LAST but not Least

The LAST Project:
Lower Anogenital Squamous Terminology Standardization of HPV-associated Neoplasia

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References: The LAST Project

The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology.

Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC, for Members of the Last Project Work Groups.

- Archives of Pathology and Laboratory Medicine:
  - June 28, 2012. [Epub ahead of print]
  - October 2012 – Volume 135 – p 1266-1297.
- Journal of Lower Genital Tract Disease:
  - June 28, 2012. [Epub ahead of print]
  - July 2012 – Volume 16 – p 205-242

Primary Goals

- Standardize terminology for reporting diagnoses of HPV-related squamous lesion of LAT, including intraepithelial lesions and minimally invasive cancers
- Harmonize terminology across LAT sites with current evidence-based knowledge regarding biology of HPV-related squamous lesion and their clinical management
- Assess use of new technologies (biomarkers) to validate proposed terminology standards, provide guidelines for appropriate use

Project Overview

44 Members and 13 advisors: Multidisciplinary panel of experts and thought leaders in the field, including…

- Expertise in pathology specialties, e.g.
  - Cytopathology
  - Dermatopathology
  - Gynecologic pathology
  - Surgical pathology
- Expertise in clinical specialties, e.g.
  - Dermatology
  - Gynecology & Gynecologic Oncology
  - Internal Medicine, Infectious Diseases & Medical Oncology
  - Surgery
  - Epidemiology & Public Health

LAST Work Groups

- WG 1 – Historical Review of Lower Anogenital Tract Terminology Across Disciplines
- WG2 – Terminology for Intraepithelial Lesions, Integrating Morphology, Biology, and Clinical Management
- WG3 - Terminology for Minimally Invasive Cancers, Integrating Morphology, Biology, and Clinical Management
- WG4 – Molecular Markers for Histopathology
- WG5 – Implications and Implementation of Standardized Terminology

Literature Review

WG2-4: Intraepithelial, Invasive and Molecular

- Reviewed:
  - 6,063 titles/abstracts
- Read
  - 1,210 Full text articles
- Completed
  - 452 data extractions
- Provided
  - 11 recommendations and 5 definitions for a proposed standardized terminology and appropriate use of biomarkers

Methods Used to Produce Recommendations

- WG2-3: Intraepithelial, Invasive
  - The recommendations are based on comprehensive literature review, expert opinion, open comment period responses, and consensus conference discussion.

- WG4: Biomarkers
  - As above, plus:
  - The recommendations and the evidence used to support them, were evaluated by an independent reviewer with experience in the development of evidence-based guidelines (Evan R. Myers, M.D., M.P.H., Duke University Department of Obstetrics & Gynecology) prior to the consensus conference

Methods Used to Produce Recommendations

- The LAST Consensus Conference was held March 13 -14, 2012 in San Francisco
- 35 participating organizations sent representatives to review, discuss, and revise the recommendations.
- Each recommendation required a two-thirds majority (66% or higher) to pass
- Recommendations not achieving consensus on the first vote were revised by the WGs and submitted for a revote.
- All recommendations achieved the required majority votes.
- Observers in attendance did not vote.

Participating Organizations at LAST Consensus Conference, March 2012

- **American Academy of Family Physicians**
- **American Board of Obstetrics and Gynecology**
- American Board of Pathology
- **American Cancer Society**
- American College Health Association
- **American College of Obstetricians & Gynecologists**
- American Sexually Transmitted Diseases Association (ASTDA)
- American Society for Clinical Pathology
- American Society for Colon and Rectal Surgeons
- **American Society for Colposcopy and Cervical Pathology**
- American Society for Cytopathology
- The American Society of Dermatopathology
- American Urological Association
- Association for Directors of Anatomic and Surgical Pathology
- **CDC - Cancer Prevention & Control**
- CDC - Laboratory Science and Standards (Office of Surveillance, Epidemiology and Laboratory Services)
- CDC - High-Consequence Pathogens and Pathology
- College of American Pathologists
- **Food & Drug Administration (OIVD)**
- International Agency for Research on Cancer (WHO/IARC)
- International Anal Neoplasia Society
- International Federation for Cervical Pathology and Colposcopy
- **International Gynecologic Cancer Society**
- International Society for Gynecological Pathologists
- **International Society for the Study of Vulvovaginal Disease**
- **National Cancer Institute**
- **Nurse Practitioners in Women's Health**
- Papanicolaou Society of Cytopathology
- **Planned Parenthood Federation of America**
- Society of Canadian Colposcopists
- **Society of Gynecologic Oncologists**
- Society of Gynecologic Oncologists of Canada
- Society of Obstetricians & Gynaecologists of Canada
- **United States Surveillance, Epidemiology and End Results (SEER) Program**
- United States and Canadian Academy of Pathology
- **United States Cancer Registries**
- Veterans Health Administration

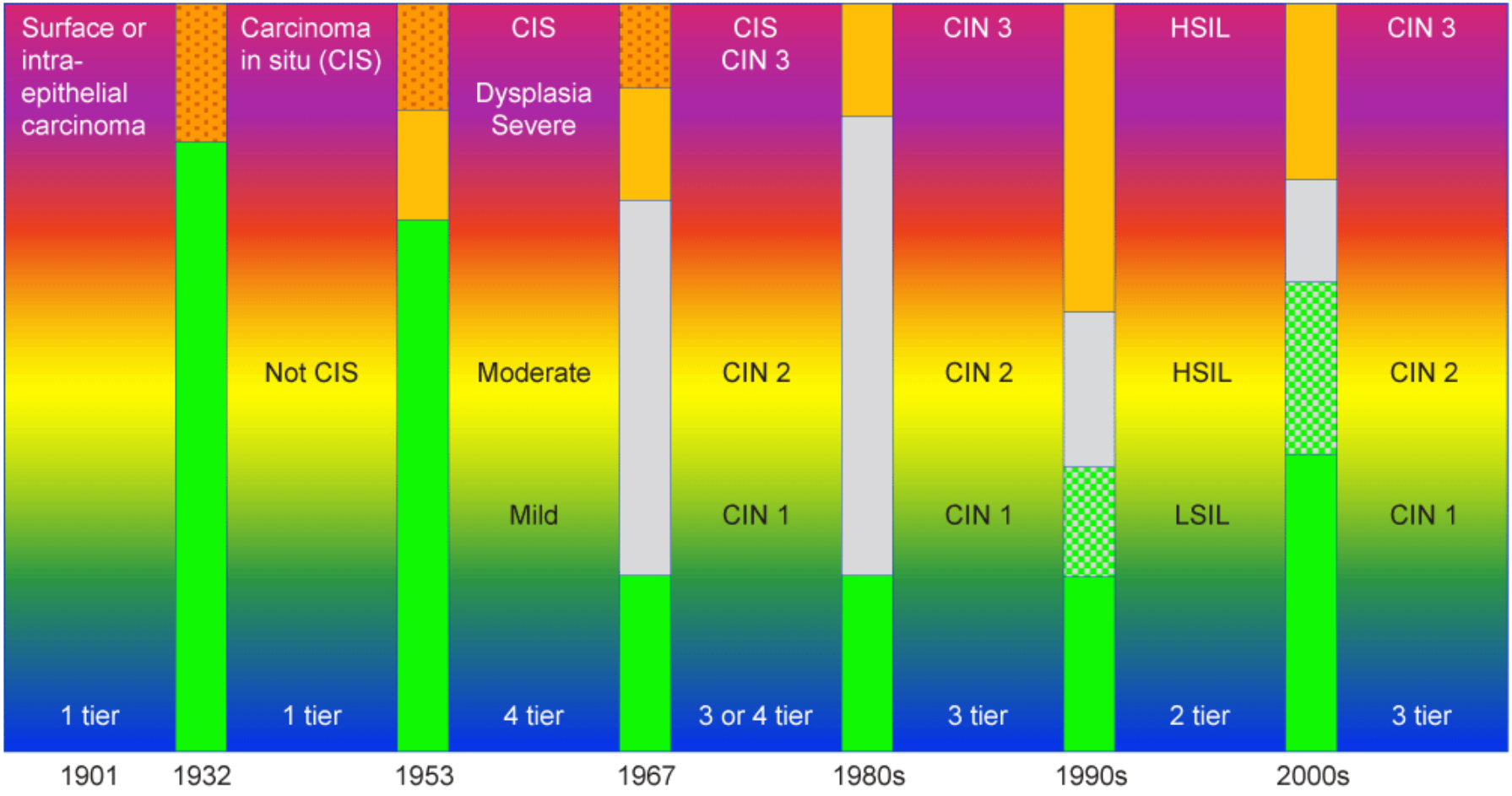
WG1 Historical Review:
History of terminology of LAT lesions

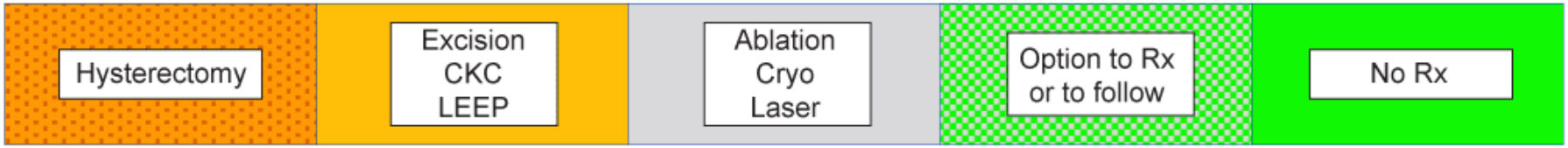
- Varies historically over time
- Developed along two separate paths
  - Mucosal lesions (cervix, vagina, anus)
    - General pathologists, gynecologic pathologists, gynecologists, cytopathologists
  - Cutaneous lesions (vulva, penis, perianal)
    - Dermatologists, dermatopathologists
- Leads to potential communication issues between pathologists and clinicians

Terminologies of mucosal infection/precancer

- 1888: Intraepithelial precancer→CIS
- 1953: Dysplasia
  - mild, moderate, severe, carcinoma in situ
- 1967: Cervical carcinogenesis thought to be a continuum of disease (intraepithelial neoplasia)
  - CIN 1-3
  - VaIN 1-3
  - AIN 1-3
- 1980's: 2-tiered system proposed (TBS)
  - LSIL / HSIL

Terminology





Procedure

The Bethesda System: A Historical Perspective

Terminology : 3 fundamental principles

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

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

Squamous Intraepithelial Lesions

WG2 – Terminology for Intraepithelial Lesions, Integrating Morphology, Biology, and Clinical Management

WG2 Intraepithelial Lesions Recommendations

1. A unified histopathological nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the lower anogenital tract (LAT).

Recommendation #1

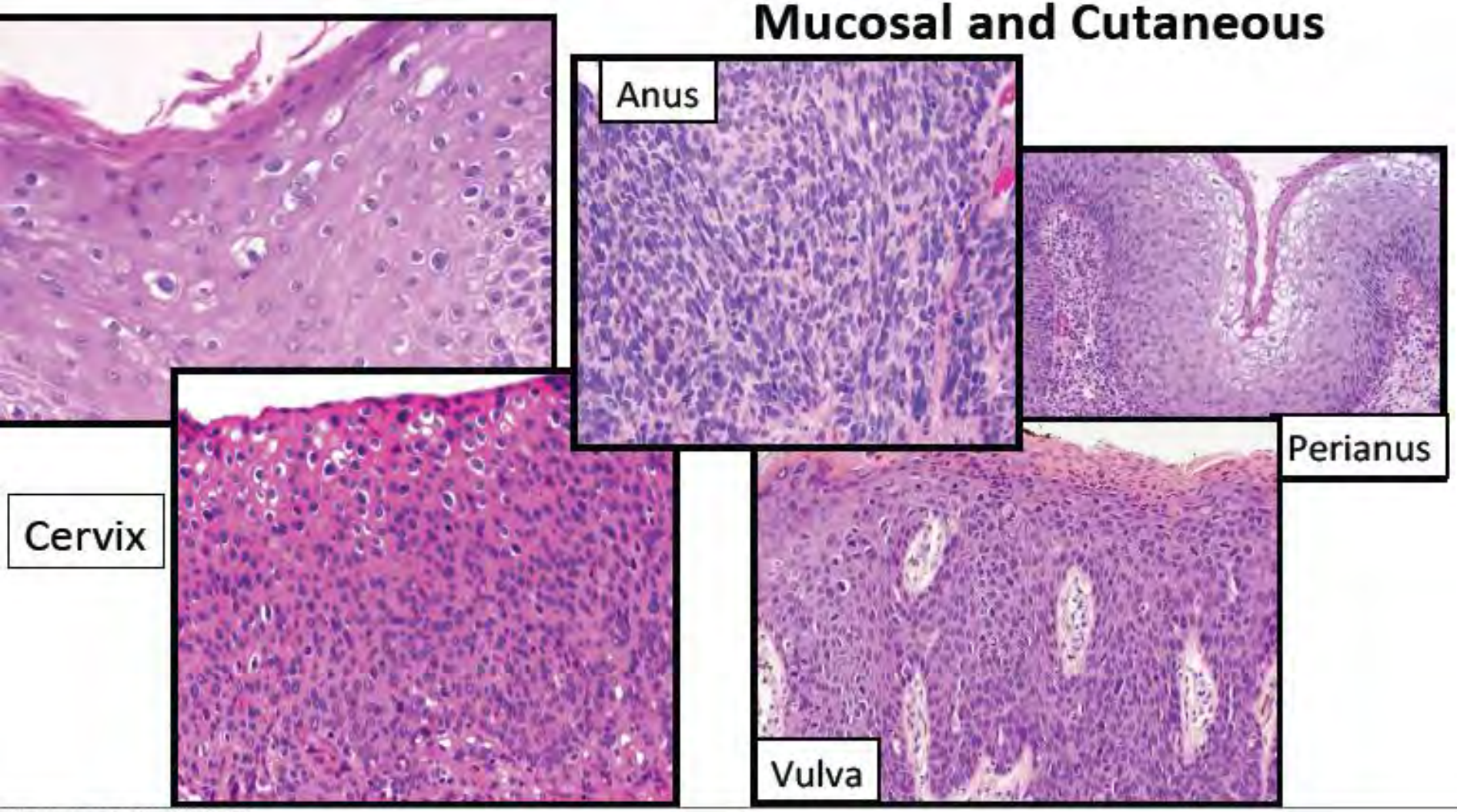
- Rationale: From the literature review from WG2 and WG4, there is evidence of biologic and morphologic similarity of HPV-related squamous lesions across the lower anogenital tract.

- Non-HPV-related squamous lesions should have a separate distinctive nomenclature. i.e. differentiated VIN in the vulva.

There is a unified HPV related biology:

Across body sites:

Mucosal and Cutaneous



WG2 Intraepithelial Lesions Recommendations

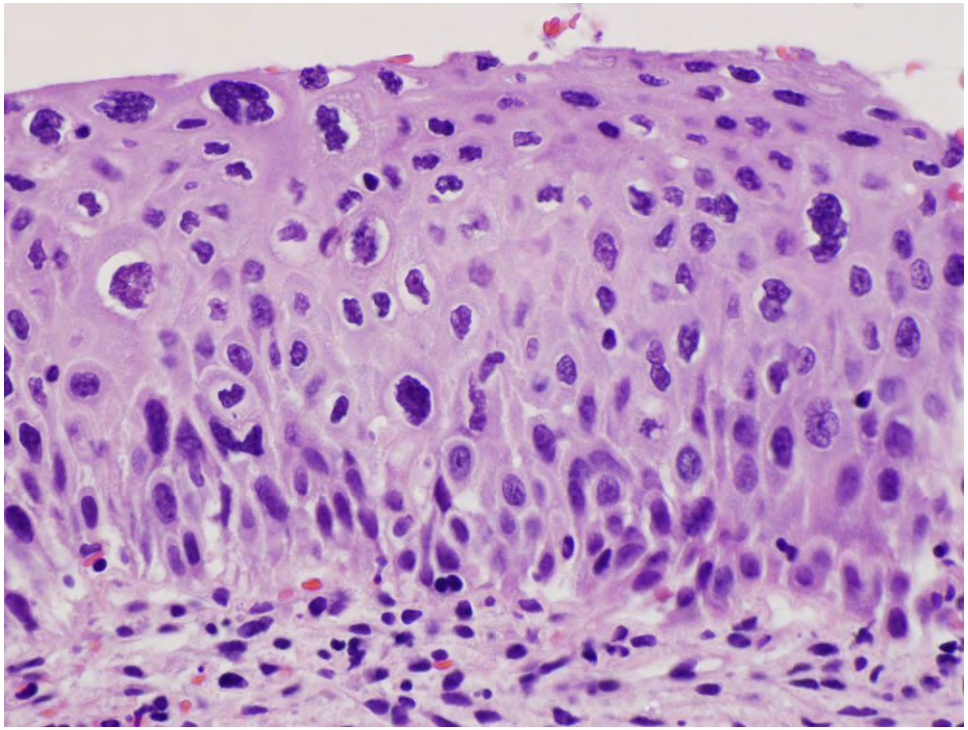
2. A 2-tiered nomenclature is recommended for non-invasive HPV-associated squamous proliferations of the LAT which may be further qualified with the appropriate –IN terminology.
   - -IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location, the appropriate complete term should be used. Thus for an –IN3 lesion: cervix = CIN3, vagina = VaIN3, vulva = VIN3, anus = AIN3, perianus = PAIN3, and penis = PeIN3

Recommendation 2: Rationale

There is evidence that a 2-tiered system for cervical disease is more reproducible (with higher kappa statistics).

- For 2 tiers: Kappa statistics ranged from .30 to .71.
  - Studies are case series or cross sectional with low numbers other than one study from the ALTS trial which has high numbers and is a blinded study comparing 2 expert panel groups.
- For 3 tiers: Kappa statistics ranged from .12 to .58.
  - All studies are case series or cross sectional and have low numbers.
  - CIN2 has the lowest reproducibility of the 3 tiers.

Histology: 'CIN2'



- CIN2 is poorly reproducible
- In ALTS, Clinical site vs study pathologists
  - Only 43%, CIN2→CIN2
  - 27% upgraded to CIN3
  - 29% downgraded to CIN1 or normal

Castle PE, Stoler MH, Solomon D, Schiffman. Am J Clin Pathol 2007;127:805-15.

Recommendation 3:
Diagnostic terminology for a 2-tiered system

Low Grade Squamous Intraepithelial Lesion (LSIL)

High Grade Squamous Intraepithelial Lesion (HSIL)

(These may be further subclassified by the applicable –IN classification)

Rationale:

- Some current textbooks use this terminology
- Would match cytology nomenclature.
- This received the most support from the public comments

Concerns

- There were some public comments expressing concern that using identical terminology to cytology would not be appropriate and might be confusing.
- Clinical guidelines will need to be adjusted to a 2-tiered system

Biomarkers

WG4 – Molecular Markers for Histopathology

Markers evaluated after 1st tier review

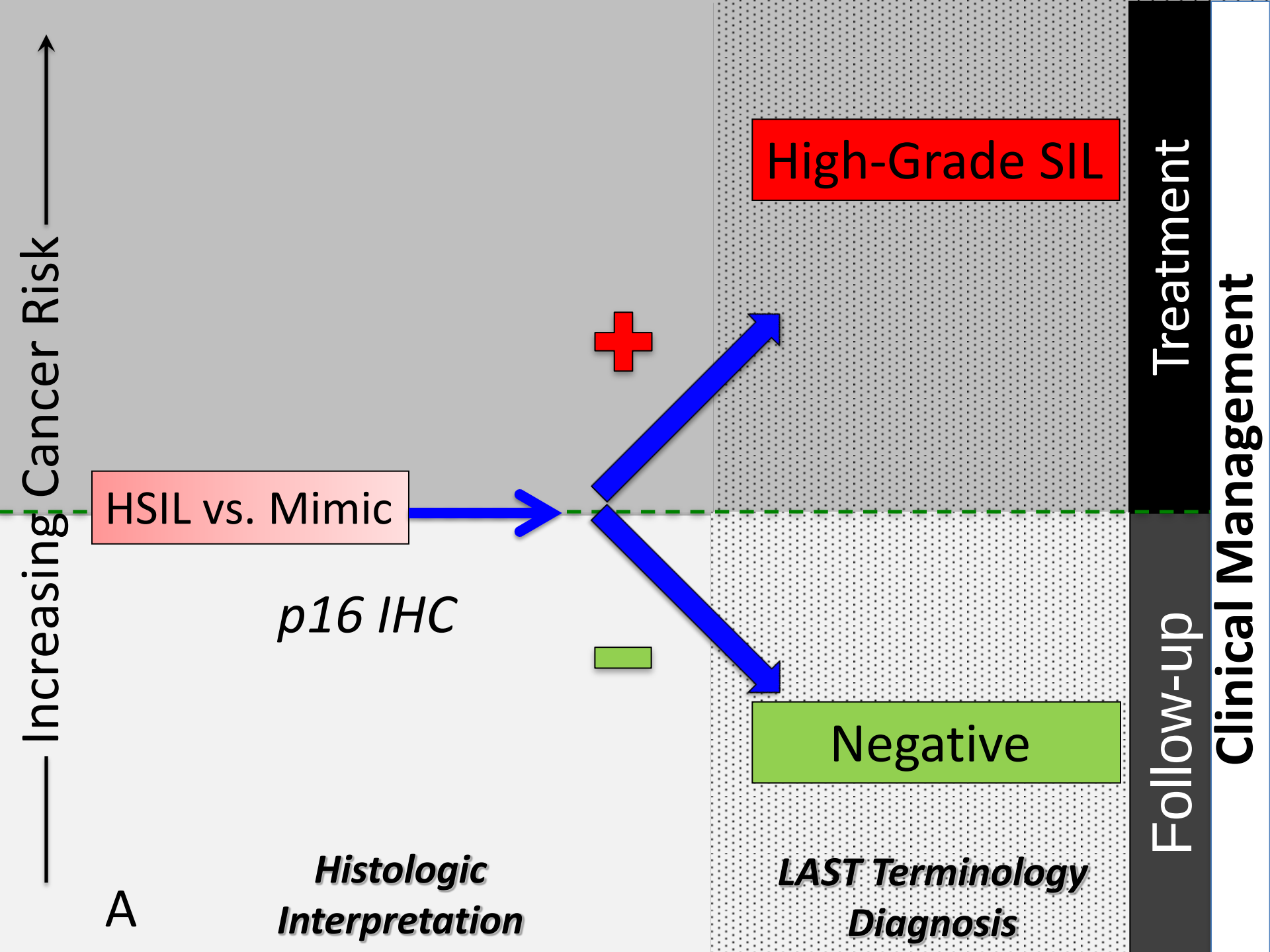
- p16
- Ki67 (Mib1)
- ProEx C
- L1
- HPV 16/18 mRNA
- Telomerase (TERC)
- HPV genotyping

Adaptability across lower anogenital tract

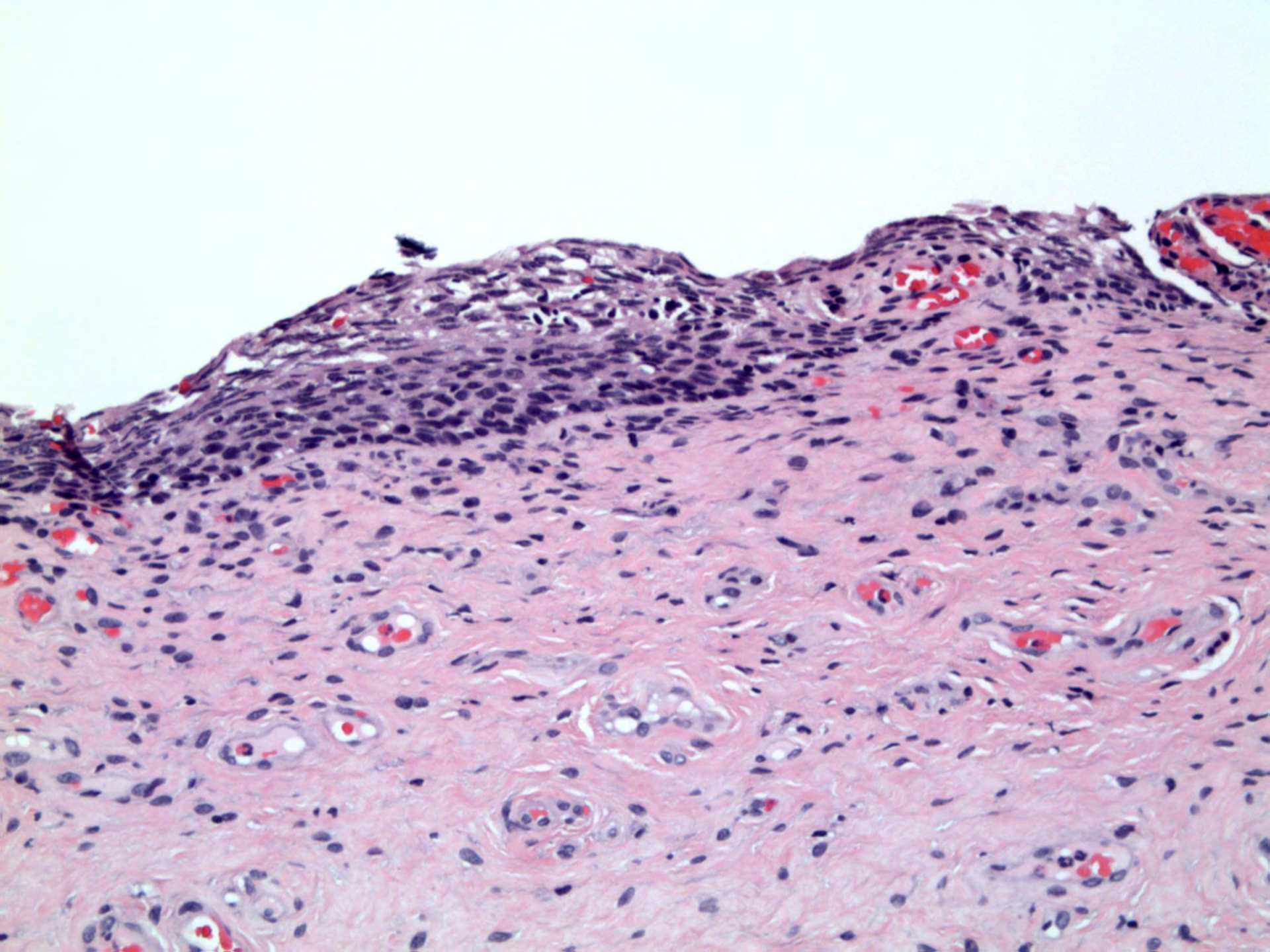
- Most studies focus on cervix
- Few studies available for other sites
- All studies for other sites show similar results to cervix.
- Given similarity of underlying HPV-associated biology:
- WG4 concludes that recommendations should apply across all HPV-associated lower anogenital tract lesions.

WG4 Biomarkers Recommendations

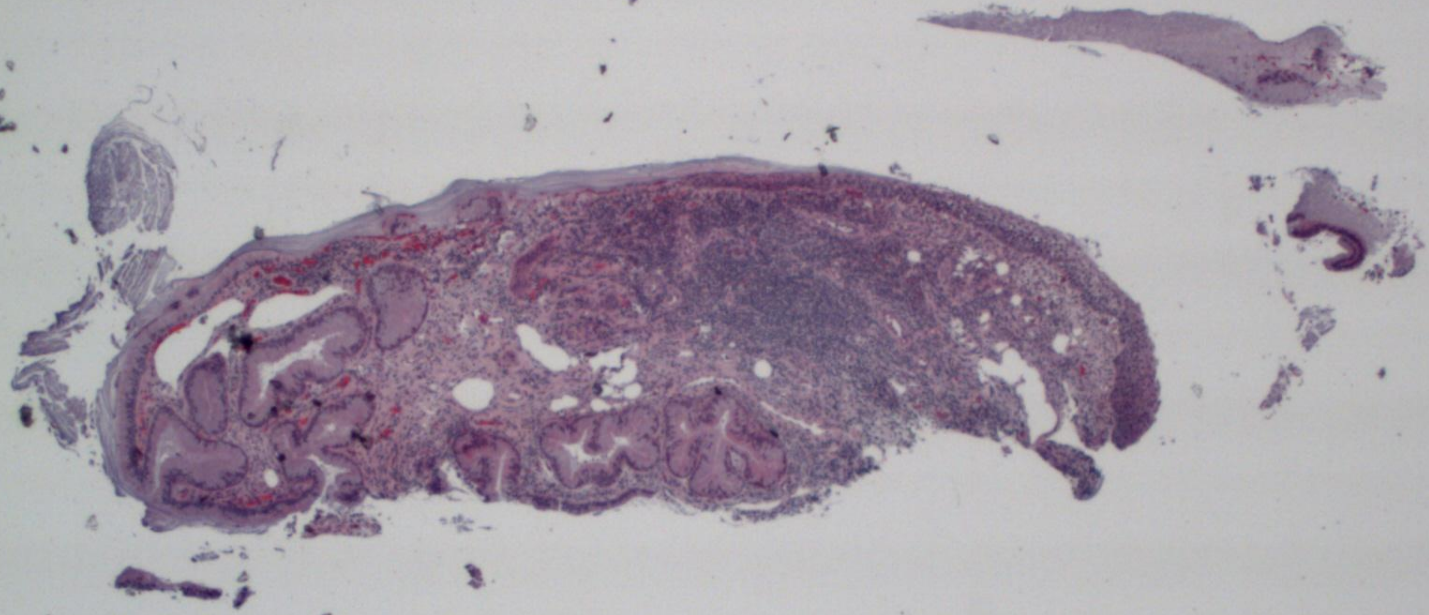
1. p16 IHC is *recommended* when the H&E morphologic differential diagnosis is between precancer (–IN2 or – IN3) and a mimic of precancer (e.g., processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting).
   - Strong and diffuse block-positive p16 results support a categorization of precancerous disease.

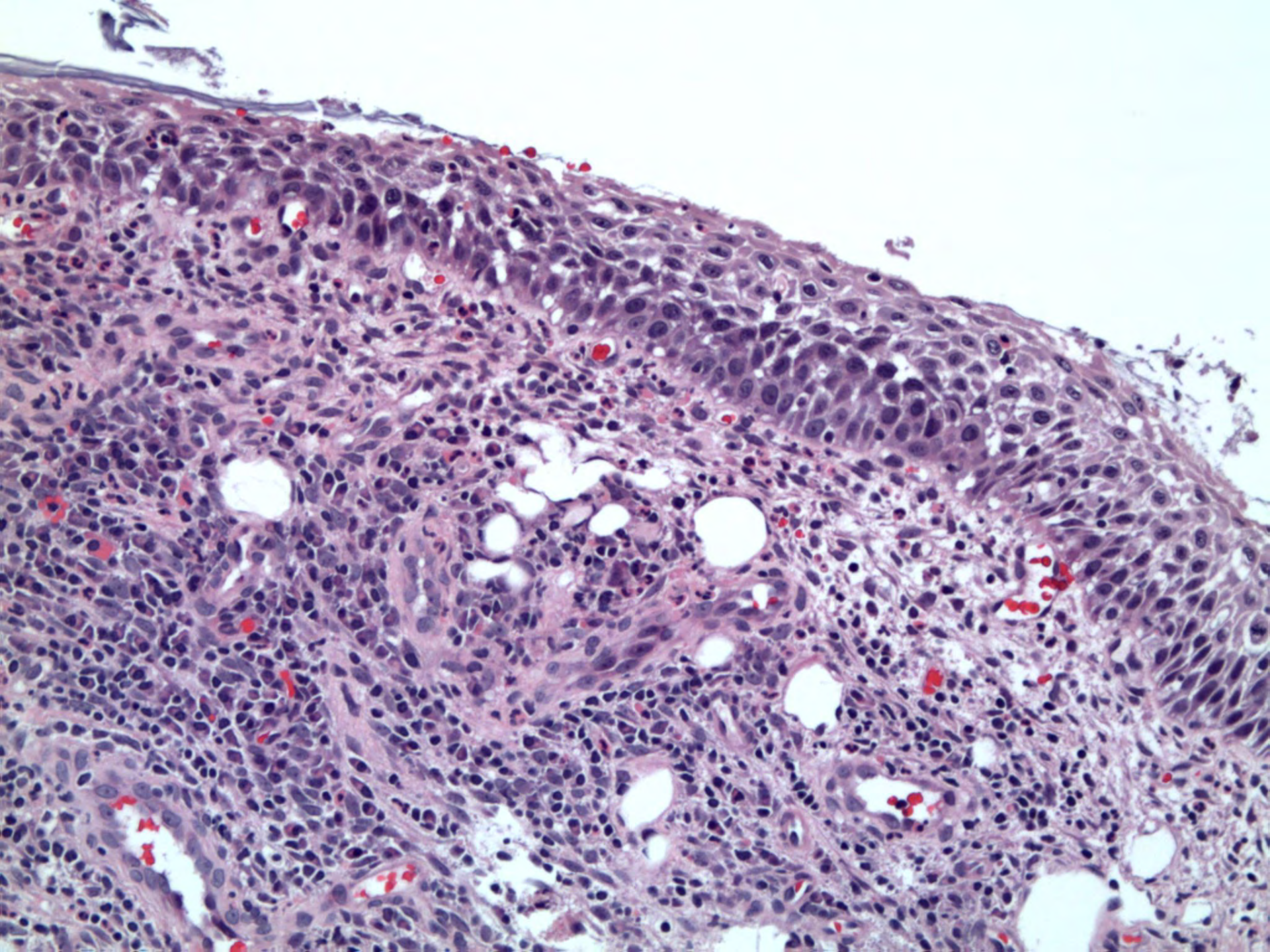

Increasing Cancer Risk
HSIL vs. Mimic
p16 IHC
+
–
High-Grade SIL
Negative
Treatment
Follow-up
Clinical Management
A
Histologic Interpretation
LAST Terminology Diagnosis

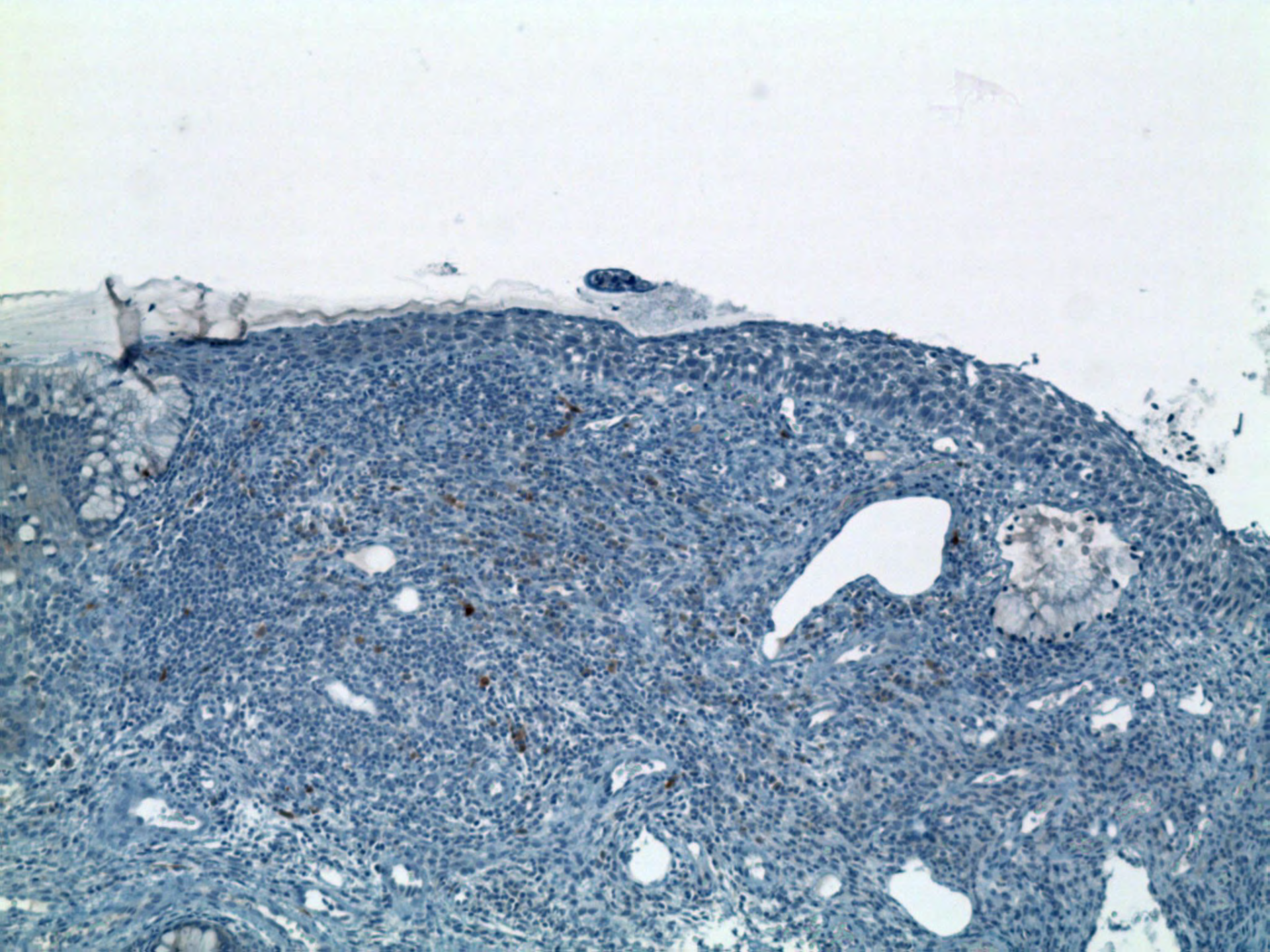
SG: 69 yo, s/p hysterectomy, abnormal pap, vaginal cuff biopsies



HK: 26 yo, cx bx







WG4 Biomarkers Recommendations

2. If the pathologist is entertaining an H&E morphologic interpretation of –IN2 (under the old terminology, which is a biologically equivocal lesion falling between the morphologic changes of HPV infection [low-grade lesion] and precancer), p16 IHC is *recommended* to help clarify the situation.
   - Strong and diffuse block positive p16 results support a categorization of precancer. Negative or non-block-positive staining strongly favors an interpretation of low-grade disease or a non-HPV associated pathology.