, biopsies previously called CIN 1 and p16-negative CIN 2 will be diagnosed as LSIL. Because p16-negative CIN 2 is expected to behave clinically similarly to CIN 1, the management of LSIL should be the same as is currently recommended for CIN 1. Should p16 staining inadvertently be used for a biopsy previously called CIN 1, even if positive, the diagnosis should be LSIL. In most cases, the 2006 American Society for Colposcopy and Cervical Pathology Consensus Guidelines[22] call for close clinical follow-up without treatment. CIN 1 preceded by a cytologic report of atypical squamous cells of uncertain significance, LSIL, or atypical squamous cell-H can be managed by 1) cytology alone in 6 months and, if negative, again at 12 months; or 2) alternatively, an HPV test in 12 months. An analysis of Atypical Squamous Cells of Uncertain Significance–LSIL Triage Study trial data (mean age 25.2 years) showed the sensitivity of these two options to subsequently diagnose CIN 2 or worse after a biopsy of CIN 1 or less severe was 88.0% and 92.2%, respectively. Close follow-up is important because there is a small risk of an undetected high-grade lesion in this group. When an LSIL biopsy is preceded by a Pap test result of HSIL, atypical glandular cells not otherwise specified or atypical endocervical cells (not otherwise specified), three options are appropriate: 1) close follow-up with cytology and colposcopy at 6 month intervals for up to 1 year provided the colposcopy is satisfactory and there is no disease in the endocervical canal and that there is no additional HSIL found on cytology or biopsy; 2) review of the cytology, colposcopy, and histopathology; or 3) diagnostic excision.[22] The last option is discouraged in young women still considering future pregnancy.

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Treatment of Women With a Histology Diagnosis of High-Grade Squamous Intraepithelial Lesion

The 2006 American Society for Colposcopy and Cervical Pathology Consensus Guidelines recommend treatment with excision or ablation for most women with a biopsy diagnosis of CIN 2 or CIN 3.[22] The new diagnosis of HSIL consists of all prior CIN 3 and p16-positive CIN 2. Consequently, the new diagnosis maps directly to the group for which treatment is currently recommended. In most cases, the new LAST Project terminology should not affect this management. The revised screening guidelines by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society of Clinical Pathology[23] and U.S. Preventive Services Task Force[24] both considered minimizing overtreatment in their revisions. By separating out lower risk patients (p16-negative CIN 2) and allowing them to avoid the potential harms of unnecessary treatment, the revised terminology takes a significant step toward optimizing patient treatment and outcomes.

The 2006 American Society for Colposcopy and Cervical Pathology Consensus Guidelines[22] identify adolescents and "young" women as a special population to be considered for conservative management of CIN 2 and CIN 2–3. Updated screening recommendations[23,24] recommend against screening adolescents. The 2006 American Society for Colposcopy and Cervical Pathology management guidelines[22] do not precisely define what constitutes a "young" woman but base their recommendations for conservative management on reports of increased risk of pregnancy complications among women with a history of a prior excisional procedure.[25–27]

In the 2006 guidelines, conservative management with semiannual cytology plus colposcopy for up to 2 years is preferred when CIN 2 is specified, and excisional treatment is recommended for CIN 3.[22] It was recognized that many pathologists already do not distinguish between CIN 2 and CIN 3 and report biopsies as CIN 2–3. The 2006 guidelines include specific recommendations for CIN 2–3 and allow either treatment or observation.[22] Observation consists of cytology and colposcopy every 6 months. If the colposcopic appearance of the lesion worsens or if HSIL cytology or a high-grade-appearing colposcopic lesion persists for 1 year, repeat biopsy is recommended. The guidelines recommend treatment for young women with CIN 2–3 if one of three conditions is met: 1) high-grade lesions persist beyond 2 years; 2) the full extent of the transformation zone is not visualized on colposcopy; or 3) the disease progresses to definitive CIN 3 or cancer. Patients can return to routine screening after normal colposcopy and two consecutive negative cytology results.

Implications of LAST Project Terminology in Young Women

The 2006 American Society for Colposcopy and Cervical Pathology guidelines manage CIN 2 and CIN 3 differently in young women.[22] The new LAST Project terminology does not differentiate these categories, so current management guidelines cannot be applied directly, leading to the need for guidance. We recommend that HSIL in young women be managed with an individualized decision for treatment or observation as per the 2006 American Society for Colposcopy and Cervical Pathology recommendations for CIN 2–3 in young women and adolescents. A preference should be given for initial observation as discussed above. Although the 2006 Guidelines do not specifically discuss treatment for patients with

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lesions progressing on colposcopic appearance, it would be reasonable to consider treatment for these women as well. If there is a parenthetical explanation (CIN 2 or CIN 3), management in young women can be per current guidelines, with CIN 3 referred for excision or ablation and CIN 2 considered for observation.

Conservative management of HSIL in young women has some risk of lesion progression (as does conservative management of CIN 2 or CIN 2–3), so the decision between treatment and observation will require individualization and clinical judgment, particularly in determining whether a patient should be considered a "young" woman and whether follow-up colposcopy suggests lesion progression. The clinician must balance the potential of loss to follow-up against the harms of overtreating lesions destined to resolve spontaneously and the potential for perinatal morbidity in women who desire future reproductive capability. Consultation with the pathologist may give the clinician more information to make a final management decision.

Rationale for Guidance

The safety of managing HSIL conservatively, even with the understanding that it involves monitoring lesions currently diagnosed as CIN 3, is supported for a number of reasons. The 2006 American Society for Colposcopy and Cervical Pathology Consensus Conference recognized that 1) a long timeframe is needed for progression of CIN 2–3 to cancer, and in young women, most HPV-associated lesions are of relatively recent onset.[28] Women typically acquire their first HPV infection shortly after the onset of sexual intercourse.[29] Most of these infections are no longer detected by 1 year,[8,30,31] and 90% "clear" by 2–3 years.[8,30,32,33] A small percentage of cervical HPV infections do progress to HSIL. Human papillomavirus–associated lesions detected in adolescents and young women mostly reflect new infections, and repeated infections are extremely common.[31,32] By contrast, positive HPV tests in older women are more likely to represent persistent infections that have had more opportunity to produce neoplastic transformation.[28] Cancer results when an HPV infection persists long enough for increased expression of the E6 and E7 oncogenes to destabilize the host DNA.[7] Although HSIL may develop over a short time period after a new HPV infection,[34] the progression from HSIL to invasive cancer typically takes years or decades.[8] Although CIN 3 has been most commonly diagnosed between the ages of 25 and 35 years,[8] the median age of diagnosis of invasive cervical cancer is 48 years.[35] In the United States, the rate of invasive cancer in women aged 20–24 years is only 1.5 per 100,000 women. The rate increases to 5.7 per 100,000 among women aged 25–30 years. Women aged 30 years and older have significantly higher incidence rates of 11–15 per 100,000 for each 5-year age group.[35] Cancer risk in young women is low compared with older women.

Data and clinical experience support the safety of short-term follow-up of young women with HSIL. Several small studies validate the safety of conservatively after CIN 2 in adolescents and young women.[32,36,37] These studies showed a 65–75% rate of regression to normal over 18 months to 3 years. Moscicki followed 95 women aged 13–24 years with biopsy-confirmed CIN 2 and found 38% reverted to negative in the first year and 63% by 2 years with only 2% and 12% progressing to CIN 3 in 1 and 2 years, respectively. None of

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the women in these small studies developed cancer.[32,36,37] There have been no studies looking specifically at the safety of short-term observation of women with CIN 3. We have routine clinical experience monitoring women with HSIL, including CIN 3, during pregnancy, in which the American Society for Colposcopy and Cervical Pathology Guidelines[22] recommend observation.[22] The length of pregnancy is short relative to the timeline for the natural history of potential malignant transformation of high-grade lesions and not much shorter than the allowable 2-year observation period in the recommendations. Many women with a diagnosis of CIN 2 or CIN 2–3 truly have CIN 3 and are being managed conservatively under existing guidelines. Long-term conservative management is clearly inappropriate. In the "unfortunate experiment" in New Zealand 1955–1976,[38] 31% of women with an average age in the mid- to late 30s with a diagnosis of carcinoma in situ (CIN 3) followed without adequate treatment developed invasive cancer. However, this occurred over a prolonged period, up to 30 years. The American Society for Colposcopy and Cervical Pathology Guidelines do not allow observation of young women with persistent CIN 2–3 to continue beyond 2 years before recommending treatment.

The inclusion of colposcopy every 6 months during the observation period adds an additional margin of safety. A lesion with colposcopic high-grade features that appears to be progressing during this observation period warrants repeat biopsies. Treatment is justified if widespread HSIL is confirmed in a large or enlarging lesion, if the entire transformation zone cannot be visualized, or, as noted, if HSIL persists for 2 years. More often, however, close follow-up will confirm resolution of both the cytologic and histologic abnormalities.

Summary Points

The College of American Pathologists and American Society for Colposcopy and Cervical Pathology cosponsored LAST Project recommends new histopathology terminology of HPV-related squamous lesions across all anogenital sites.

A two-tiered nomenclature, LSIL and HSIL, is recommended as a replacement for the former threetiered "(-IN)" terminology.

The category, IN grade 2 (eg, CIN 2) is an equivocal diagnosis of poor reproducibility that includes lesions behaving like -IN 1 and -IN 3. The project recommendations seek to clarify this equivocal category. Lesions previously diagnosed as -IN 2 should be p16-immunostained; if p16-positive, they should be classified as HSIL, and, if negative, as LSIL.

Low-grade squamous intraepithelial lesion histopathology in women should be managed with observation according to the 2006 American Society for Colposcopy and Cervical Pathology Guidelines. In general, HSIL histopathology in women should be managed with excisional or ablative treatment according to the 2006 American Society for Colposcopy and Cervical Pathology Guidelines.

High-grade squamous intraepithelial lesion in young women should be managed as per the 2006 American Society for Colposcopy and Cervical Pathology Guidelines for adolescents and young women with CIN 2–3. Either treatment or conservative management with semiannual cytology and colposcopy for up to 2 years is appropriate with conservative

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management preferred if future childbearing is a concern. Repeat biopsy is recommended if the colposcopic appearance of the lesion worsens or if HSIL on cytology persists for 1 year. Treatment is recommended if the colposcopy is unsatisfactory, if a diagnosis of HSIL (CIN 3) is made, or if biopsy-confirmed HSIL persists for 2 years. After two consecutive negative cytology and colposcopy examinations at 6-month intervals, a young woman may return to routine screening.[22]

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