

Challenges in GYN Cytology - Dealing with Uncertainty -

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The willingness to
consider possibility
requires a tolerance
of uncertainty

Rachel Naomi Remen

Uncertain / Equivocal

- Open to more than one interpretation
- Considering 2, often opposing, diagnoses

Keywords: cervical cancer; screening; cervical cytology; HPV immunisation; colposcopy

HPV immunisation and cervical screening—confirmation of changed performance of cytology as a screening test in immunised women: a retrospective population-based cohort study

T J Palmer^{*,1}, M McFadden², K G J Pollock³, K Kavanagh⁴, K Cuschieri⁵, M Cruickshank⁶, S Cotton⁶, S Nicoll⁷ and C Robertson⁴

- The PPVs of high-grade dyskaryosis for both CIN2+ and CIN3+ reduced in fully immunised women by 16% and 14% respectively

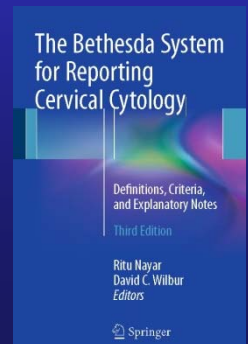
Common Equivocal Diagnoses

- Diagnostic decision making is often based on weighing the criteria for 2 distinct diagnoses

	DDx1	DDx2
Atypical squamous cells - undetermined significance	Negative	LSIL
Atypical squamous cells – cannot exclude HSIL	Negative	HSIL
LSIL, cannot exclude HSIL	LSIL	HSIL

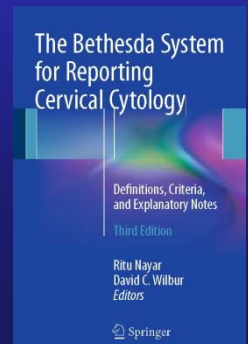
Atypical Squamous Cells

- ASC-US
 - changes that are suggestive of LSIL but are insufficient for a definitive interpretation
 - although suggestive of LSIL, the qualifier “undetermined significance” is preferred because ~ 10–20 % of women with ASC-US have an underlying HSIL



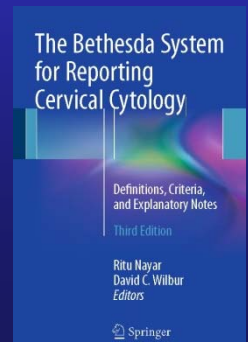
Atypical Squamous Cells

- ASC-H
 - minority of ASC cases (<10% of ASC)
 - changes that are suggestive of HSIL but are insufficient for a definitive interpretation
 - PPV for predicting HSIL on biopsy
ASC-US < ASC-H < HSIL



ASC-H

- ASC-H cells are usually sparse.
- Several patterns including
 - atypical immature metaplastic cells
 - crowded sheets of cells
 - markedly atypical repair
 - severe atrophy
 - post-radiation changes



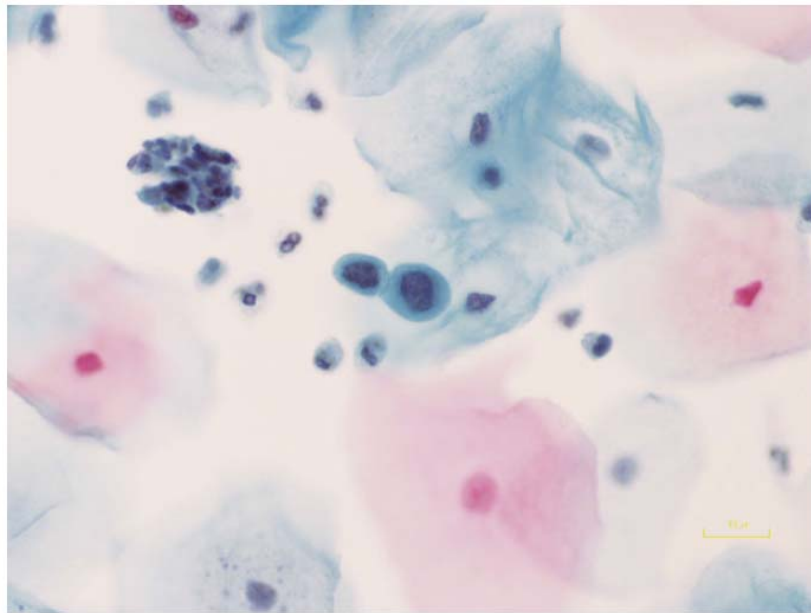
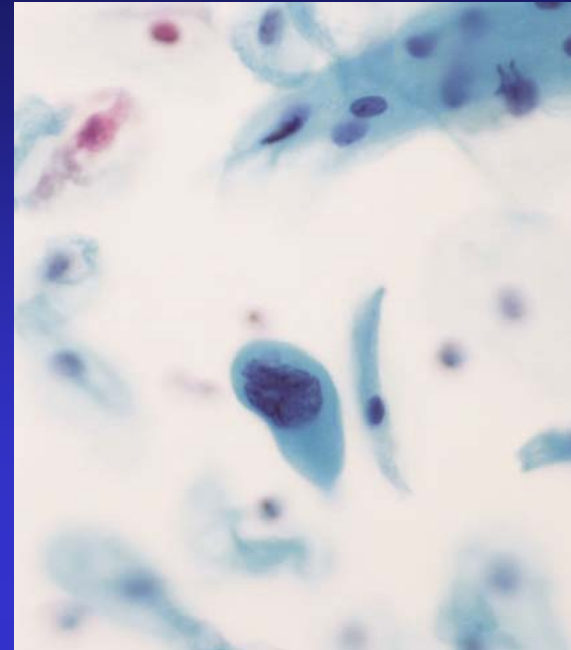
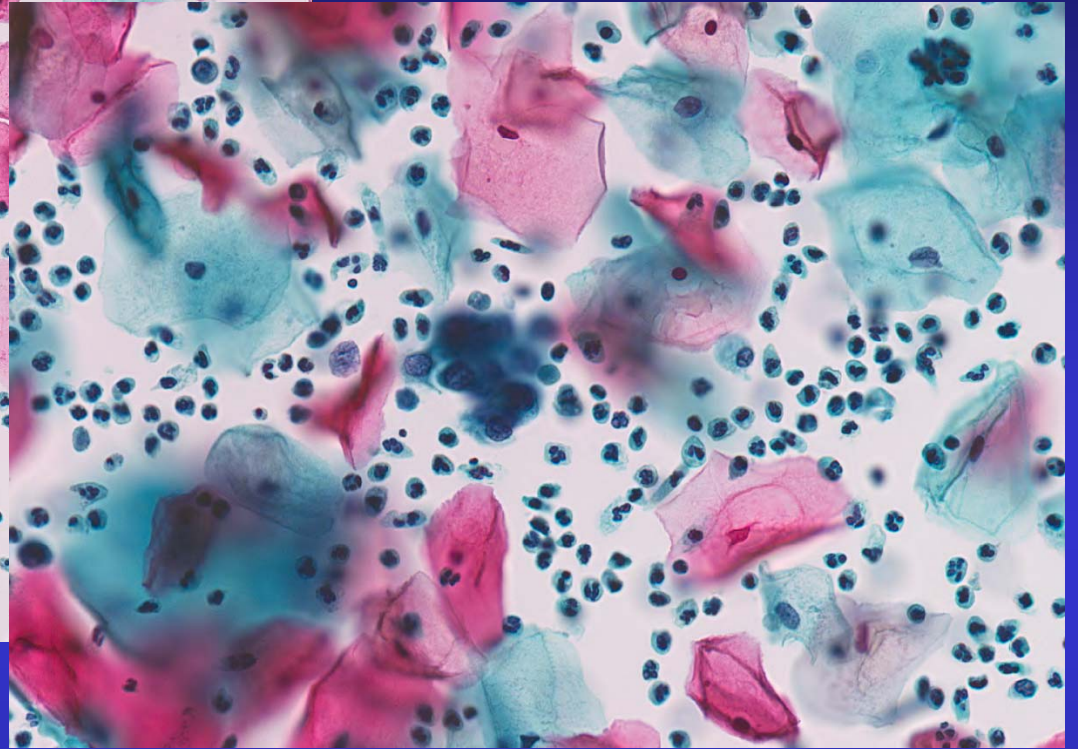
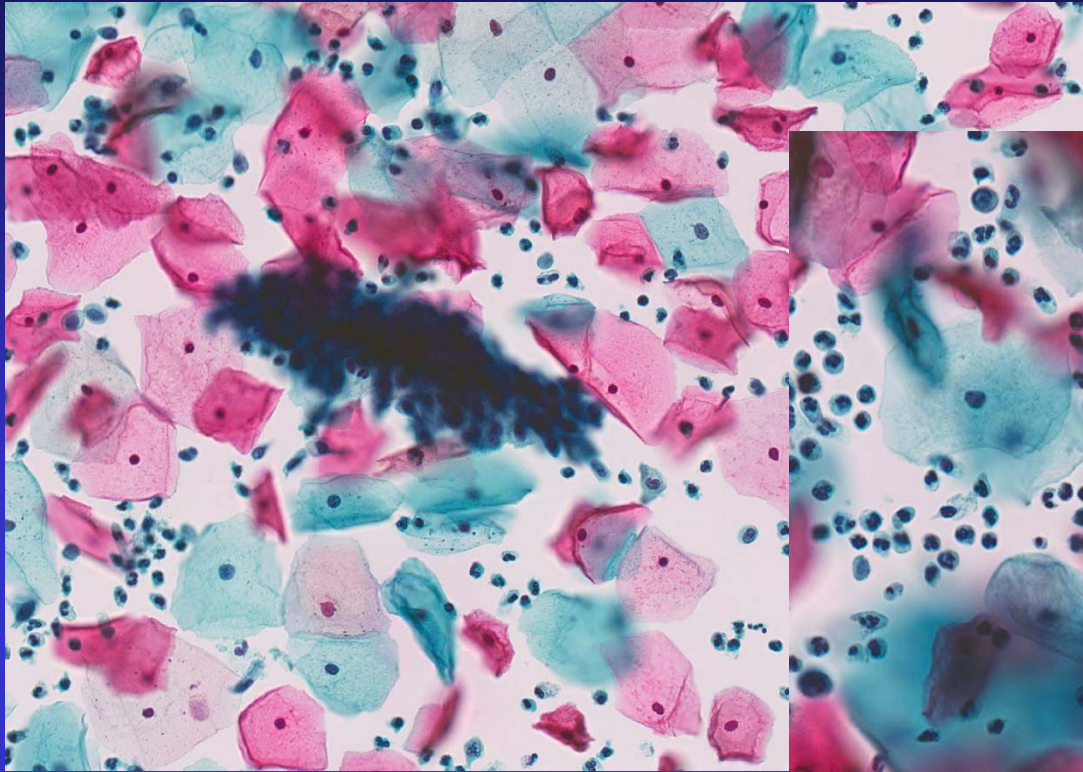


Fig. 4.21 ASC-H (*LBP, SurePath*). Routine cytology for a 30-year-old woman. Rare metaplastic cells with dense cytoplasm and nuclear enlargement with hyperchromasia are present in a back-



Immature Metaplasia vs. ASC-H

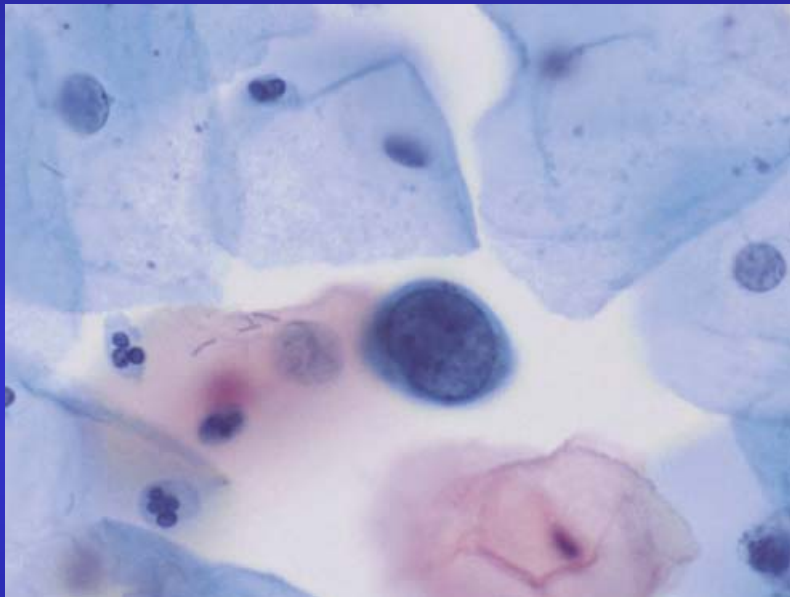
- Metaplastic cells may vary considerably in cell size and shape, nuclear size, and nuclear to cytoplasmic ratios.
- Concern > mild nuclear enlargement, membrane irregularity, uneven chromatin distribution, or hyperchromasia.
- Advice > The range in size and nuclear appearance of normal metaplastic squamous cells provides a standard for judging whether cells of concern warrant an interpretation of ASC-H.



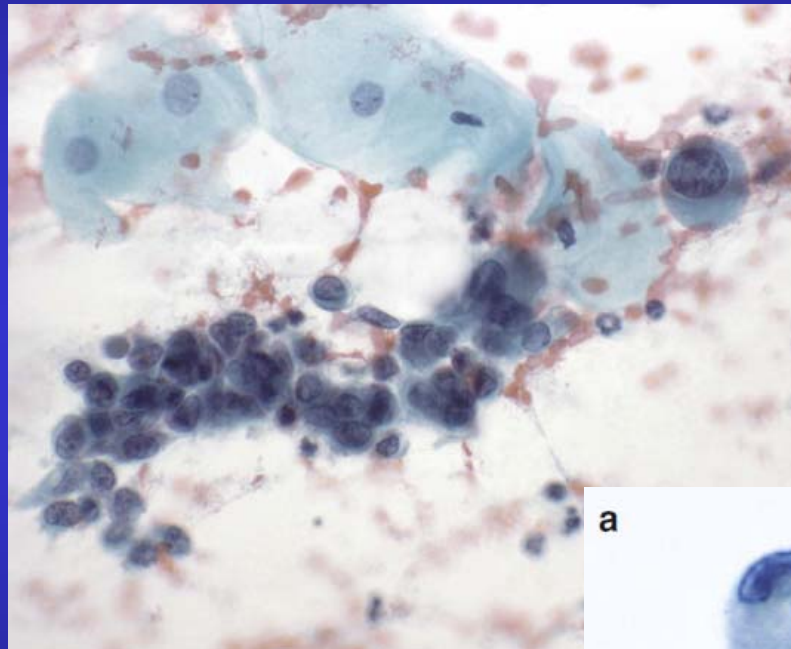
Crowded Groups

- “microbiopsy” - crowded squamous cells containing nuclei that may show atypical features, loss of polarity.
- often difficult to visualize
- prominent nucleoli are more typical of repair than HSIL
- nuclear pleomorphism or loss of cohesion may indicate ASC-H

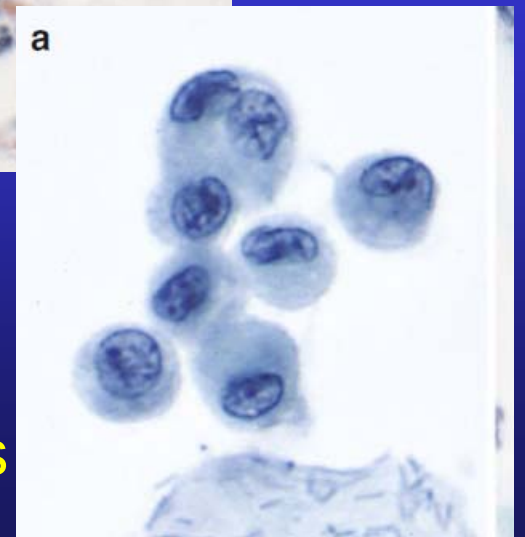
ASC-H Mimics



Isolated endocervical
cells



Endometrial Cells



Histiocytes

Low-Grade Squamous Intraepithelial Lesion/Cannot Exclude High-Grade Squamous Intraepithelial Lesion (LSIL-H) Is a Unique Category of Cytologic Abnormality Associated With Distinctive HPV and Histopathologic CIN 2+ Detection Rates

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Key Words: LSIL-H; Follow-up; CIN; Pap test; HPV

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ABSTRACT

Objectives: To examine data correlating high-risk human papillomavirus (hrHPV) results in patients with both low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H) cytology findings (LSIL-H) with follow-up histopathology.

Methods: A total of 494 LSIL-H ThinPrep (Hologic, Marlborough, MA) cases with hrHPV testing were identified. Histopathologic follow-up was available in 347 patients.

Results: Among 347 patients with follow-up histopathology after LSIL-H cytology and hrHPV testing, 90.5% tested hrHPV positive. Cervical intraepithelial neoplasia (CIN) 2/3 was diagnosed in 29.4% and CIN 1 in 53.6%. CIN 2/3 was diagnosed in significantly more patients with hrHPV-positive LSIL-H than following hrHPV-negative LSIL-H results. Compared with published institutional data, LSIL-H had significantly lower hrHPV and histopathologic CIN 2/3+ rates (90.5% and 29.4%, with no cervical cancers) than high-grade squamous intraepithelial lesion (HSIL) (95.7% and 70.5%, with 2.4% cervical cancers) but higher rates than LSIL (80.2% and 12.9%) or atypical squamous cells/cannot exclude HSIL (ASC-H) (54.3% and 17.2%). Whereas CIN 2/3 detection rates were similar in HPV-positive LSIL-H and HPV-positive ASC-H, CIN 2/3 findings were more likely with HPV-negative LSIL-H than with HPV-negative ASC-H.

Conclusions: LSIL-H is a unique category of cytologic abnormality associated with distinctive hrHPV and CIN 2/3+

Upon completion of this activity you will be able to:

- define low-grade squamous intraepithelial lesion/cannot exclude high-grade squamous intraepithelial lesion (LSIL-H) as a unique category of cervical cytologic abnormality.
- predict the prevalence of high-risk human papillomavirus and high-grade squamous dysplasia in patients with LSIL-H cytologic abnormality.
- discuss appropriate follow-up exams in patients with LSIL-H cytologic abnormality.

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The authors of this article and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose. Questions appear on p 294. Exam is located at www.ascp.org/ajcpeme.

The 2001 Bethesda System (TBS2001) updated standardized interpretive categories for pathologists to communicate cytologic findings on Papanicolaou (Pap) tests.¹ The 2006 and recent 2012 American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines for follow-up management of abnormal cervical screening tests reflect TBS2001 interpretive categories.^{2,3} The categories of squamous cell abnormalities in the initial TBS2001 publication included high-grade squamous intraepithelial lesion (HSIL), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASC-US), and atypical squamous cells/cannot exclude HSIL (ASC-H). The atypical squamous cells (ASC) categories denote indeterminate abnormal cytologic findings suggestive but not diagnostic for either LSIL

Cite 23 similar studies

“recently published 2012 ASCCP management guidelines again failed to address this category of cytologic abnormality”

The Interpretation of LSIL-H

Am J Clin Pathol August 2014;142:278-279

DOI: 10.1309/AJCPUABD4R3TMIAC

To the Editor

Barron et al¹ present data and arguments for the introduction of a new category of cytologic interpretation of LSIL-H—low-grade squamous intraepithelial lesion (LSIL)/cannot rule out high-grade squamous intraepithelial lesion (HSIL)—into The Bethesda System (TBS) for reporting cervical cytologic diagnoses.² They report that the percent of high-risk human papillomavirus (hrHPV) and the risk of cervical intraepithelial neoplasia grade 2 or 3 (CIN 2/3) for LSIL-H differed from other cytologic categories—greater than for LSIL and atypical squamous cells/cannot rule out HSIL (ASC-H) and less than HSIL. The decision to distinguish LSIL-H from other cytologic interpretations should be based on the answers to two key questions: (1) Does it improve patient care and outcomes? and (2) Is it a reliable cytologic category?

The answer to the first question is **no**. To improve patient care, the use of any test, measurement, diagnostic, or, in this case, reclassification should accompany a change in care.³ That is, either a group of patients are identified who are at lower risk such that they would receive less aggressive/invasive care or at higher risk that they would receive more aggressive/invasive care. However, with these cytologic classifications, including LSIL-H, all women would have a colposcopy, and only women with HSIL are at sufficiently high risk that, under specific circumstances, immediate treatment is warranted without histopathologic verification of CIN 2/3 or cancer.⁴ Therefore, there is seemingly no benefit to patients.

The answer to the second question is **probably no**. There are no studies of intra- or interrater agreement of LSIL-H

or even ASC-H. In general, the interrater agreement of cytology is only fair,⁵ likely because of the lack of agreement for cytologic features that underlie those categorizations.⁶ However, we can learn about LSIL-H indirectly from its related cytologic category, ASC-H. In the analysis by Barron et al,¹ the percent of hrHPV was 54.3% and the risk of CIN 2/3 was 17.2% for ASC-H, both significantly lower than previously reported.^{7,8} In fact, the LSIL-H in this analysis more closely resembles ASC-H in risk of CIN2/3 and percent hrHPV positive from those previous reports, suggesting that there is a continuous spectrum of morphologic features, between mild abnormalities of atypical squamous cells of undetermined significance (ASC-US) and LSIL at one end and severe abnormality of HSIL at the other, which are probably poorly distinguished and cannot be reliably divided into subgroups. And because of the rarity of LSIL-H (0.18%), it is unlikely that any cytopathologist will become practiced at making the call of LSIL-H reliably.

Therefore, given the (1) growing complexity of screening⁹ and management⁴ guidelines, (2) lack of benefit to patients, (3) the likely unreliability of the LSIL-H interpretation, and (4) the rarity of its occurrence (if it is a real, distinct entity), there seems little reason to introduce LSIL-H as a category in TBS. Cervical cytopathology does not need new categories of classification. It needs to make the current categories more reliable.

Philip E. Castle, PhD, MPH
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Evidence for Increasing Usage of Low-Grade Squamous Intraepithelial Lesion, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (LSIL-H) Pap Test Interpretations

Vighnesh Walavalkar, MD¹; Douglas Tommet, MS¹; Andrew H. Fischer, MD¹; Yuxin Liu, MD, PhD¹; Debra M. Papa, MD²; and Christopher L. Owens, MD¹

BACKGROUND: Pap test (PT) interpretations of low-grade squamous intraepithelial lesion (LSIL), cannot exclude high-grade squamous intraepithelial lesion (HSIL), or LSIL-H, are used in many laboratories; however monitoring its usage for quality assurance purposes is understudied. **METHODS:** PTs from 2005 to 2010 were collected, and yearly frequencies of LSIL, HSIL, LSIL-H, and atypical squamous cells, cannot exclude HSIL (ASC-H) as a function of total PTs and total squamous intraepithelial lesions (SILs) were calculated. Two-year risk of cervical intraepithelial neoplasia 2 (CIN2) or worse (CIN2+) and CIN 3 or worse (CIN3+) was calculated. **RESULTS:** A total of 352,220 PTs were identified including 17,301 abnormal PTs. LSIL-H usage increased from 2005 to 2010 (from 0.28% of total PTs in 2005 to 0.61% in 2010, $P < .01$; from 5.8% of total SILs in 2005 to 12% in 2010, $P < .001$). HSIL usage decreased significantly from 2005 to 2010 (from 0.7% of total PTs in 2005 to 0.48% in 2010, $P = .048$; from 14.5% of total SILs in 2005 to 9.5% in 2010, $P < .01$). Usage of LSIL and ASC-H did not change. Two-year risk of CIN2+ and CIN3+ for HSIL increased significantly from 2005 to 2010 ($P < .01$). Two-year risk of CIN2+ and CIN3+ for LSIL-H did not change significantly from 2005 to 2010. **CONCLUSIONS:** The frequency of LSIL-H interpretations is significantly increasing at our institution, with a significant decrease in HSIL interpretations over the same period. Two-year risk of CIN2+ and CIN3+ for HSIL increased significantly as usage of LSIL-H increased and that of HSIL decreased. Laboratories using LSIL-H may benefit from monitoring its frequency to ensure its appropriate use. *Cancer (Cancer Cytopathol)* 2014;122:123-7. © 2013 American Cancer Society.

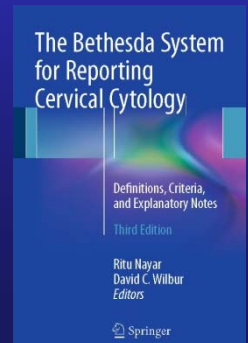
KEY WORDS: LSIL-H; low-grade squamous intraepithelial lesion cannot exclude high-grade squamous intraepithelial lesion; QA; quality assurance; Pap test.

LSIL-H

- No new category was created for squamous lesions with LSIL and few cells suggestive of concurrent HSIL

Rationale: Occasionally, a specimen is encountered with cytologic features that lie between LSIL and HSIL; however, attention to morphologic features usually supports classification as either LSIL or HSIL.

In cases with unequivocal HSIL, the presence of concurrent LSIL is not necessary to make an interpretation of HSIL.



LSIL-H

TBS Consensus to exclude LSIL-H

- Adding terminology such as “LSIL-H” would lead to a de facto 3-tiered system.
- Current management guidelines all use LSIL and HSIL nomenclature without an intermediate category, and
- Recent histopathology reporting recommendations also encourage reporting as LSIL or HSIL.
- Poor reproducibility and overuse of any new indeterminate cytology terminology would likely lead to confusion among clinicians and, possibly, inappropriate management.

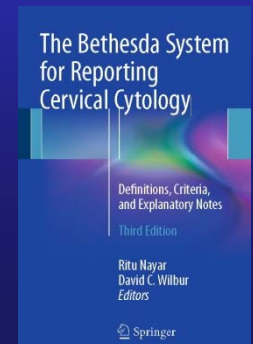


Figure 7: Recommended non-HPV clinical pathway for workup and treatment: SIL referral in women ≥ 25

