**Topic:** Lower Anogenital Squamous Terminology (LAST)

**Date:** June 28, 2012

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**What are the benefits to changing terminology?**

The naming systems used for HPV-associated squamous lesions of the lower anogenital tract (LAT) have varied historically by body site, and even within medical specialties. Some terms do not reflect our current understanding of the natural history of HPV infections and precancer. When patients transfer care between health care systems, change geographic locations or clinical specialists, this variability may lead to miscommunication and misunderstanding between pathologists and clinicians, and may potentially result in patient harms. The LAST Project was conceived to align LAT terminology for HPV-associated squamous lesions with our current understanding of the similar biology and morphology of these lesions and to improve communication between pathologists making diagnoses and clinicians using these diagnoses so that patients may be managed optimally and consistently.

**Why now? Our laboratory and clinicians are working fine with what we have in place currently.**

Our understanding of HPV-associated squamous lesions of the LAT has vastly expanded in recent decades. Many terms currently used for histopathologic diagnoses do not reflect this increased understanding. The principles* underlying the Bethesda System for gynecologic cytology also apply to the diagnostic histopathology of these lesions:

- The terminology must communicate clinically relevant information from the laboratory to the patient's health-care provider.
- The terminology should be uniform and reasonably reproducible across different pathologists and laboratories, and also flexible enough to be adapted in a wide variety of laboratory settings and geographic locations.
- The terminology must reflect the most current understanding of cervical neoplasia.

*Robert J. Kurman, MD Forward to the Bethesda Atlas, 2nd edition

**How do pathologists communicate the new terms to their clinical colleagues?**

The initial means of disseminating the new terminology to clinicians will be through mailed notification to all the professional organizations that participated in the LAST Project consensus conference, anticipating subsequent communication to each organization's membership. The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations was jointly published online (June 28, 2012) in the Journal of Lower Genital Tract Disease and Archives of Pathology and Laboratory Medicine. Plans for reprinting the article in the International journal of Gynecologic Pathology are also underway. Follow up editorial commentary will be published in clinician-focused journals like Obstetrics & Gynecology and AUANews®. Editorials to cover other clinical disciplines (eg, dermatopathology, colorectal diseases) are also being planned along with a WebMD program focusing on clinicians dealing in obstetrics and gynecology. Several presentations at upcoming medical society meetings are scheduled. A PowerPoint presentation will be made available for laboratories to present the new terminology during grand rounds, etc.

**How do we distinguish between cytologic High-Grade Squamous Intraepithelial Lesion (HSIL) and a biopsy with HSIL?**
The origin of the material, tissue biopsy or excision versus cytology, can have considerable clinical implications. For example, under the current ASCCP guidelines, a diagnosis of HSIL on cytology usually leads to a colposcopic evaluation with biopsy examination. On the other hand, for a diagnosis of HSIL (cervical intraepithelial neoplasia 3 [CIN 3]) on biopsy, treatment is recommended in most circumstances.

It is very important when communicating with clinicians and patients, to distinguish the specimen type (cytology or histology) along with the specimen source (site) of lesions diagnosed as Low-Grade Squamous Intraepithelial Lesion (LSIL) or HSIL. Additionally, the LAST recommendations allow for further classification of histologic LSIL/HSIL by the applicable intraepithelial neoplasia (-IN) subcategorization.

How will clinicians manage their younger patients with CIN 2 if this is not specifically designated?
The ASCCP anticipates addressing management issues related to the change in terminology from the 3-tier cervical intraepithelial neoplasia (CIN) to the 2-tier LSIL/HSIL through a consensus process in early 2013. This FAQ page will be updated when the recommendations are published. In the interim, there are a few comments that can be made to help guide clinicians on the management of histologic HSIL. First, there is a general consensus that the term “young women”, as applied in the 2006 ASCCP guidelines, usually refers to women age 25 and younger, for in this age group progression of CIN 3 to cervical cancer is extremely rare. Other than age – a surrogate for the length of time a high-grade (HSIL) lesion has been present -- the risk of invasion is related to the size of the high-grade lesion and to its location, as lesions extending into the endocervical canal increase concern. Hence, it is reasonable to manage young women with a histologic diagnosis of HSIL on the basis of their age, and on the location and size of the lesion, rather than on the basis of an often irreproducible interpretation of CIN 2.

How will we know if patients are being treated more appropriately and not over-treated since we are now placing CIN 2 with CIN 3?
This question is inextricably tied to the preceding question (5). Optimal management of HSIL considers patient age, and lesion size and location. Additionally, laboratories have the option to qualify the 2-tier diagnosis with the appropriate intraepithelial (-IN) category in parentheses. If (CIN 2) follows the diagnosis of HSIL then the patient can be managed per the 2006 ASCCP Consensus guidelines as CIN 2. If (CIN 3) follows the diagnosis of HSIL then the patient can be managed as CIN 3. If the diagnosis is HSIL with no qualification in parentheses about the (-IN) category, there are two options: 1) The patient can be managed by current ASCCP management guidelines for CIN 2, 3; i.e. by either close observation or by treatment, depending on factors such as patient age, lesion size and location, and on the reliability of the patient to return for recommended follow-up. 2) Alternatively, the clinician may request that the pathologist further sub-classify the HSIL diagnosis utilizing the appropriate -IN category and base management on the -IN category interpretation.

Why isn’t there a category of “Uncertain or -IN-Indeterminate”? The major focus of the LAST Project was to create a histologic terminology that was biologically grounded and would hopefully lead to increased diagnostic reproducibility. Creating an uncertainty category for histologic interpretations analogous to Atypical Squamous Cells (ASC) for cytology was seen as not only counterproductive but almost impossible to define. Furthermore the use of biomarkers, as recommended by LAST, addresses resolving diagnostic uncertainty making the need for such a highly variable category a rarity.

The new terminology requires a change in our LIS system and we are unable to complete until next year. Will we be penalized?
No, there are no penalties for not converting to the updated terminology. There are no regulations which require the use of a certain set of diagnostic terms for HPV–associated squamous lesions. It is expected that, with widespread adoption, these changes will take time and many factors, including LIS capability, will impact the adoption of these new terms.

Is the terminology applicable to HPV-associated lesions of the oropharynx?
The LAST Project evaluated the literature for LAT body sites only. While the terminology may be applicable to the oropharynx, since this specific literature was not assessed, no recommendations for this site can be made at this time.

Does the terminology apply to cervical glandular lesions?
No, the LAST Project was limited to squamous lesions of the LAT. While reviewing the nomenclature of HPV-associated glandular lesions was initially contemplated, it was decided that there was insufficient time to adequately address these glandular lesions. This may be addressed in the future.

Will cancer registries collect data on HSIL in the same manner they’ve collected CIN 3 and will it impact current and future epidemiologic trends?
Cancer registries which have previously collected data from cases diagnosed as CIN 3 will need to decide, on an individual basis, if they will now collect HSIL cases that may include those previously considered CIN 2. This has clear implications for the volume of reported cases and could potentially alter the baseline conditions used in collecting prior case reports. Representatives from the Centers for Disease Control and Prevention’s (CDC) National Program of Cancer Registries (NPCR), National Cancer Institute’s (NCI) Surveillance Epidemiology and End Results (SEER) Program and the LAST Project Implications and Implementation Work Group (WG5) will continue to work toward a best solution after publication of the recommended new terminology.

Why “superficially invasive” and not “microinvasive”?
The term “microinvasive” has had a variety of definitions in various sites over the years. To avoid further terminological confusion the LAST Project is proposing that the term “microinvasive” be retired, and that the term “superficially invasive” squamous cell carcinoma (SISCCA) be adopted for invasive carcinomas which have been completely excised and are potentially amenable to conservative therapy.

How can the criteria for “superficially invasive” be different for each body site?
“Superficially invasive” squamous cell carcinomas (SISCCA) are those carcinomas which are completely excised and may be managed conservatively. The behavior or natural history of carcinomas varies by genital site. For example, the same depth of invasion at two different sites may be associated with different risks of regional lymph node disease. Consequently, the definition of SISCCA must be defined on a site-by-site basis.

How will this new terminology affect training for residents, fellows and their program directors?
The LAST Project’s consensus recommendations are likely to create a gap in the knowledge and clinical performance in residency and fellowship training programs. Training programs will need to respond by providing adequate training and communication. Since the LAST terminology is in harmony with recently published major pathology textbooks and the proposed revisions to the World Health Organization (WHO) nomenclature for LAT squamous lesions, it will be necessary to alter the training curriculum particulars to be current with the well-agreed upon state of the art consensus in this area. Evidence-based recommendations for biomarker testing will need to be included in updated clinical algorithms utilized for proper application of immunohistochemistry routinely taught in both graduate and post-graduate training settings.
How will the new terminology be asked on the boards?
The typical method by which topics appear in questions on the American Board of Pathology (ABP) examinations is for ABP trustees to solicit questions regarding new information from each ABP subspecialty test committee. The LAST Project’s consensus recommendations would be under the purview of the Anatomic Pathology Test Development and Advisory Committee. Questions regarding LAST terminology could be selected for ABP examinations within 2 years following publication.

Where in the report should lymph-vascular invasion (LVI) be stated?
LVI is not a criterion in the definition of SISCCA for most anogenital sites. LVI is a criterion solely for penile cancer and the current American Joint Committee on Cancer (AJCC) staging definition uses this parameter. Nevertheless, since LVI may play a role in the management of LAT squamous carcinomas, the presence or absence of LVI should be clearly stated in every report.

What is the definition of the perianus since clinicians from multiple specialties may be using different treatment protocols?
The perianus is defined as the region extending 5 cm from the anal opening or verge as visualized by gentle retraction on the buttocks. This region overlaps anatomically with the vulvar perineum. In women, SISCCA of the perineum should be considered part of the vulva for staging and management purposes.

Why do the recommendations specifically suggest the use of p16 as an ancillary test?
The LAST Project’s evidence-based recommendations for biomarkers was reached based on a comprehensive literature review and independent grading of the quality of the literature. At the present time, p16 has by far the most comprehensive literature. We anticipate that other biomarkers will have sufficient scientific evidence to support their use in the future. In our manuscript, we detail the circumstances where p16 should and should not be used for adjudication of HPV-associated squamous lesions. When used as recommended, p16 ancillary testing will more reliably categorize lesions as true precancers or not.

Is p16 the only recommended method of confirming HPV in tissue? Can I use another marker in conjunction with p16?
To be clear, p16 is not used as a direct HPV confirmation method. While it is accurate that in the context of a true high-grade lesion very, very few are p16 negative, many (but not all) true LSILs are HPV positive and p16 negative. p16 expression is best correlated in the context of cervical neoplasia with E6/E7 oncogene activation. Although the scientific literature is less robust, other markers like Ki-67 and ProEx™C appear to perform similarly and in rare cases they may complement the use of p16; however, their routine use adds little diagnostic discrimination with marginal gains in performance. Therefore, p16 alone is recommended when a biomarker is needed as an aid in diagnosing LAT lesions.

How will p16 use be monitored?
In practice it would be difficult to monitor the overall use of p16; however, the LAST Project’s Implications and Implementation Work Group (WG5) plans to survey CAP anatomic pathologists who interpret cervical biopsies to identify trends in current usage levels and indications for use. Follow up surveys over time will document any differences from baseline that emerge in the wake of the LAST Project’s evidence-based recommendations.

How will CIN 2 p16-positive and CIN 2 p16-negative patients be monitored in routine settings to determine if the division is clinically relevant?
In reality, we have no such monitoring systems in routine use. It is also a reality that there is no direct monitoring for the clinical relevance of CIN 2 as it is currently diagnosed without
biomarkers; however, CIN 2 is a treatment threshold and the most variable histologic interpretation. In contrast, the medical literature clearly shows that a p16-positive CIN 2 lesion is biologically more like a CIN 3 lesion than CIN 1. In addition, a biomarker-adjudicated CIN 2 is a more reproducible diagnosis than an adjudicated H&E standard. The consensus, therefore, was that such a split is a potential improvement both biologically and clinically. Further, the use of p16 to up- or downgrade difficult cases represents current practice. Results are incorporated as a final combined interpretation that is the best judgment of the pathologist and will guide the clinician in her/his management options. The specific situations in which p16 are recommended are detailed in the LAST Project’s evidence-based recommendations for biomarkers. As such, a substantial fraction of p16 negative/ CIN 2 interpretations will be downgraded to a final diagnosis of LSIL. However, the fact that a p16 stain was applied communicates that diagnostic uncertainty meriting the biomarker’s use. Clearly, it will be important to monitor CIN 2 diagnostic outcomes to try and address the question.

How will I know if a morphologically indeterminate lesion between LSIL and HSIL is a true HSIL when a large number of LSILs are p16-positive?
It is true that some morphologic LSIL cases will be p16- positive. In addition, early reports suggest that p16-positive LSIL lesions may be at increased risk for association with, or progression to HSIL. However, at the present time, the literature is inconclusive and no recommendation regarding altered management for LSIL/p16+ lesions beyond that already in place for LSIL alone can currently be made. The LAST Project’s biomarker recommendations do not recommend the use of p16 in cases of morphologic LSIL. They do indicate its use for lesions that are indeterminate between LSIL and HSIL; p16-positive cases should be classified as HSIL and p16-negative cases as LSIL. This will allow the proper classification of the majority of these indeterminate lesions and further, begs the question for future research about the ultimate fate of LSIL lesions that stain positively for p16.

What about the use of genotyping to aid in diagnosis of HPV-associated lesions?
The LAST Project’s consensus recommendations are for histologic interpretation of biopsies or resection specimens. Clinical HPV genotyping, a tool that is just really starting to take hold, is performed on cytology specimens. There are no routine, tissue based genotyping tests. Further, there are no guidelines or clinical rationales identified in the recent medical literature to support the current clinical use of such a test on tissue biopsies. Given a histologic diagnosis of HSIL (CIN 3) would you treat it differently based on genotype? If so, based on what data? While other scenarios could be discussed, currently, there is insufficient literature on the subject to merit a broad recommendation for tissue-based genotyping in routine clinical practice.

What resources are available for learning this new terminology and improving interpretations of p16 staining in LAT lesions?
The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations have clear definitions of entities, amply illustrated. In addition, separate publications are being planned for further discussion of SISCCA, intraepithelial lesions and interpretation of p16 on LAT lesions. Numerous professional meeting presentations will occur during the fall of 2012, beginning with the CAP ‘12 annual meeting. The ASCCP will host an online atlas with case presentations and a self-assessment module which will be cross referenced by the CAP and other professional organizations. Additionally, Dr. Mark Stoler will present a CAP Personalized Healthcare Committee (PHC) Webinar entitled “Biomarkers in HPV-associated Lower Anogenital Squamous Lesions” on September 27, 2012 and an algorithm chart will also be available. Download the LAST Summary of Consensus Recommendations for handy reference.