Abstract: The classification of cervical precancers has evolved over the past 40 years as knowledge concerning the pathogenesis of these human papillomavirus-related lesions has expanded. This commentary reviews the current classification scheme in light of (1) the historical classification systems and (2) the ability of the target epithelium, that is the transformation zone to exhibit varied morphology depending on the cell type that is infected with human papillomavirus. The evolution in our understanding of preinvasive glandular neoplasia is also summarized, with particular attention to so-called superficial (or early) adenocarcinoma in situ. In addition, practical issues in the diagnosis and management of squamous epithelial lesions, particularly the recognition of nonconventional variants and the application of biomarkers, are discussed.

Key Words: HSIL, LSIL, HPV, adenocarcinoma in situ

The concept that invasive squamous cell carcinoma of the cervix is preceded by a morphologically identifiable noninvasive precursor, whether identified by histology or cytology, has long been established. In fact, the observation by Dr Papanicolaou that precursor lesions could be cytologically detected through the examination of vaginal smears dates to the early 1940s. However, despite the wide acceptance of the existence of a precancerous lesion, terminology has varied and at least 3 classification systems have been proposed, including (in order of their inception): (1) dysplasia-carcinoma in situ (CIS), (2) cervical intraepithelial neoplasia (CIN), and (3) squamous intraepithelial lesions (SILs) also known as the Bethesda (binary) system.

In the first half of the 20th century, the term CIS was widely used, because lesions classified as such were shown to confer an increased risk of subsequent invasive carcinoma in limited followup studies. The first well established CIN classification in which CIS was distinguished from dysplasia (ie, lesions with less atypia) came to prominence in the 1960s after its proposal by the International Committee on Histologic Terminology for Lesions of the Uterine Cervix. In their proposal, the committee offered histologic criteria for distinguishing CIS from dysplasia, which in turn allowed clinicians to temper their management of the patient based on the presence or absence of CIS. However, this proposal was soon fraught with a number of concerns, most of which challenged the concept that dysplasia and CIS could be considered (and reproducibly distinguished) as separate entities. Some of the observations that led to these concerns included: (1) dysplasia and CIS share similar genetic abnormalities, (2) lesions classified as severe dysplasia that have morphologic overlap with CIS are also at risk for progression to invasive carcinoma, (3) patients with lesions classified as dysplasia have a 20-fold increased risk for CIS than patients with normal Papanicolaou smears, CIS or carcinoma is detected in up to 40% of smears subsequent to a smear containing mild or moderate dysplasia and (5) in patients with a cytologic diagnosis of dysplasia, there is a 100-fold increased projected incidence of invasive carcinoma as compared to women with normal smears. As a direct result of these observations, the CIS-dysplasia classification was replaced by one that merged dysplasia and CIS into one category—CIN—defined as a full-thickness population of atypical cells subdivided according to degree of atypia and maturation.

In 1955, Koss and Durfee observed that some squamous atypias exhibited nuclear atypia in the surface epithelial cells only, and termed these lesions “koilocytotic atypia.” Twenty years later, the viral pathogenesis of cervical precursor lesions began to gain credibility with the direct demonstration of human papillomavirus (HPV) in koilocytotic atypia, prompting the alternate term of flat or exophytic condyloma of the cervix. HPV 16, was soon cloned, and found in a high percentage of squamous carcinomas and CIN. Other cancer-associated HPV were subsequently cloned, and found in flat cervical condyloma and CIN. Approximately 70% of flat condylomas contained high-risk HPVs, but were segregated with greater efficiency from CIN by HPV16, which was associated with CIN in about 85% of infections that produced a morphologic abnormality, and which was found 4 to 5 times more frequently in CIN. Because HPV infections caused both CINs (as traditionally defined) and flat and exophytic condylomas, some confusion followed regarding the classification of...
lesions that had a common origin but did not fall within the classic definitions of a cervical cancer precursor. Some authors chose to separate flat condyloma from CIN I, others chose to assign the term “CIN I” to flat condyloma, and reserving CIN II and CIN III for those lesions that fell into the traditional CIN classification. This evolution of terminology was not a smooth one, hampered in part by the fact that many pathologists could not consistently distinguish CIN or condyloma from non-neoplastic epithelial alterations.

In 1988, a conference sponsored by the National Cancer Institute proposed classifying cervical precancers into 2 categories in cytologic practice—low and high-grade squamous intraepithelial lesions (HSILs)—which became known as the Bethesda System for classifying cervical precancers. In this classification scheme, lesions formerly considered CIN I were merged with condyloma into the low-grade group whereas lesions formerly classified as CIN II or III were merged into the high-grade category. Two criticisms quickly emerged after the introduction of this classification system: (1) although condyloma and CIN I can share a similar cytologic appearance, they differ in their classic (or original) histologic description and (2) the apparent differing risk of progression to invasive carcinoma for CIN II as compared to CIN III. This latter concern posed less of a challenge to overcome, as both CIN II and CIN III are similarly associated with high risk HPV. Moreover, the distinction between these 2 grades has been shown to have poor reproducibility among pathologists although either designation elicits the same therapeutic (ablative) outcome, rendering this separation less important. By redefining CIN I as only those lesions that fulfill morphologic criteria for flat and exophytic condyloma, the former concern could also be addressed. In doing so, this revision of the Bethesda system, which is the current accepted classification system, would allow a category, CIN I, to identify a process that could, with good reproducibility, be distinguished histologically from higher-grade lesions with a greater risk of progression to invasive carcinoma. Based on the illustrations in a number of textbooks and reviews, low-grade squamous intraepithelial lesions (LSILs) now typically include those lesions left out of the traditional CIN classification, and overlapping with some lesions traditionally classified as CIN I, whereas high grade SILs, are well within the upper part of the spectrum of traditional CIN II or III (Table 1).

The practitioner who applies the current criteria for LSIL and HSIL must be able to navigate the variables that impact on morphologic presentation, including the transformation zone and intervening conditions that produce abnormalities in epithelial growth and differentiation. These are discussed below.

**THE TRANSFORMATION ZONE**

Although the revised Bethesda classification scheme depicts a traditional pattern of squamous alterations secondary to HPV infection, it is clear that there is a morphologic spectrum of cervical epithelial alterations some of which are not encompassed by this system. This spectrum of morphologic alterations likely reflects the plasticity of the epithelium that may be infected, as the epithelium that comprises the transformation zone can show differences in their differentiation level and differences in their differentiation pathway (Fig. 1). Reserve (or indifferent) cells within the transformation zone may differentiate toward squamous, columnar, or a combination of phenotypes, which when infected by HPV can account for a similar morphologic range of lesions including mature and immature squamous (eg, mature LSILs, immature condyloma, immature “metaplastic” HSILs), columnar [adenocarcinoma in situ (AIS)], or a combination (stratified mucinous intraepithelial lesions). Therefore an understanding of the range of normal phenotypic expression of cervical epithelium helps

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**TABLE 1. Categories of CIN**

<table>
<thead>
<tr>
<th>SIL</th>
<th>Classification</th>
<th>Descriptor</th>
<th>Other Terms</th>
<th>HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL</td>
<td>Exophytic condyloma</td>
<td>CIN I</td>
<td>LR</td>
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<tr>
<td>Flat condyloma</td>
<td></td>
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<td>HR</td>
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<tr>
<td>Immature condyloma</td>
<td>Papilloma</td>
<td>Transitional papilloma</td>
<td>LR</td>
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<tr>
<td>CIN I</td>
<td></td>
<td></td>
<td>HR</td>
<td></td>
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<tr>
<td>HSIL</td>
<td>Atypical condyloma</td>
<td>Koliocytotic CIN II</td>
<td>HR</td>
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<tr>
<td>CIN II</td>
<td></td>
<td></td>
<td>HR</td>
<td></td>
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<tr>
<td>CIN III</td>
<td></td>
<td></td>
<td>HR</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic dysplasia</td>
<td></td>
<td>CIN II</td>
<td>HR</td>
<td></td>
</tr>
<tr>
<td>Atypical immature metaplasia</td>
<td></td>
<td>CIN II and III</td>
<td>HR</td>
<td></td>
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<tr>
<td>SMILE</td>
<td>Adenosquamous CIS</td>
<td></td>
<td>HR</td>
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</table>

HR indicates high risk; LR, low risk.

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**FIGURE 1.** A, Reserve cells in the cervical transformation zone, associated with a focus of microglandular hyperplasia (top) and established between columnar epithelium (bottom). B, Transition from reserve cells to squamous metaplasia in an evolving microglandular hyperplasia (bottom).
explain the varied differentiation level (mature vs. immature) and differentiation state (squamous vs. columnar) of the diverse number of cervical precancers lesions that may occur.

SQUAMOUS LESIONS

The Threshold for LSIL

Distinguishing LSIL from non-HPV–related conditions of the cervix has been an issue in practice since the early 1980s when HPV was first associated with early cervical neoplasia. The consequences of an over-diagnosis of LSIL (then referred to as condyloma or CIN I) were not trivial, inasmuch as the patient was often informed that she had a sexually transmitted disease and in the eyes of some practitioners, required an ablative technique, such as cryotherapy or carbon dioxide laser, to remove the lesion. Similar lesions in the vagina were routinely managed with topical applications of 5-fluoro-uracil, an approach that could lead to chronic dyspareunia if carried out too aggressively. Such complications mandated a morphologically definable and reproducible threshold for LSIL. With the advent of LEEP excision in the 1990s, LSIL was increasingly managed more conservatively, and a recent study suggests that the woman with an abnormal smear (ASCUS or LSIL) has a similar risk of HSIL at 24 months (11% to 13%) irrespective of whether the pathologist recognizes LSIL in the biopsy. Nonetheless, an accurate distinction of LSIL from normal or reactive mucosa is important to avoid misclassification of an sexually transmitted disease and provide reliable diagnostic information to the clinician.

FIGURE 2. Mimics of LSIL include (A) mild disturbances in maturation associated with reactive changes, (B) cytoplasmic halos, and (C) dyskeratosis. Panel (D) contains a subtle LSIL for comparison.
The strongest correlate for the presence of HPV was superficial nuclear atypia in the form of koilocytotic atypia. However, other parameters are helpful and the following approach to the diagnosis of LSIL facilitates its recognition as well as allows its separation from potential mimics such as nonspecific cellular changes due to disturbances in maturation or inflammatory-related cellular changes.

One of the earliest indications that a cervical epithelial alteration represents an LSIL is the presence of alterations in the low power appearance of the epithelium in comparison to adjacent normal, which may include increased nuclear density near the surface, abnormal surface keratinization with increased eosinophilia of the cytoplasm, conspicuous superficial nuclear atypia, and alterations of the epithelial thickness (Fig. 2). Low power suspicion requires high power confirmation with an assessment of the type, degree, and location of nuclear atypia. LSILs are characterized by nuclear atypia in the upper portion of the epithelium with lack of a high mitotic index (and atypical mitotic figures), lack of atypia in the lower epithelial layers (basal and parabasal), and maintenance of cellular polarity (particularly at the base). The HPV-related nuclear changes typically present in LSIL show alterations in size and staining of the affected epithelium, with the nuclei showing at least a 3-fold difference in size and variable degrees of hyperchromasia. Other findings, though not specific, are often helpful in confirming the diagnosis when present in association with the aforementioned histologic features. These include cytoplasmic halos of irregular size and shape and binucleated cells with enlarged, hyperchromatic nuclei, the latter occurring in greater than 90% of LSIL. It is important to remember that binucleation is nonspecific and may occur in association with reactive epithelial changes; however, if there are multiple binucleated cells that have enlarged, hyperchromatic nuclei in a given high power field, this strongly supports the diagnosis of an LSIL. Cytoplasmic halos are also a nonspecific feature, however, those associated with LSIL are usually irregular in shape and size and surrounded by a rim of hypereosinophilic cytoplasm that imparts a basket weave appearance in contrast to the halos of reactive epithelium, which typically lacks these features.

**LSIL and its Variants**

The diagnosis of LSIL carries with it a significant responsibility. In making this diagnosis, the pathologist is essentially stating that the patient does not require a return visit for the next 12 months. The cytology should match the biopsy; if an HSIL is suspected, a repeat colposcopy may be required.

The diagnosis of LSIL should be reserved for a select group of entities within a narrow spectrum of histologic changes. The fundamental premise for this diagnosis is the absence of atypia that confers a diagnosis of HSIL (CIN II or III) or its variants. Another useful perspective is to require the presence of cells in the epithelium which, taken in a cytologic context, merit classification as LSIL. Given this, LSIL can be divided into 4 morphologic subsets: (1) condyloma acuminatum (exophytic condyloma), (2) immature condyloma (squamous papilloma, papillary immature metaplasia), (3) flat condyloma (CIN I), and (4) flat lesions with surface atypia and inconspicuous halos (also termed CIN I). Exophytic condyloma (Fig. 3), which is highly associated with HPV types 6 and 11 and is relatively uncommon in the cervix, is characterized by verruciform growth, blunt-shaped papillae, acanthosis, and superficial koilocytotic atypia (viral cytopathic effect). Immature condyloma (Fig. 3) is characterized by slender, filiform papillae lined by squamous epithelium only showing slight nuclear crowding and mild superficial koilocytotic atypia mimicking immature metaplasia. The relative lack of koilocytotic atypia reflects the dependence of viral cytopathic effect on maturation, which is limited in these lesions; however, similar to exophytic condyloma, immature condyloma is associated with HPV types 6 and 11, which supports its classification as a type of condyloma.24,25 As lesions described as papillary immature metaplasia and squamous papillomas are histologically identical to immature condyloma and also contain HPV types 6 and 11, the term immature condyloma not only best reflects their pathogenesis but will also result in the appropriate clinical response.24,25 Flat condyloma (CIN I) lacks an exophytic growth pattern but is otherwise morphologically similar to condyloma acuminatum with atypia confined to the upper third of the epithelium (Fig. 3). As these lesions are usually associated with HPV types that confer an intermediate or high risk, they are considered separately from immature and exophytic condyloma.14,26

Some LSILs have the mild parabasal hypercellularity of flat condyloma, and exhibit increased nuclear density in the upper epithelial layers with anisokaryosis, yet lack the prominent cytoplasmic halos. Purists would not classify these as flat condyloma because of the absence of koilocytosis, and might prefer to use the term CIN I. Nevertheless, the appropriate diagnosis from a management perspective is LSIL.

**Distinguishing LSIL From HSIL**

The distinction of LSIL from HSIL is one of the most important decisions in the laboratory management of precursor lesions. A verdict of LSIL will result in a followup evaluation in 12 months. In contrast a diagnosis of HSIL will set into motion a chain of events eventuating in (often) an appointment to day surgery, anesthesia, and a cone or LEEP excision. For this reason, the practitioner should be wary of overdiagnosing CIN II. If the pathologist is unsure whether to make a diagnosis of LSIL or HSIL, a second opinion from a colleague is recommended, inasmuch as the decision will have significant impact on the immediate plans of the patient in question. This is particularly important in young patients, who are at a low short-term risk for an adverse (cancer) outcome, often revert to normal, and may rarely suffer adverse sequelae (cervical incompetence) from LEEP or cone biopsy. In these patients particularly, the pathologist...
should be certain of his or her diagnosis; if not, uncertainty in lesion grade should be communicated to the clinician.

It is not uncommon for the basal and parabasal area of an LSIL to exhibit increased cellularity and some degree of nuclear enlargement, particularly in those lesions that are inflamed. In such cases, distinction from an HSIL may be particularly difficult as this separation is based on the assessment of atypia and epithelial organization in the lower epithelial layers. If there is no loss of cell polarity and the nuclei in the lower layers show only minimal nuclear pleomorphism and lack coarse chromatin, then the lesion is best classified as an LSIL.

The diagnosis of HSIL is based on atypia in the lower epithelial layers that exceeds the threshold for LSIL/condyloma, that is the cells contain a high nuclear/cytoplasmic ratio and coarse-appearing chromatin. Lesions with full-thickness atypia and surface maturation (often discernible as koilocytotic atypia or abnormal keratinization) correspond to lesions classified as CIN II whereas those with little to no maturation correspond to CIN III (Fig. 4). Additional features that aid in distinguishing LSIL from HSIL are: (1) lack of nuclear atypia in the lower epithelial layers, (2) fewer number of mitoses, which when present are confined to the basal and parabasal areas, (3) maintenance of cell polarity (particularly at the base of the epithelium which is often disorganized in high grade lesions), and generally, (4) lack of abnormal mitotic figures. As a rule of thumb, if cells are present in the lower epithelial layers that would merit the diagnosis of HSIL on cytology, a diagnosis of HSIL should be strongly considered.

As implied earlier, this classification system differs from the classic descriptions of CIN in the 1960s, which required full-thickness atypia for all CIN diagnoses. However, as flat and exophytic condylomata are now

![FIGURE 3. Morphologic spectrum of LSIL, including (A) exophytic condyloma, (B) flat condyloma (or CIN I, and (C) immature condyloma. The immature cell layers of the latter exhibit uniform nuclei and small chromocenters (Panel D).](image)
incorporated into the family of intraepithelial lesions, the classification has been altered somewhat to equate flat condyloma with CIN I. In equating the two, we now use similar criteria for their diagnosis, and designate all lesions with full-thickness atypia as either CIN II or III (HSIL).

Nonconventional SIL Variants

Most of the aforementioned subsets SIL fall into the well-described continuum that is depicted in most textbooks. In this system the distinction of LSIL from HSIL is usually relatively straightforward and the transition from the former to the latter is marked by the criteria outlined above. However, the reader has likely encountered a wider range of abnormalities than illustrated so far in this review, because of the plasticity of the transformation zone and the fact that both high and low risk HPVs can infect a range of cells, including from the mature portio, reserve cell, columnar cell, and cells in transition between the two. The following list designates each group by its proposed cell of origin and HPV category.

Immature metaplasia and low risk HPV: This results in the immature condyloma (LSIL) discussed above, by infection of immature squamous metaplasia with HPV 6 or 11 (Fig. 3). Immature metaplasia and high risk HPV: This results in HSIL with an immature metaplastic phenotype. These lesions are expansile proliferations in which the cells lack normal maturation, have abundant eosinophilic cytoplasm with distinct cell membranes, distinct nucleoli, a modest increase in nuclear to cytoplasmic ratio and focal nuclear dysplastic features with mild nuclear enlargement, hyperchromasia and irregular nuclear membrane contour (Fig. 6A). These lesions are commonly associated with an adjacent conventional appearing HSIL or LSIL and are commonly associated with intermediate HPV.

FIGURE 4. Morphologic patterns spanning LSIL and HSIL (CIN II). A, LSIL with mild parabasal nuclear enlargement, (B) a problematic lesion with many features of LSIL but containing an abnormal (tripolar) mitotic figure. C, CIN II (HSIL) containing koilocytic atypia and parabasal nuclear crowding and atypia.

FIGURE 5. HSIL with an immature metaplastic phenotype. Note the focal basal nuclear enlargement and preservation of columnar cells on the surface.
or high-risk HPV types, they likely represent a variant of HSIL. As the epithelium that comprises the transformation zone can show differences in their differentiation level and differences in their differentiation pathway, it is conceivable that this lesion’s unusual morphologic appearance is due to HPV infection of target cells in the transformation zone with a phenotype of intermediate differentiation between immature and mature epithelium.

(3) SIL occurring in the setting of microglandular change. This is an uncommon lesion characterized by its close resemblance to squamous metaplasia involving microglandular change. It is composed of a lobulated proliferation of squamous epithelial cells that are evenly spaced with moderate nuclear density and a low mitotic rate, which may be admixed with mucin droplets but which also show prominent nuclear enlargement and multinucleation (Fig. 6B). These lesions are often associated with high-risk type HPV, are best classified as “SIL of uncertain grade,” and are distinguished from early metaplasia by conspicuous anisokaryosis, albeit with a low mitotic index.

GLANDULAR LESIONS

Early (Superficial) AIS

The majority of adenocarcinomas in situ are easily recognized by a constellation of findings, including discrete clusters of glandular epithelium with hyperchromatic nuclei, increased mitotic index and karyorrhexis. However, a subset of AIS occurring in younger women may be diagnostically challenging. Witkiewicz et al recently described a series of these lesions that were found on the surface mucosa or in papillae. This entity which was termed superficial or early AIS, presented in younger women, exhibited a variable degree of hyperchromasia, mitotic activity, nuclear atypia, and karyorrhexis, yet were strongly positive for p16 and contained HPV nucleic acids in a dot-forming or “integrated” localization pattern. This entity underscores the subtle nature of some AISs yet emphasizes that these lesions share all of the biologic attributes of conventional AIS. For this reason, we do not use the term “glandular dysplasia” for these subtle lesions but rely more heavily on biomarker staining in problematic cases (Fig. 7).

Stratified Mucin-producing Intraepithelial Lesions

Most HSILs exhibit minimal columnar differentiation and most mucin detected in these lesions is contained within normal columnar cells displaced to the surface of the lesion as it undermines normal mucosa. However, an uncommon precursor variant exhibits both the stratification of an HSIL and discrete mucin production in all layers of the epithelium. This entity, which has been termed “stratified mucin-producing intraepithelial lesion” or SMILE, frequently coexists with both HSIL and AIS and immunophenotypically is more consistent with a stratified variant of AIS. In limited numbers of cases, it has been found to frequently coexist with invasive carcinoma, usually with an “adenosquamous” pattern of differentiation (Fig. 7). Our approach in practice is to classify SMILE as such, specifying that it is most likely a variant of AIS. The management of SMILE is identical to AIS, which is cone biopsy to ensure complete removal and exclude invasive carcinoma.

BIOMARKERS FOR DIAGNOSIS

Recognition and correct classification of cervical precancers is clinically relevant as management is based upon both the presence and type of cervical SIL. Although in most cases the diagnosis is straightforward, some inflammatory-related atypias and disturbances in maturation may mimic a SIL. Conversely, as discussed above, some SILs may be subtle and less conspicuous on histologic examination rendering them difficult to confirm. In these instances, application of certain biomarkers may be useful in supporting or refuting one’s histologic impression. The biomarkers that are most useful in daily practice are proliferation marker Ki-67 and cell cycle marker p16, the latter acting as a surrogate marker of HPV infection as HPV oncoproteins produce...
disturbances in the cell cycle that result in overexpression of this protein.\textsuperscript{31,32} As a general rule, these biomarkers are useful in identifying whether or not a SIL is present and are not useful in assigning a grade, high versus low, for cervical precancer disease. In contrast to normal, atrophic, or reactive squamous epithelium, Ki-67 will show positive nuclear staining in the upper epithelial layers of a SIL, typically in greater than 30\% of nuclei (Fig. 8). p16, which is strongly expressed in lesions associated with intermediate and high risk HPV will exhibit diffuse nuclear and cytoplasmic reactivity in both LSIL and HSIL in contrast to reactive or immature metaplastic proliferations (Fig. 8). Therefore, confirmation of a SIL can be made when both Ki-67 shows increased staining in the upper epithelial layers and there is diffuse p16 positivity throughout the epithelium. The same markers are useful for confirming AIS, taking into account the comments below.

The practitioner who uses these biomarkers must be cognizant of the following:

1. p16 will stain columnar epithelium, including endometrium and lower uterine segment.
2. Ki-67 is particularly difficult to interpret in the setting of partially denuded inflamed epithelium.
3. Neither marker should be used routinely to distinguish LSIL from reactive squamous epithelium. The distinction of the two is not usually clinically relevant, notwithstanding the importance of precise diagnosis in general.
4. p16 is most useful for distinguishing immature metaplasia from HSIL; Ki-67 for distinguishing atrophic changes from HSIL.
5. Both markers should be used concurrently until the practitioner is comfortable with one or the other.

**FUTURE CONSIDERATIONS IN PRACTICE**

Management of CIN II in young women and the role of HPV: There is increasing emphasis on avoiding unnecessary ablative procedures, particularly in young women, and the target of these efforts will be the changing clinical approach to CIN II. In our experience, CIN II is more likely to harbor so-called “intermediate risk” (or those on the lower end of the high risk spectrum) HPVs. In view of the much weaker association between these HPVs and the development of CIN III and their association with cancers of lower mortality, there is a rationale for following young women with CIN II rather than resorting to cone biopsy. This applies in particular to women under age 20. It is conceivable that biopsies with this diagnosis (or their concurrent smears) could be tested for HPV and managed with LEEP or followup according to HPV type.
CIN in the vaccine era: The widespread use of vaccines will theoretically reinforce the above approach as the percentage of CINs with a higher rate of progression decrease and efforts are increased to reduce the proportion of CINs that require ablation. This process will change the relative roles of HPV testing, cytologic screening, and biopsy-directed management. Although the impact of vaccines will take years to be realized, the prospect and anticipation of their success will very likely inspire novel approaches to management designed to enrich for both patients at risk (who will be treated) and those with minimal risk (who will be followed). Under ideal conditions, the latter will expand over time and with it, a progressive reduction in biopsies and ablative procedures.

REFERENCES
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FIGURE 8. SIL with a metaplastic growth pattern (A) AIS (B) and immature condyloma (LSIL; C), respectively stained for p16 (D–F) and MiB1 (G–I).