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Authors
Wilbur, David C
Darragh, Teresa M

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Harmony at LAST

David C. Wilbur, MD[1]; and Teresa M. Darragh, MD[2]

In medicine, harmony can be achieved in a number of areas: harmonization of terminology; harmonization of biology; harmonization of management for similar risk; and harmonization across similarly affected body sites. All 4 have come to fruition in the recent publication of the recommendations from the Lower Anogenital HPV-associated Squamous Terminology (LAST) Project, a joint undertaking between the College of American Pathologists (CAP) and the American Society for Colposcopy and Cervical Pathology (ASCCP).[1,2] The LAST Project arose from the need for a coordinated terminology that reflected the commonality of human papillomavirus (HPV)-associated squamous lesions, both mucosal and cutaneous, throughout the lower anogenital tracts in both sexes.

Over time, as we have learned more about these lesions and their cause, our approach to their diagnosis and management has evolved. So too, their given designations have morphed. Gynecologic pathologists used terminology reflective of their specialty's evolution, as did dermatologists, gastroenterologists, urologists, and all the other "interested" subspecialists. A plethora of divergent terms evolved, all essentially for the same entities. Advances in our understanding of the pathobiology of HPV, particularly in the last 3 decades, have shown that all these squamous sites are affected by the virus in essentially 2 ways: either as viral infection or as viral-associated precancer. Because of this divergent evolution of terms across specialties, miscommunication between pathologists and clinicians became a real problem. As patients and their clinicians crossed specialty boundaries, confusion sometimes arose concerning what entity was actually present and what management was most appropriate. Terms such as carcinoma in situ, CIN3, usual VIN, erythroplasia of Queyrat, and Bowen's disease were all used to define a single histomorphologic entity, albeit occurring at various body sites. The terms reflected the historical evolution of each specialty, rather than current understanding of the disease process.

If this scenario sounds familiar to cytologists, it should. This is essentially the same situation that gynecologic cytology dealt with during the pre-Bethesda System period. Cytologists used an assortment of jargon that often left caregivers with an incomplete understanding of the actual meaning of a Papanicolaou test result. One laboratory's Papanicolaou class 2A might not translate to another laboratory's class 2A, and what does class 2A mean after all? It is not a term that has any intrinsic biologic or site-specific meaning. Added to this was a panoply of descriptors: dysplasia, metaplastic dysplasia, euplasia, proplasia, dyskaryosis, and the list goes on and on. It was jargon, pure and simple.

Starting in 1988, with the first iteration of the Bethesda System (TBS), this terminological morass was untangled. A group of cytologists, guided by the able duo of Robert Kurman and Diane Solomon, assembled in Bethesda, Maryland, under the sponsorship of the National Cancer Institute. They commenced the task of bringing order to this bedlam, steered by 3 underlying principles that medical terminology should[3,4]:

Corresponding author: Teresa M. Darragh, MD, Professor of Clinical Pathology, UCSF/Mt. Zion Medical Center, Departments of Pathology and OB/Gyn, Box 1785, 1600 Divisadero Street, Room B618, San Francisco, CA 94115; Fax: (415) 353-7447; teresa.darragh@ucsf.edu

[1]Director of Clinical Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [2]Professor of Clinical Pathology, University of California, San Francisco, California

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1. Communicate clinically relevant information from the laboratory to the patient's health care provider.
2. Be uniform and reasonably reproducible between different pathologists and laboratories and also flexible enough to be adapted in a wide variety of laboratory settings and geographic locations.
3. Reflect the most current understanding of the disease process.

Change is difficult, and there were early detractors to TBS. Some did not like the consensus terms, possibly because they were not their familiar ones. Others thought that the 2-tiered system that TBS promoted limited diagnostic specificity, sacrificing supposedly precise diagnostic categories for better reproducibility between observers. Despite the naysayers, TBS terminology has achieved remarkable success. With refinements in 1991 and 2001, it has become the worldwide norm for the terminology and criteria used for reporting gynecologic cytology.[4] Its use has afforded more consistent studies, allowing comparison between populations, and has spawned a new generation of management guidelines directed by the principle of similar treatment for similar risk of precancer.[5–7]

Harmonization of histopathologic terminology for HPV-associated squamous lesions, based on our current knowledge, has arrived late to the standardization process, and for good reason. There are more clinical and pathology specialties involved and more body sites and more clinical management issues to consider. Cervicovaginal cytology, by comparison, is a relatively singular entity. Standardization of histopathologic terminology is a bigger task and requires a more concerted effort.

With these issues in mind, the ASCCP and the CAP Pathology and Laboratory Quality Center joined expertise in the LAST Project to embrace the task of standardizing terminology for histopathologic diagnoses of HPV-associated squamous lesions of the lower anogenital tract. Guided by the initial literature review, the LAST Project's members developed an overall approach that included cognizance of the pathology and clinical management issues associated with HPV infection, its precancerous lesions, and early invasive carcinomas. Several relevant and well-documented premises framed this multidisciplinary, collaborative effort based on our current understanding of HPV-associated disease. The foundations that grounded the LAST Project include:

1. HPV-associated squamous lesions are similar across all lower anogenital tract sites. The lower anogenital tract includes the cervix, vagina, vulva, perianus, anal canal, penis, and scrotum.
2. Our understanding of preinvasive HPV-associated squamous lesions supports only 2 conceptual divisions: HPV infection and true precancer.
3. The current intermediate category of –intraepithelial neoplasia 2 (–IN2) does not represent a true biologic entity, but rather an equivocal category with ambiguous morphology between infection and precancer. (By analogy, –IN2 is akin to the concept of atypical squamous cells [ASC] in TBS which defines a morphologically equivocal category between normal and squamous intraepithelial lesion [SIL]).
4. Pathologic diagnoses are more reproducible using a 2-tiered scheme by condensing the 3 tiers of the current histopathologic –IN classification and are made more precise with the aid of biomarkers (again mirroring the cytology process, which uses 2 tiers and HPV testing for equivocal case triage).
5. Reproducibility of morphologic diagnoses using the current 3-tiered nomenclature cannot be substantially improved by education of practitioners. The use of objective biomarkers helps reduce interobserver variability in histopathologic diagnoses.
6. The adjective "microinvasive," initially used to label an early invasive cervical carcinoma that could be treated by conservative surgical excision, has been defined in many ways with differing criteria and applied to noncervical sites. This leads to potential miscommunication between pathologists and clinicians.

With these broad premises as foundation, 5 working groups (WGs) of the LAST Project were tasked to evaluate these issues:

WG1—provide a historical review of the genesis of current terminology to frame the development of a new system;

WG2—propose terminology and criteria for preinvasive squamous lesions;

WG3—propose terminology and criteria for early invasive squamous cell carcinoma (that has the potential for conservative treatment);

WG4— propose recommendations on the usefulness of biomarkers to support and clarify diagnostic categorization, and;

WG5—develop an implementation plan to disseminate information about the proposed terminology recommendations and to monitor their penetration, impact, and effects.

Experts from diverse pathology and clinical specialties were recruited for the WGs, and they embarked on a

comprehensive literature review using appropriate keyword searches. More than 6000 articles were initially reviewed and culled down to those that presented relevant and scientifically sound studies that provided the basis of the draft recommendations. Draft recommendations were posted on the Internet for public comment and then revised if indicated; this was another lesson learned from the TBS process. In March 2012, these revised draft recommendations were presented at a consensus conference attended by representatives from 35 interested professional societies, governmental agencies, and clinical and patient advocacy groups, along with LAST Project WG members. Lively discussions ensued, and the recommendations were further refined. Final recommendations required a supermajority (two-thirds) vote for acceptance. The final consensus recommendations and commentary were then simultaneously published in the journals of both the ASCCP and CAP.[1,2] Highlights of the final recommendations from the LAST Project include:

1. The same terminology should be applied to HPV-associated squamous lesions across all lower anogenital tract sites, in males and females.
2. The terminology should have 2 tiers, true to our current biologic understanding of the disease process as HPV-infection and precancer.
3. Low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) are the preferred terms.
4. Judicious use of biomarkers can aid in the resolution of morphologically equivocal cases and mimics of HSIL.
5. The new term, superficially invasive squamous cell carcinoma (SISCCA), should apply to early invasive squamous carcinomas that have the potential to be conservatively managed. Both general criteria, applicable across all lower anogenital sites, and site-specific criteria for SISCCA were proposed. The term "microinvasive" should be retired due to its multiplicity of definitions and criteria that have been historically applied to this entity.

Most germane to the cytopathology community was the discussion among the working groups, on the Internet bulletin boards, and at the consensus conference regarding the use of the terminology of LSIL and HSIL for histopathologic specimens. These are the same terms used in TBS when the analogous biologic entities are identified in cytology specimens. Strong opinions were expressed that the terminologies for cytologic interpretations and tissue diagnoses should remain distinct. Would clinicians be able to differentiate whether an LSIL or HSIL diagnosis was from a cytologic or a histologic specimen? The initial clinical management could be different in such circumstances. Alternative histopathologic terms, such as "low-grade and high-grade squamous dysplasia" or "squamous intraepithelial neoplasia (SIN)" were proposed. The latter was immediately discarded due to its unfortunate and pejorative acronym. The prime argument for using terminology analogous to cytology was that similar biologic entities should have the same name. This viewpoint prevailed, and the LSIL-HSIL terminology won the consensus vote. On the basis of this outcome, one could add another harmony associated with the LAST Project: harmonization of cytologic and histologic terminology.

As mentioned previously, TBS was not embraced initially by all. Yet, its widespread adoption has ultimately resulted in substantial benefits, bringing a standardized terminology and interpretative criteria that are applied worldwide. It took years for this to occur. Adoption of the LAST Project's recommendations will undoubtedly follow a similar initial course. Elimination of –IN2 as a diagnostic category may cause some consternation in the clinical community that relies on differential management for –IN2 and –IN3, particularly for younger women who have cervical disease. However, the literature supporting the LAST recommendations show that –IN2 is a mixture of LSIL and HSIL, and probably represents morphologic mimics of HSIL, exuberant manifestations of LSIL, or undersampled or small HSIL lesions.[1,2]

The ASCCP guidelines already have protocols for conservative management of –IN2 and –IN3 in younger women.[8] Addition of biomarkers to further clarify equivocal cases should result in more accurate and consistent diagnoses and subsequently, more appropriate patient management. At least during this transition period to the new terminology, some clinicians may continue to rely on subclassification of HSIL into –IN2 or –IN3 to assist with management decisions. Weaning from the false premise of the diagnostic reliability of –IN2 will take time, and realizing this, the final recommendations allow this option. Cytologists may remember the similar history for the first generation of TBS. Initially, most cytologists qualified cytologic HSIL as favoring –IN2 or –IN3. However, with time, most have dropped the –IN designation and clinicians have become comfortable with the 2-tiered nomenclature of LSIL and HSIL without qualifiers for

cytology. Conceivably, the same will occur with the LAST Project's recommendations.

As members of the LAST Project steering committee, the authors readily acknowledge that a 2-tiered terminology for histopathologic specimens is not new. Indeed, many pathologists at the LAST consensus conference stated that they have been reporting histopathology cases using a dichotomous system for years and indicated that clinicians in their practices are well-accommodated to it. Others reported already using the same terminology of LSIL-HSIL for both cytology and histopathology. In fact, major textbooks in gynecologic pathology have already espoused the use of a 2-tiered system of reporting for histopathology.[9,10] The LAST process has, however, codified this terminology via an open forum, based on a scientific literature review, and consensus vote by participating organizations.

The LAST Project also made a novel contribution with its recommendations for the appropriate use of biomarkers in HPV-associated squamous lesions of the lower anogenital tract. These recommendations were based on its extensive literature review and strength of the evidence. Because of the ramifications of these biomarker recommendations, an independent review of the quality of the literature cited was also obtained and confirmed the WG's findings. At the consensus conference, concern was raised about potential overuse or misuse of biomarkers based on the recommendations, and hence, in addition to recommendations for use, recommendations against use were also made. The biomarker p16 was the only test with sufficient evidence in the literature to warrant recommendations for routine use. It is a cellular antigen that is overexpressed in altered cell cycle events, most commonly and universally in HPV-associated precancers. To our knowledge, these are the first scientific literature-based consensus recommendations for the use of p16 in lower anogenital tract HPV-associated lesions. Other biomarkers, such as Ki-67 and ProEx C had similar trending data in the literature, but the data were of insufficient quantity to support independent recommendations for their routine use, at present. The WGs felt that their use could be warranted in cases in which p16 was unavailable or technically inadequate. Just as TBS evolved between 1988 and 2001, the LAST Project recommendations may need to be adjusted as additional data and new biomarkers become available.

Overall, the LAST recommendations do for histopathology what TBS did for cytopathology. The LAST Project recommendations align terminology across all lower anogenital tract sites with our current knowledge of HPV biology, acknowledge the lack of reproducibility of our current 3-tiered system based on hematoxylin and eosin staining morphology alone, provide guidance on the use of ancillary testing that generates more objective and reproducible diagnoses, and offer a uniform definition and criteria for superficially invasive squamous cell carcinoma.

Harmony is here at last for cytopathology and histopathology. It is hoped this will be the beginning of a trend linking biology with medical terminology in other areas. Plans are already underway for a similar harmonization of terminology for head and neck HPV-associated squamous lesions. As we continue to gain more insight into disease processes and fully enter the age of molecular medicine, perhaps other areas relying on outdated and potentially confusing terminology will follow.

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CONFLICT OF INTEREST DISCLOSURE

David C. Wilbur is a shareholder in Merck (less than $10,000). Teresa M. Darragh has received research supplies for anal cytology for Hologic, and has been on the advisory board of OncoHealth.

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