Managing Abnormal Pap Smears: 
*Incorporating biomarkers and new guidelines into your practice*
Disclosures

• None
Objectives

Participant should be able to:

- Use p16 testing
- Access and apply new ASCCP guidelines for the management of abnormal cytology and cervical cancer precursors
What has changed...

- The way we screen for cervical disease
- The way we talk about histology
- The way we triage “mid-grade” histology
- The way we manage and follow abnormal cytology

...so, pretty much everything
Bethesda (2001) standardized cytology reporting

No such standardized system for histology reporting
- Confusion over biological equivalents can lead to over-treatment
- Many practitioners were already using a two-tiered system due to difficulties with diagnosis of CIN 2

Lower Anogenital Tract Squamous Terminology Project - 2012
- Consensus conference CAP and ASCCP
LAST Recommendations

- Unified, 2-tiered histopath nomenclature for all HPV-associated pre-invasive squamous lesions of the LAT
  - LSIL or HSIL

- Further classification using “-IN” terminology is appropriate
  - This distinguishes site (CIN, cervical; VIN, vulvar)
  - Can also separate grades (-IN 2 vs. –IN 3)
P16 Biomarker

p16

- Biomarker, tested via immunohistochemistry
- Presence reflects activation HPV oncogene-driven cell proliferation

Image from incyte diagnostics
Indications and Utility of p16 Testing

- Distinguishing true pre-cancer from:
  - Mimics such as immature metaplasia, atrophy
  - Low grade disease

- Adjudication tool for inter-observer differences in interpretation

- Evaluating cytologic and histologic discrepancies
  - Cytology of HSIL, ASC-H, AGC, or ASCUS/ HPV 16+ and histology interpreted as normal or LSIL

- **Not intended for use in “clear” cases of –IN 1 or –IN 3**
New Format of Results

- **Cervical Biopsy Results following an ASC-H pap smear**
- **SURG PATH FINAL REPORT:**

- *** ADDENDUM PRESENT ***
- Addendum Discussion
- A. CERVIX, LABELED AS "7 O'CLOCK", BIOPSY:
  - HIGH GRADE INTRAEPITHELIAL LESION, (CIN II, MODERATE DYSPLASIA)
  - IMMUNOHISTOCHEMICAL STAIN RESULT:
    - p16: POSITIVE

- B. CERVIX, LABELED AS "1 O'CLOCK", BIOPSY:
  - HIGH GRADE INTRAEPITHELIAL LESION, (CIN II, MODERATE DYSPLASIA)
  - WITH SUPERFICIAL ENDOCERVICAL GLAND INVOLVEMENT
  - IMMUNOHISTOCHEMICAL STAIN RESULT:
    - p16: POSITIVE
New Guidelines for Managing Abnormal Cytology

2001 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia

Thomas C. Wright, Jr, MD,a J. Thomas Cox, MD,b L. Stewart Massad, MD,c Jay Carlson, DO,d Leo B. Twiggs, MD,e and Edward J. Wilkinson, MD,f for the 2001 ASCCP-sponsored Consensus Workshop

New York, NY; Durham, NC; Springfield, Ill; Washington, DC; Miami and Gainesville, Fla

2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ

Thomas C. Wright Jr, MD; L. Stewart Massad, MD; Charles J. Dunton, MD; Mark Spitzer, MD; Edward J. Wilkinson, MD; Diane Solomon, MD; for the 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference

2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

L. Stewart Massad, MD, Mark H. Einstein, MD, Warner K. Huh, MD, Hormuzd A. Katki, PhD, Walter K. Kinney, MD, Mark Schiffman, MD, Diane Solomon, MD, Nicolas Wentzensen, MD, and Herschel W. Lawson, MD, for the 2012 ASCCP Consensus Guidelines Conference

Massad LS et al. Obstet Gynecol, April 2013
Why new guidelines?

- Reflect new screening recommendations
  - Handling results of co-testing
  - Return to “routine screening” when intervals are longer

- New data, esp regarding management of high grade abnormalities
  - Kaiser, 1.4 million women, 8 years of follow up

- More extensive incorporation of HPV testing

- Guidelines for women under 21 no longer applicable
Guiding Principles

- **Equal management for women at equal risk**
  - Diagnoses with similar risks should be managed similarly
  - Guidelines based upon currently available data

- **Screening goal is to reduce, but not eliminate, risk of cervical cancer**

- **Guidelines do not trump clinical judgment**
Benchmarking

Katki, HA J Low Gen Tract Dis, April 2013
Equal Management for Equal Risk

<table>
<thead>
<tr>
<th>5 year risk of Cin 3</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>2-5%</td>
<td>Repeat testing in 6-12 months</td>
</tr>
<tr>
<td>0.1-2%</td>
<td>Repeat testing in 3 years</td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td>Repeat testing in 5 years</td>
</tr>
</tbody>
</table>
The Young Patient

21 year old with first pap ever = ASCUS or LSIL

HPV Testing
Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

Repeat Cytology @ 12 months Preferred

- Negative, ASC-US or LSIL
  - Repeat Cytology @ 12 months
    - Negative x 2
      - > ASC
      - Colposcopy
  - ASC-H, AGC, HSIL

Reflex HPV Testing
Acceptable for ASC-US only

- HPV Positive
  - ASC-H, AGC, HSIL

- HPV Negative
  - Routine Screening

60% of ASCUS are HPV +
HSIL in the Young Patient

Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2,3 (CIN2,3) in Special Circumstances

Young Women with CIN2,3

Either treatment or observation is acceptable, provided colposcopy is adequate. When CIN2 is specified, observation is preferred. When CIN3 is specified, or colposcopy is inadequate, treatment is preferred.

Observation — Colposcopy & Cytology at 6 month intervals for 12 months

- 2x Cytology Negative and Normal Colposcopy
  - Cotest in 1 year
  - Both tests negative
  - Cotest in 3 years
- Either test abnormal

Treatment using Excision or Ablation of T-zone

- Colposcopy worsens or High-grade Cytology or Colposcopy persists for 1 year
  - Repeat Colposcopy/Biopsy Recommended
  - CIN3 or CIN2,3 persists for 24 months
  - Treatment Recommended

Note: Observation is colpo and cytology q 6 mos
Co-Testing Dilemmas

Cytology negative, HPV positive

4% of women undergoing co-testing will have this result.

5 year risk of CIN 3+ was 4.5%

Cumulative risk of disease in women at 30-64 with baseline negative cytology / HPV +

Katki, HA et al. J Low Genit Tract Dis, April 2013
Management of Women $\geq$ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable
  - Cytology Negative and HPV Negative → Repeat cotesting @ 3 years
  - $\geq$ASC or HPV positive → HPV DNA Typing

- **HPV DNA Typing**
  - Acceptable
  - HPV 16 or 18 Positive → Colposcopy
    - Manage per ASCCP Guideline
  - HPV 16 and 18 Negative → Repeat Cotesting @ 1 year
    - Manage per ASCCP Guideline
Co-testing Dilemmas

Pap LSIL, HPV negative

12-30% of LSIL are HPV negative

Katki, HA J Low Gen Tract Dis, April 2013
Co-testing Dilemmas

Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)†‡

**LSIL with negative HPV test**
- Among women ≥ 30 with cotesting
- **Preferred**
  - **Repeat Cotesting @ 1 year**
  - **Cytology Negative and HPV Negative**
  - **Repeat Cotesting @ 3 years**

**LSIL with no HPV test**
- **Acceptable**
  - **Colposcopy**
  - ≥ ASC† or HPV positive
  - Non-pregnant and no lesion identified
  - Inadequate colposcopic examination
  - Adequate colposcopy and lesion identified

**LSIL with positive HPV test**
- Among women ≥ 30 with cotesting

Endocervical sampling “preferred”
Endocervical sampling “acceptable”

**No CIN2,3**
- **Manage per ASCCP Guideline**

**CIN2,3**
- **Manage per ASCCP Guideline**

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* Management options may vary if the woman is pregnant or ages 21-24 years
† Manage women ages 25-29 as having LSIL with no HPV test

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Disease Surveillance: Getting back to “routine” screening

Antecedent pap affects long term risk of high grade disease

Katki, HA J Low Gen Tract Dis, April 2013
Follow Up After Colpo Dx of Normal or CIN 1

Antecedent ASCUS/HPV+ or LSIL

Antecedent ASC-H, HSIL, AGC

Katki, HA J Low Gen Tract Dis, April 2013
Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by “Lesser Abnormalities”

Follow-up without Treatment

- Cotesting at 12 months
- HPV(-) and Cytology Negative
- Age appropriate retesting in 3 years

≥ ASC or HPV(+)

Colposcopy

- No CIN
  - CIN2,3
  - CIN1

- Manage per ASCCP Guideline
- If persists for at least 2 years

Follow-up or Treatment

* “Lesser abnormalities” include ASC-US or LSIL Cytology, HPV 16+ or 18+, and persistent HPV

∞ Management options may vary if the woman is pregnant or ages 21-24.

† Cytology if age <30 years, cotesting if age ≥30 years

Either ablative or excisional methods. Excision preferred if colposcopy inadequate, positive ECC, or previously treated.
Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by ASC-H or HSIL Cytology

**Cotesting at 12 and 24 months***

- **HPV(-) and Cytology Negative at both visits**
  - **Age-specific Retesting in 3 years***

- **HPV(+) or Any cytology abnormality except HSIL**
  - **Colposcopy**

- **HSIL at either visit**
  - **Diagnostic Excision Procedure***
  - **Review of cytological, histological, and colposcopic findings**
    - **Manage per ASCCP Guideline for revised diagnosis**

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*Only if colposcopy was adequate and endocervical sampling is negative
^ Except in special populations (may include pregnant women and those ages 21-24)
* Cytology if age <30, cotesting if age ≥30 years
**Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2 and 3 (CIN2,3)*

*Management options will vary in special circumstances or if the woman is pregnant or ages 21-24.

†If CIN2,3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4-6mo is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.

- **Adequate Colposcopy**
  - **Either Excision† or Ablation of T-zone†**
    - Cotesting at 12 and 24 months
    - 2x Negative Results
    - Repeat cotesting in 3 years

- **Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3**
  - Diagnostic Excisional Procedure†
    - Any test abnormal
    - Colposcopy with endocervical sampling

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ASCUS/ HPV negative: “Normal”, or Not?

Katki, HA J Low Gen Tract Dis, April 2013
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*

- **Repeat Cytology**
  - @ 1 year
  - Acceptable
  - Negative
  - > ASC
  - Routine Screening

- **HPV Testing**
  - Preferred
  - HPV Positive
    - (managed the same as women with LSIL)
  - HPV Negative
    - Repeat Cotesting @ 3 years

- **Colposcopy**
  - Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others
  - Manage per ASCCP Guideline

*Management options may vary if the woman is pregnant or ages 21-24.
*Cytology at 3 year intervals
Exiting Screening

Katki, HA J Low Gen Tract Dis, April 2013
Postmenopausal women with ASC-US should be managed in the same manner as women in the general population

- **Except when considering exit from screening:**
  - Women aged 65 years and older with HPV-negative ASC-US should have repeat co-testing in one year
Updated Consensus Guidelines Algorithms

Click on the Image to see the algorithms as a PDF in a new window.

The algorithms in this PDF are for personal use only.

To download the ASCCP Consensus Guidelines App, please visit the iTunes Store here for iPhone and iPad or please visit Google Play here for the Droid format version.
Thank You