Current Issues in Cytology

Teresa M. Darragh, MD
Hologic: Research supplies for anal cytology; Research Support, Advisory Board: OncoHealth; Other Financial or Material Interest

J. Thomas Cox, MD
Roche Diagnostics, Non-paid Co-Chair of the Data Steering Committee for the ATHENA cervical screening trial Gen-Probe, Scientific Advisory Board; Consultant, Roche, HPV testing; Speakers Bureau

Michael R. Henry, MD
There is no disclosure necessary

Ritu Nayar, MD
There is no disclosure necessary

Mark H. Stoler, MD
Merck: Consultant, Roche: Consultant, Genprobe: Consultant, BD: Consultant, Hologic: Consultant

David C. Wilbur, MD
There is no disclosure necessary
Screen Better, Interpret Better, Manage Better: Insights from the LAST Project

Teresa M. Darragh, MD
University of California, San Francisco
J. Thomas Cox, MD
University of California, Santa Barbara (retired)
Michael R. Henry, MD
Mayo Clinic, Rochester
Ritu Nayar, MD
Northwestern University, School of Medicine
Mark H. Stoler, MD
University of Virginia
David C. Wilbur, MD
Harvard Medical School, Massachusetts General Hospital

Conflict of interest

In the past 12 months, I have had a significant financial interest or other relationship with the manufacturer(s) of the following product(s) or provider(s) of the following service(s) that will be discussed in my presentation.

Dr. Darragh
Hologic: Research supplies for anal cytology
OncoHealth: Advisory Board

Dr. Cox
Roche Speakers Bureau, OncoHealth Advisory Board, Gen-Probe Scientific Advisory Board, Merck HPV Vaccine DSMB

Dr. Henry: None

Dr. Nayar: None

Dr. Stoler
Consultant for Merck, Qiagen, BD, Roche, Ventana, mtn, Gen-Probe, Hologic

Dr. Wilbur
Merck - shareholder, <$10,000

This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA or unapproved or "off-label" uses of pharmaceuticals or devices.

Course Objectives

• Understand the new and revised terminologies for the HPV-associated lesions of all lower anogenital tract body sites (cervix, vulva, vagina, penis, scrotum, anal canal and perianus)

• Understand how select biomarkers are used to improve accuracy and reproducibility of diagnosis in the revised terminology

• Understand the appropriate use for select molecular markers for HPV-related lesions of the lower anogenital tract body sites

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Inception of the CAP-ASCCP LAST Project

Teresa M. Darragh, MD
University of California, San Francisco

Beware of raising your hand...
Focus: words...
Terminology /ter·mi·nol·o·gy/ (ter‘mi-nol´ah-je)
• 1. the vocabulary of an art or science.
• 2. the science which deals with the investigation, arrangement, and construction of terms.

Medicine = Art + Science
Nomenclature (nō´menklā´chur):
• the formally adopted terminology of a science, art, or discipline;
• the system of names or terms used in a particular branch of science.

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

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
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

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.

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.


- 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
Central Tenets = Underlying Premises

- There is unified epithelial biology to HPV-related squamous neoplasia.
- Each patient sample is only a statistical representation of the patient’s true biology.
- The more samples or data points available, the closer you get to the patient’s “true” biology.
- The true biology represents “risk” for “cancer” at the current time and to a lesser extent “risk” over time.
- IN2 is like ASCUS: an indistinct poorly defined entity.
- Diagnostic variation can be improved by:
  - Limiting the number of tiers
  - The use of biologic markers

? False Premises

- Biopsy is perfect representation and contains everything you need to know to manage the patient.
- Everybody reads the biopsy the same way.
- CIN2 is a distinct biologically defined category.
- Interpretative variation can be eliminated through education on morphologic criteria alone.
There is a unified HPV-related biology: Which is Female vs. Male?

- Male – Perianal Condyloma
- Cervix - Condyloma

There is a unified HPV-related biology: Which is Female vs. Male?

- VIN3
- PeIN3

High Grade or High Risk or Precancer

- CIN3
- PAIN3
- AIN3
- PeIN3
-IN2 is poorly reproducible

In ALTS, clinical site vs study pathologists
- Only 46%, CIN2→CIN2
- 27% upgraded to CIN3
- 27% downgraded to CIN1 or normal

Not reflective of biology of HPV-related lesions
What is -IN2?

• A DISTINCT BIOLOGIC STAGE?

• UGLY LOOKING CIN1?

• NOT SO UGLY CIN3?

-IN2 is …

• The ASCUS of CIN
• An equivocation that is NOT reproducible
• A representation of incomplete sampling
• ~2/3s HSIL; ~1/3 LSIL
• A management safety net?

COLPOSCOPIC VARIATION

• Colposcopic Sampling
  – Location of T-zone
  – Size of lesion
  – Location of lesion
  – Visual criteria
  – Size forceps
  – Skill
Colposcopic Impression is Highly Variable
(>300 colpos per examiner in ALTS)

Accuracy of Colpo Biopsy?

- OVERALL PERFECT AGREEMENT: 42%
- BX UNDERESTIMATES: 21%
- OVERESTIMATE or REMOVE: 36%

- Overall underestimation of CIN3+ = 42%
- Overall underestimation of CIN2+ = 26%
- Biopsy is somewhat inaccurate and also potentially therapeutic


Kappa values:
- Strength of agreement
  - < 0.20 Poor
  - 0.21 - 0.40 Fair
  - 0.41 - 0.60 Moderate
  - 0.61 - 0.80 Good
  - 0.81 - 1.00 Very good
Hypotheses

- Diagnostic variation can be improved by:
  - Limiting the number of tiers
  - The use of biologic markers, such as:
    - p16
    - Ki-67
    - ProEx C

WHAT'S THE PROBLEM?

WHAT IF?
ARE BIOMARKERS THE SOLUTION?
DATA ON ~1500 ADJUDICATED BIOPSIES WITH 3+ p16 STAINING

- NIL 5%
- CIN1 39%
- CIN2 77%
- CIN3 99%


Underlying Premises

- There is unified epithelial biology to HPV-related squamous neoplasia
- Each patient sample is only a statistical representation of the patient’s true biology
- The more samples or data points available, the closer you get to the patient’s “true” biology
- The true biology represents “risk” for “cancer” at the current time and to a lesser extent “risk” over time
- CIN2 is like ASCUS: an indistinct poorly defined entity
- Diagnostic variation can be improved by:
  - Limiting the number of tiers
  - The use of biologic markers

History – Terminology

J. Thomas Cox, MD
University of California, Santa Barbara (retired)
LAST Work Groups

- WG 1 – Historical Review of Lower Anogenital Tract Terminology Across Disciplines
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- WG5 – Implications and Implementation of Standardized Terminology

Issues and controversies: Terminology

- Varies historically over time
- Varies by clinical orientation
  - Dermatology / dermatopathology
  - Gynecology / gynecologic pathology
  - Surgery / surgical pathologists
  - Cytology
- Based on biology of disease...
- Leads to potential communication issues between pathologists and clinicians

Terminologies of mucosal infection/precancer

- Dysplasia
  - mild, moderate, severe, carcinoma in situ
- Intraepithelial neoplasia
  - CIN1-3
  - VaIN1-3
  - AIN1-3
- Squamous intraepithelial lesion
  - LSIL / HSIL
Terminologies of cutaneous infection/precancer

- VIN1-3, PeIN1-3, PAI1-3
- LSIL / HSIL
- VIN, usual type
- Carcinoma in situ
- Bowen’s disease / Erythroplasia of Queyrat
- Bowenoid papulosis

WG1 Historical Review

- A whole lotta terms over a whole lotta years...
- The beginning of wisdom is getting things by their right name.
  
  Chinese saying
Squamous Intraepithelial Lesions

Michael R. Henry, MD
Mayo Clinic,
Rochester, MN

LAST Work Groups

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WG2 Scope

• To integrate current knowledge of HPV-related biology with histopathologic terminology across all lower anogenital body sites.
• To assess tiering of terminology and its impact on clinical utility.
• To optimize communication between pathologists and clinicians in clear and relevant fashion.
• To evaluate how the histopathologic diagnosis is reconciled with clinical management.
• To recommend new or unified terminology as appropriate.
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

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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

- WG4 could find no molecular marker-based studies to support 3-tiered biology.

- WG4 found that the use of p16 to potentially upgrade or downgrade equivocal (CIN2) lesions effectively leads to a 2-tiered classification system.

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.
**Recommendation 2: Rationale**

- In reality, CIN2 represents a mixture of low-grade (risk) and high-grade lesions with borderline histopathologic features between classic CIN1 or condyloma and CIN3.
- Recent gynecologic pathology textbooks use a 2-tiered nomenclature for cervix/vagina lesions.
- The most recent ISSVD recommended terminology for vulvar HPV-related squamous lesions is essentially a 2-tiered system with the older term VIN1 relegated to condyloma.
- The public comments strongly supported this recommendation.
- Some pathology practices, academic and private, have used a 2-tiered system for many years.

**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 classified by the applicable –IN subcategorization)

**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**

David C. Wilbur, MD
Harvard Medical School,
Massachusetts General Hospital
LAST Work Groups

- WG 1 – Historical Review of Lower Anogenital Tract Terminology Across Disciplines
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WG 4 Issues

- Assess the use of molecular markers in conjunction with morphology for HPV-related lesions
- Potential markers?
- Which are ready for primetime?
- How should they be used?
- Does marker use define any classification?
- Do markers affect interobserver variability?
- Single marker vs. combinations of markers?
- Does marker use affect clinical management?

Comprehensive literature review

- 2291 relevant articles identified (1985-2012)
- Pre-specified criteria
  - Study type
  - Scope
  - Number of subjects
- Systematic title/abstract and full text review process
- 72 articles for data extraction (53 for p16)
- Vast majority – cervix related
- Prospective and histology-adjudicated studies given most weight
Quality of evidence review

- Only WG with this review
- Independent evaluation of the evidence quality (18 articles)
- Conducted by Evan Myers, M.D., M.P.H.
- Use of terminology for qualification of the recommendations
  - “recommend” – WG’s recommendation is unlikely to change based on future studies
  - “suggest” – WG’s recommendation is most likely correct but could be better supported by additional data

Key Question #1

- What (if any) are the molecular markers and when should they be used?
  - Utility on histologic specimens
  - Aid to differential diagnosis
  - Potentially definitional of the patient’s biologic state

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.

Key Question #2

- Is any biomarker ready for prime time use?
  - It could be used commonly
  - It is reliable
  - Refines diagnostic issues

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

Histologic Interpretation

LAST Terminology Diagnosis

Follow-Up Clinical Management

Treatment

High-Grade SIL

p16 IHC

Negative

A

p16 positive lesions in all sites

p16 "block" positive

Transitional Cell Metaplasia
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.

---

query CIN2
Recommendation #2 Notes

- p16 should *not* be used if the H&E morphologic differential diagnosis is between low grade disease (CIN1) and negative, as CIN1 can be either p16 negative or positive.
- If the pathologist’s histologic diagnosis is “obvious” CIN1, the WG does **not** recommend further IHC.
  - There is insufficient evidence to determine whether there is a difference in the natural history between p16 positive and p16 negative CIN1. Hence at the present time, it is recommended that clinical management of CIN1 be based on the histologic diagnosis alone.

Rationale for recommendations #1 and #2

- In the largest prospective adjudicated study and other supporting studies, diffuse strong (block positive) staining with p16 showed similar accuracy for high grade disease when compared to an adjudicated histology standard.
- p16 IHC improves the accuracy of a single pathologist’s interpretation of high grade vs. low grade disease relative to an adjudicated pathology panel.
- Addition of a p16 result leads to a more accurate prediction of the patient’s risk for high grade disease.

Recommendations #1 & 2

- Strength of Evidence – Dr. Myers
  - “The quality of the evidence for the test characteristics of H&E + p16 is moderate-high.”
  - “The quality of the evidence for improved consistency of readings with p16 is high.”
WG4 Biomarkers
Recommendations

3. p16 is recommended for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (−IN2 or −IN3).

Rationale for recommendation #3

- A number of studies address interobserver variability in the interpretation of lower anogenital tract squamous lesions.
- These studies all show that there is substantial improvement in agreement between observers when p16 IHC is used.
- Therefore in association with recommendation #1, the addition of p16 provides a more objective adjudication of the differential diagnosis than does H&E histologic assessment alone.

Recommendation #3

- Strength of Evidence – Dr. Myers
- “The quality of the evidence is high.”
WG4 Biomarkers Recommendations

4. WG4 recommends against the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN1, and –IN3.

WG4 Biomarkers Recommendations

4. SPECIAL CIRCUMSTANCE

(a) p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤−IN1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV16 +, or AGC (NOS).

- Any identified p16 positive area must meet H&E morphologic criteria for a high-grade lesion to be interpreted as such.

Rationale for recommendation #4

• Based on the high sensitivity of p16 for precancerous lesions, areas of small or equivocal high grade disease have been identified on histologic sections using p16, which were not readily identifiable on H&E sections alone.

• In a “high risk” situation, p16 block positive areas are most likely to represent precancerous disease.
**Biomarker Caveat**

- Ki67 and ProEx C show similar but less well-documented operating characteristics when compared to p16.
- If p16 is unavailable, technically inadequate, or equivocal;
- Ki67 and/or ProEx C may be considered for use.

**Recommendation #4**

- Strength of Evidence – Dr. Myers
- “...the quality of the evidence for superior sensitivity of H&E + p16 is high-moderate.”
Clinical Implications and Implementation

J. Thomas Cox, MD (retired)
University of California, Santa Barbara

LAST: Clinician’s Concerns

Concerns from the public comment period and working group are predominantly focused on two aspects.
- The clinical guidelines for treating cervical lesions are based on a 3-tiered (i.e., CIN) system.
- Concern was expressed that a 2-tiered system for cervical disease where most CIN2 lesions would fall into a high grade category would lead to potential over-treatment of patients, especially young women.
  - Potential perinatal morbidity associated with treatment

LAST: Clinicians’ Concerns

- Abuse of p16
  - While LAST proscribes use of p16 with CIN1, there is a fear among some clinicians that it will be used.
  - Diagnosis of CIN1-2
  - There is some data suggesting that CIN1/p16-positive lesions are more likely to progress than CIN1/p16-negative.
  - Will CIN1/p16-positive now be called “HSIL”?
    - Will clinicians manage HSIL (CIN1/p16-positive) with unnecessary treatment?
LAST: Benefits of Eliminating CIN2

• A 2-tiered system using p16 for adjudication of equivocal high grade lesions results in a much more reproducible diagnosis in pathology practice which will result in better clinical care.

• The poorly reproducible diagnosis of CIN2 may have resulted in overtreatment of lesions with low likelihood of becoming cancer.

LAST: Benefits of Eliminating CIN2

• Most clinicians are not aware that CIN2 is an equivocal diagnosis

• Implementing LAST terminology will probably not affect most clinicians’ practice.

• Accustomed to cytology reporting of LSIL / HSIL – Parenthetical reporting of CIN terminology after “SIL” designation has been the norm for many labs since first Bethesda Conference in 1988.

Management Concerns for Clinicians

Current ASCCP management recommendations:

• CIN1
  – In most cases, follow conservatively over 12 months with repeat cytology X 2 or HPV

• CIN2+
  – In most cases, treat with excision or ablation
  – (except in adolescents and young women)
Management Concerns for Clinicians

• How will the ASCCP management guidelines work with new endpoints?
  – LSIL = CIN1 and CIN2 (p16-negative)
  – HSIL = CIN3 and CIN2 (p16-positive)

• ASCCP guidelines based on data from multiple studies -- largely influenced by ALTS

Management Concerns for Clinicians

• Unknown clinical course of LSIL(CIN2/p16-neg)
  – Can this be managed expectantly as confidently as morphologic CIN1?
    – Probably, but no data
  – Conservative management of “LSIL”
    – Low likelihood of cancer in 6-12 months
    – Persistent abnormal cytology or positive HPV will lead to repeat colposcopy.

Management Concerns for Clinicians

• There is one scenario in which recommended clinical management is different for CIN2 and CIN3.
  – Adolescents and “young women”.
  – How do we deal with this if CIN2 and CIN3 are combined into “HSIL”?
A 21 y.o. has HSIL on cytology. Colposcopy was satisfactory and a biopsy was performed at 11:00. The biopsy revealed CIN2. How should she be managed?

A. LEEP
B. Follow with Pap test in 6 and 12 months
C. Follow with Pap test plus colposcopy in 6 and 12 months
D. HPV DNA test in 12 months

Natural History of Untreated CIN2 in Adolescents and Young Women

<table>
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<tr>
<th>Author</th>
<th>N</th>
<th>Age</th>
<th>Mean f/u</th>
<th>Regression to neg</th>
<th>Progression to CIN3</th>
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<td>Moore</td>
<td>23</td>
<td>&lt; 21</td>
<td>18 mo</td>
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<td>Fuchs</td>
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<td></td>
<td></td>
<td>3 yr</td>
<td>68%</td>
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No cases progressed to cancer in any study.

What if her biopsy showed CIN3? Would your management differ?

A. LEEP
B. Follow with Pap test in 6 and 12 months
C. Follow with Pap test plus colposcopy in 6 and 12 months
D. HPV DNA test in 12 months
2006 ASCCP Guidelines
CIN2,3 in Teens and Young Women

Adolescent and Young Women with CIN2,3

- Satisfactory and CIN2
- Colposcopy and Cytology at 6 month intervals up to 24 mos

- Neg x 2
- Annual Pap
- CIN2 persists
- 2 yrs
- Excisional Procedure

2006 ASCCP Guidelines
CIN2,3 in Teens and Young Women

Adolescent and Young Women with CIN2,3

- Satisfactory CIN2,3
- Colposcopy and Cytology at 6 month intervals up to 24 mos

- Neg x 2
- Annual Pap
- CIN2 persists
- 2 yrs
- Excisional Procedure

- Satisfactory & CIN3
- Unsatisfactory and CIN 2 or CIN3

Proposed Management Regimen

- There is no direct data on conservative management of young women with “HSIL” with HSIL defined as CIN2 / p16-positive or CIN3.

- Progression from HPV infection to cancer usually takes decades.
- Most infections in young women are new infections
  - 90% no longer detectable in 2-3 years
  - Those that develop HSIL have a long latent period before development of cancer in the few that will progress.
- Rate of invasive cancer under age 25 is 1.5/100,000 (SEER)
### Proposed Management Regimen

- **LSIL** – manage as CIN1
  - LSIL (CIN2 / p16-negative) should be safely followed with cytology q 6 months x 2 or HPV in 12 months
- **HSIL in most women** – manage as CIN2 or 3
- **HSIL in young women**
  - If HSIL (CIN3) – treatment with excision or ablation
  - If HSIL (CIN2 or NOS) manage with q 6 month cytology and colposcopy
    - Treat if persists for 24 months
    - Treat if colposcopy unsatisfactory
    - Treat if lesion enlarges or appears more severe on colposcopy

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We already have the option to manage young women with CIN2,3 with close follow-up if satisfactory colposcopy. Most clinicians would be more likely to follow CIN2,3 in a young woman when the lesion is small, less apparent and not extending into the canal as seen here.

Whereas no one would follow this CIN2,3

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**Wrap up and Q&A**

Ritu Nayar, MD  
Northwestern University  
School of Medicine
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

Working Group 5: Implications and Implementation of Standardizing Lower Anogenital Terminology

- To develop action plans to implement the terminology for pathologists and clinicians
  - Presentations at medical society meetings
  - Publication of recommendations/commentaries in journals and development of web based resources
- To address the potential implications to the following areas:
  - Data collection/recording/billing: tumor registries/cancer protocols, SNOMED/CPT/ICD codes
  - Education/Testing bodies: training programs, examinations
  - Regulatory agencies: CMS, CDC, CAP/JC checklists
- To assess uptake and impact
  - Baseline and follow up surveys of pathologists/clinicians

Summary: The LAST Project
LAST Project Resources

• Summary of recommendations
• Links to articles
• FAQs
• Biomarker Algorithms
• LAST Project PowerPoint presentation

www.cap.org  www.asccp.org

LAST Project Staff

• CAP
  – Lisa Fatheree, CT (ASCP)

• ASCCP
  – Kathy Poole
  – Kerry Curtis

The LAST Project

Thank you for participating!