Why are new guidelines needed?

- NCI workshop revised criteria for cytologic interpretations and new terminology was introduced (Bethesda 2001).
- Knowledge about HPV has changed (NCI ASCUS/LSIL Triage Study).
- Previous guidelines were not evidence-based and were developed before sensitive methods for detecting HPV DNA were available (JAMA 1994).
- Previous guidelines were based on conventional Pap smear data (Bethesda 1989).
The 2001 Bethesda System

Do we need new guidelines?

“ASCUS, maybe LSIL, maybe reactive, somewhere in between, but maybe not, but lots of inflammatory cells”

Comment: Cancer cannot be ruled out in this smear. Colposcopy is recommended.
General Categorization

- **Eliminated.**
  - Within normal limits.
  - Benign cellular changes. (combined into negative for intraepithelial lesion or malignancy).
  - Hormonal evaluation.

- **Retained.**
  - Negative for intraepithelial lesion or malignancy (includes organisms).
  - Epithelial cell abnormality.
  - Other:
    - Endometrial cells.

---

2001: Endometrial cells

- “Other” category.
  - Endometrial cell presence in women older than 40 years.
2001- Endometrial cells on Pap

- Endometrial cells do not need to be reported in women < 40 years (Ng, Gondos, Gray).
- Endometrial cells in all women > 40 years, regardless of hormonal therapy, should be reported (Ng, Cherkis, Zucker).

- “The Pap smear is a screening tool for squamous lesions. It is an inaccurate test for detection of endometrial lesions and should not be used to evaluate suspected endometrial abnormalities”.

2001 Recommendation - Adequacy

- Maintain the “satisfactory for evaluation” and “unsatisfactory for evaluation” categories.
- Eliminate the “satisfactory but limited by…. ”.
  - Oxymoron - is it satisfactory or limited?
  - Describe presence or absence of endocervical/transformation zone component and any other quality factors immediately after “satisfactory” and “unsatisfactory” terms (will now be just a comment).
- Any specimen with abnormal cells is by definition “satisfactory for evaluation”.
Satisfactory but limited by…(SBLB)

- Eliminated because it was confusing to many clinicians and there were conflicting data regarding value of an early repeat Pap.

- Big question……. Will there be more unsatisfactory smears???

Quality indicators: partial obscuring

- Satisfactory for evaluation.
  - “Partially obscuring” blood or inflammatory cells (50-75% of cells).
    - Little data on partially obscuring factors.
    - Retrospective studies fail to show that partial obscuring factors indicate risk for a false-negative report (O’Sullivan, Mitchell).
    - Prospective studies not available.
Quality indicators: obscuring factors

- Negative Pap smear with partial obscuring factors (blood, inflammation, air-drying).
  - Annual Pap preferred for most women.
  - Postpartum Pap for pregnant women.
  - Early repeat (6 months) may be beneficial for some women.
    - Previous abnormal Pap smear.
    - Multiple partners in one year.

Unsatisfactory Pap

- Longitudinal studies: More often from high risk patients (Ransdell).
  - Significantly more CIN/cancer on follow-up.
- Early repeat (2-4 months) should be performed.
  - If repeat Pap is unsatisfactory due to “obscuring” factors, colposcopy is recommended.
Caution with unsatisfactory Paps

- Inflammation and bleeding associated with cancer, CIN 2/3, or benign conditions that produce unsatisfactory Pap smears.
- Liquid-based cytology may reduce obscuring factors.

Summary of Pap Adequacy

- **12 month repeat** (or postpartum) preferred management for a woman with:
  - A negative Pap lacking EC/TZ component.
  - A negative pap that has partially obscuring blood, inflammation, air-drying.
    - **6-month repeat** beneficial for **some** women with risk factors.
- **2-4 month repeat** recommended follow-up for an unsatisfactory Pap.
ASCPC Consensus Conference
NCI, Bethesda, MD, September 2001

- Developed evidence-based guidelines following internet bulletin boards and data extraction by committees.
- 29 participating professional and health organizations and federal agencies (121 invited participants).
- Each guideline voted upon and accepted by a minimum 2/3’s majority vote.
- Guidelines and recommendations at the ASCCP website (http://www.asccp.org)

What is ALTS and why is it important?

- NCI-sponsored study of ASCUS/LSIL Triage Study (ALTS).
- 3400 women with ASCUS; 1500 women with LSIL.
- Triaged randomly to immediate colposcopy, HPV testing or Pap smear follow-up.
- Used liquid based cytology.
2001 ASCCP Consensus Guidelines for the Management of Cytological Abnormalities and Cervical Cancer Precursors


JAMA 2002;287:2120-2129.

Rating system for recommendations

- Strength of recommendation (A-E).
- Quality of evidence (I-III).
- Terminology was assigned:
  - Recommended (one option available).
  - Preferred (best when multiple options available).
  - Acceptable (multiple options available- another approach is superior or no data to favor any single option).
  - Unacceptable (good data against use).
ASCUS
(everybody’s favorite topic!)

Why have an “equivocal” category?

- Why not just downgrade to “negative”?
  - 10% of ASC is underlying ≥ CIN 2.
  - 1/1000 ASC is associated with invasive cancer.
  - Numerically important source of lesions ≥ CIN 2.
- Strong support to maintain an equivocal category.
Atypical squamous cells (ASC)

ASC-US

ASC-H

ASCUS-favor reactive

ASCUS-favor neoplasia

ASCUS

2001:ASC-undermined significance (ASC-US)

- Replace ASCUS with a new category “atypical squamous cells (ASC-US).
  - Emphasizes exclusion criteria rather than defining what should be included.
- Strong support for elimination of “favor reactive” in ASCUS category.
  - Frequency of CIN 2-3 and oncogenic HPV types is low in this category.
2001: Atypical squamous cells, cannot exclude HSIL (ASC-H)

- Cytologic changes suggestive of HSIL, but lacking criteria for definitive interpretation.
  - Manage as HSIL.
- ASC-H comprises about 5-10% of total ASC.
- Positive predictive value (PPV) for lesions ≥ CIN 2 is greater than ASC-US but less than HSIL.
  - Strong support of ASC-H because of high PPV.

Histologic Outcomes: ALTS
ThinPrep cytology

<table>
<thead>
<tr>
<th>Cytology Category</th>
<th>HPV+</th>
<th>≥ CIN 2</th>
<th>CIN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US*</td>
<td>63%</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>ASC-H</td>
<td>86%</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>HSIL</td>
<td>99%</td>
<td>59%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*ASC-US = ASC-L in publication (prior to TBS 02)
NCI study results (ALTS)

Intermediate triage of ASCUS focuses attention on women who are at greatest risk of having significant lesions.....

Versus

Those who have cytologic changes that are likely to go away on their own.

Solomon et al. JNCI 2001;93.

New Consensus Guidelines will consider the following...

- Interpretation of ASC is poorly reproducible.
- A woman with ASC on routine screening cervical cytology has a 5-15% risk of having CIN 2-3.
- Additional work-up or follow-up required.
- Avoid additional anxiety and cost and lack of adherence to suggested triage.
## Prevalence of SIL on follow-up of ASCUS

<table>
<thead>
<tr>
<th>Author</th>
<th>#Paps</th>
<th>%ASC</th>
<th>ASC/CIN</th>
<th>F-up(#)</th>
<th>%LSIL</th>
<th>%HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lachman</td>
<td>76,265</td>
<td>4.5</td>
<td>2.2:1</td>
<td>Bx(580)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Nyirjesy</td>
<td>7,651</td>
<td>3.1</td>
<td>2.9:1</td>
<td>Colp(227)</td>
<td>25</td>
<td>5.2</td>
</tr>
<tr>
<td>Manos</td>
<td>46,009</td>
<td>3.5</td>
<td>2.9:1</td>
<td>Colp(995)</td>
<td>13</td>
<td>6.8</td>
</tr>
<tr>
<td>Bergeron</td>
<td>420,000</td>
<td>1.0</td>
<td>1.0:3</td>
<td>Colp(111)</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Shlay</td>
<td>3,600</td>
<td>5.4</td>
<td>NA</td>
<td>Colp(195)</td>
<td>28</td>
<td>7.6</td>
</tr>
</tbody>
</table>
Liquid vs Conventional Cytology

1. **Liquid cytology does not eliminate ASC.**
2. Impact of method on prevalence of CIN in ASC is unknown.
3. Having residual sample for molecular testing has significant impact on selection of triage options however.

Comparison of ASC Categories in ALTS

<table>
<thead>
<tr>
<th>Cytology</th>
<th>HPV High Risk</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIN 2</td>
<td>CIN 3+</td>
</tr>
<tr>
<td>Smear ASC-US</td>
<td>58.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Smear ASC-H</td>
<td>69.8%</td>
<td>10.4%</td>
</tr>
<tr>
<td>ThinPrep ASC-US</td>
<td>63.2%</td>
<td>6.9%</td>
</tr>
<tr>
<td>ThinPrep ASC-H</td>
<td>85.6%</td>
<td>16.4%</td>
</tr>
</tbody>
</table>
Let’s look first at the data on triage of ASC-US

Management Options for ASC-US

Immediate colposcopy
Repeat cervical cytology
HPV DNA testing
Ancillary test (lacking data at this time)
ASC-US

Repeat cytology  Colposcopy  HPV Testing

All 3 triage arms are “safe” and effective (A1).

When liquid-based cytology or co-collection is used, reflex HPV testing is preferred. (A1)


Immediate Colposcopy
For ASC-US
Immediate Colposcopy

**Advantages:**
- Immediately informs of the presence of absence of disease.
- Considered sensitive technique.

**Disadvantages:**
- Patients hear cancer.
- Relatively expensive.
- Not always available.
- May lead to overdiagnosis and overtreatment

Performance of Colposcopy

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Sens.</th>
<th>Spec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benedet</td>
<td>549</td>
<td>.99</td>
<td>.53</td>
</tr>
<tr>
<td>Benedet</td>
<td>3252</td>
<td>.95</td>
<td>.44</td>
</tr>
<tr>
<td>Cristoforoni</td>
<td>181</td>
<td>.98</td>
<td>.34</td>
</tr>
<tr>
<td>Edebiri</td>
<td>222</td>
<td>.87</td>
<td>.67</td>
</tr>
</tbody>
</table>

*Weighted mean*  .96  .48

Meta-analysis of studies for distinguishing normal from abnormal
Recommended management of ASC-US using immediate colposcopy

- If no CIN is found on colposcopy, repeat cytology in 12 months (B-II).
- If CIN found on colposcopy, manage according to guidelines (in press).

Repeat Cytology of ASC-US
Repeat Cytology for ASC-US

Advantages:

Clinicians are comfortable with this technology.
Cumulative detection rate for CIN 2-3 estimated to be relatively high if sequential Paps completed.
Less costly than colposcopy.

Program of Repeat Cytology

- Cut-off of repeat Pap result for referral to colposcopy should be ASC or greater.
- Sensitivity of a single repeat Pap for detecting CIN 2-3 is relatively low (0.67 - 0.85).
- Limited data on key parameters (timing of repeat Pap, number of repeats).
Repeat Cytology of ASC-US

Disadvantages:
Two repeats required before assurance that no disease is present.
- High rates of lost to follow-up
- Produces uncertainty, anxiety
- Inconvenient to patient and costly

Recommended management using repeat cytology

- Women with ASC-US should receive repeat cytology at 4-6 month intervals until 2 consecutive “negatives” are obtained (A-II).
- If ASC-US or greater on repeat, refer to colposcopy (A-II).
- After 2 repeat “negatives”, return to routine cytologic screening (A-II).
HPV DNA Testing of ASC-US

Higher sensitivity for detection of CIN 2-3 than a single repeat Pap (conventional or liquid-based).

• one HPV test appears equivalent to 2 Pap smears.
• Liquid-based cytology and reflex testing eliminate additional clinic visit.
Do we need low-risk HPV DNA report?

- Testing for low-risk HPV types adds approximately $50-$100 to the management of women with ASC-US.
- FDA approved splitting of low and high-risk HPV types.
- The only HPV types that are important are the ones that could lead to cervical cancer.
  - High risk or oncogenic types.

HPV DNA Testing

**Disadvantages:**

- Perceived as expensive (Medicare reimburses at $48.50)
- Single FDA-approved method available
- Some studies company-sponsored
- Not universally covered by insurance
- Counseling of HPV + women takes time
What if HPV testing is negative?

- Negative predictive value = 99.5% (if HPV is negative, highly unlikely disease is present.
- HPV DNA + ASC-US is similar to LSIL.
- HPV triage is at least as effective as immediate colposcopy in detecting CIN 3.
- Repeat cytology is safe at ASCUS threshold provided patient is compliant. However, trade off of sensitivity with specificity is not as good as single HPV test.

ASCUS Management

Repeat Pap smear vs HPV testing

<table>
<thead>
<tr>
<th>Author</th>
<th>Repeat Pap Sensi*</th>
<th>%Colp</th>
<th>Hybrid Capture II Sensi*</th>
<th>%Colp</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTS-NCI</td>
<td>85.3%**#</td>
<td>58.6%</td>
<td>96.3%</td>
<td>56.1%</td>
</tr>
<tr>
<td>Wright et al</td>
<td>70%**</td>
<td>56%</td>
<td>89%</td>
<td>62%</td>
</tr>
<tr>
<td>Manos et al</td>
<td>76%</td>
<td>39%</td>
<td>89%</td>
<td>40%</td>
</tr>
<tr>
<td>Bergeron et al</td>
<td>66%</td>
<td>32%</td>
<td>83%</td>
<td>43%</td>
</tr>
</tbody>
</table>

* for histologic CIN 2-3
** liquid-based cytology
# triage threshold of ASCUS or above
Recommended management of ASC-US using HPV DNA testing

- HPV DNA testing should be done with a sensitive molecular test (A-II).
  - Sample can be saved for 3 weeks so clinician should specify HPV testing on ASC-US.
- Women who test + for oncogenic HPV DNA should be referred for colposcopy (A-II).
- Women who test negative for oncogenic HPV DNA can be followed with repeat cytology at 12 months (B-II).

Recommended management of ASC-US using HPV DNA testing

- Acceptable options for women who test + for oncogenic HPV but have negative colposcopy.
  - Repeat cytology at 6-12 months (refer to colposcopy if ASC or greater is present) (B-II).
  - HPV DNA testing at 12 months (refer to colposcopy if HPV DNA +) (B-II).
ASC-US and + oncogenic HPV DNA  
These women should be treated as if they have LSIL.

ASC-US and - oncogenic HPV DNA  
These women should be treated as if they have a “negative for intraepithelial lesion or malignancy”.

ALTS data
Reflex HPV DNA testing vs co-collection

- If using conventional cytology, co-collection is option (CPT-87621).
  - Sample of HPV DNA available without incurring costs of liquid-based cytology.
- Reflex HPV DNA testing provides the same clinical benefit as performing colposcopy or repeat cytology but is less expensive.
  - 50% of women will be HPV negative and could resume annual screening and avoid colposcopy (cost savings).

Let’s look at the triage of ASC-H
Recommended management of women with ASC-H

- Recommended triage is colposcopy (A-II).
  - If no lesion identified, review of cytology, colposcopy and histology is recommended (C-III).
  - If review results in revision, follow guidelines for new interpretation.
  - If ASC-H upheld, cytology at 6 and 12 months or HPV DNA testing at 12 months is acceptable (C-III).

ASC: Summary and Triage

**ASC-US**
- 90-95% of ASC reports
- Risk of ≥ CIN 2+ ~ 10-20%
- HPV positive ~ 50%
- **Management options:**
  - Repeat cytology.
  - Immediate colposcopy.
  - HPV DNA testing.

**ASC-H**
- 5-10% of ASC reports
- Risk of ≥ CIN 2+ ~ 25-75%
- HPV positive ~ 70-85%
- **Management option:**
  - Colposcopy
60 year old postmenopausal woman (10 years). Not taking HRT. No history abnormal Pap smears. 2 sexual partners.

Pap smear: ASC-US
HPV DNA negative
28 year old G7, P4, EAB 3. Multiple sexual partners. Gonorrhea +. Drug screen + cocaine. All previous Pap smears normal but not had a Pap in 5 years.

Pap smear - ASC-H.
Recommended management of ASC-US special circumstances

- Postmenopausal women with ASC-US and atrophy.
  - Acceptable option: Repeat Pap 1 week after estrogen treatment and again at 4-6 months (C-III).
  - Return to routine screening if both repeat Paps normal or refer to colposcopy if repeat is ASC or greater (A-II).

- HIV + women with ASC-US.
  - Colposcopy is recommended triage (B-II).

Atypical Glandular Cells
Scope of Atypical Glandular Cells (AGC)

- Typical lab rates should be < 1%.
- Reported incidence of AGC is from 0.1-1.8%.
- Overlap confusion of ASCUS and AGUS.
  - The more problematic AGC may be undermanaged.
- Colposcopic criteria for glandular lesions are not as specific as squamous lesions.

Risks of AGC

- Associated with a significantly greater risk for cervical neoplasia than ASC or LSIL.
- Women with AGC:
  - 9-54% have histologic CIN.
  - 0-8% have histologic adenocarcinoma in situ (AIS).
  - 1-9% have invasive carcinoma.
- Higher risk of CIN 2 or higher among women with AGC-favor neoplasia (27-96%) than AGC-not specified (9-41%).
All methods used to evaluate AGC have limitations

♦ Sensitivity for identifying glandular neoplasia with screening cytology (50-72%).
♦ Repeat cytology is less sensitive than colposcopy for detecting CIN 2-3 and glandular lesions.
♦ Many cases of histologic AIS and adenocarcinoma have no observed colposcopic abnormalities.

Recommended management for women with AGC

♦ It is recommended that women with all subcategories of AGC receive colposcopy (A-II).
  ♦ Endometrial sampling in women > age 35 years and in younger women with unexplained vaginal bleeding (A-II).
♦ Colposcopy and endometrial sampling if AIS present on cytology.
♦ Repeat cytology as initial management of AGC or cytologic AIS is unacceptable (E-II).
Recommended management of AGC

- Women with AGC, favor neoplasia or AIS and no identifiable lesion should undergo a diagnostic excisional procedure (A-II).
  - Preferred method is cold-knife conization (B-II).
- Women with AGC-NOS and no identifiable lesion should have repeat cytology at 4-6 month intervals until 4 negative Paps (B-III).
- Women with AGC-NOS and squamous disease should be treated according to guidelines.

CIN incorporates 2 different entities

**LSIL**
- CIN 1
- HPV infection
- Koilocytosis
- Transit infection

**HSIL**
- CIN 2-3
- Monoclonal
- Aneuploidy
- True cancer precursor
Low-grade squamous intraepithelial lesion (LSIL) and mild dysplasia (CIN 1)
**LSIL**

- Rates in high-risk populations as high as 7.7%.
- Approximately 15-30% of women with LSIL will have histologic CIN 2-3.
- Majority of women with LSIL have no cervical lesion or CIN 1 (which has high rate of regression).
ALTS: HPV Typing and LSIL

- 642 women with LSIL were evaluated for the presence of HPV DNA with HPV DNA testing (Hybrid Capture II assay)
  - 532 women had detectable oncogenic HPV types.
  - 171/210 (83%) women were positive for HPV by both Hybrid Capture and polymerase chain reaction (PCR).

- Conclusion: HPV DNA typing has limited value in the triage of women with LSIL.

Koutsky LA. JNCI. 92:397-402, 2000

Recommended management for women with LSIL

- Colposcopy is the recommended management option (A-II).
- Routine use of excision or ablation is unacceptable for initial management of LSIL if no lesion found on colposcopy (D-II).
Why not repeat cytology for LSIL?

- Management by repeat cytology was considered more problematic than immediate referral to colposcopy.
  - 15-30% risk of CIN 2/3 or greater.
  - 53-76% likelihood that repeat cytology will continue to be abnormal.
  - Risk of loss to follow-up over multiple visits.

LSIL

- Satisfactory colposcopy.
- Endocervical sampling is acceptable for non-pregnant women with identified lesion (C-II) and preferred if no lesion identified (B-II).
LSIL

- Unsatisfactory colposcopy.
  - Endocervical sampling is preferred for non-pregnant women (B-II).
  - If biopsy fails to confirm CIN, acceptable options:
    - Repeat cytology at 6 and 12 months and colposcopy if >ASC-US (B-II) or HPV DNA testing at 12 months and referral to colposcopy if oncogenic HPV (B-II).

LSIL in special circumstances

- Postmenopausal women.
  - Course of intravaginal estrogen followed by repeat cytology one week after treatment (C-III).
- Postmenopausal women and adolescents.
  - Follow-up without initial colposcopy is acceptable.
  - Repeat cytology at 6-12 months with referral to colposcopy if > ASC-US or HPV DNA testing at 12 months and referral to colposcopy if oncogenic HPV DNA (C-III).
HSIL
High-grade squamous intraepithelial lesion
moderate/severe dysplasia
CIN 2 and 3

Progression of HSIL
✦ Even CIN 3 does not invariably progress to invasive cancer.
✦ HSIL (lesion) is used rather than neoplasia to convey the uncertain biologic potential in each patient.
✦ However, as a group, HSIL is more likely to persist or progress than LSIL.
✦ However, the progressive potential in an individual patient is unpredictable.
HSIL

- Uncommon cytologic diagnosis (0.45% of all Pap smears).
- Women with HSIL have 70-75% risk of having histologic CIN 2-3.
- 1-2% risk of having invasion.

2001: HSIL.. suggestive of invasion

- HSIL in which there is a suggestion that invasion may be present.
  - Allows the lab to alert the clinician without making a definitive diagnosis of invasion in questionable cases.
- Cytologic diagnosis of HSIL with added comment of “with features suspicious for invasion”.
Colposcopy with endocervical assessment is the recommended management (A-II).

- Satisfactory colposcopy.
  - No lesion identified or CIN 1 identified, review of the cytology, colposcopy and histology is recommended (B-III).
  - If HSIL upheld or review not possible, a diagnostic excisional procedure is preferred in non-pregnant women (B-II).
HSIL

- Unsatisfactory colposcopy.
  - No lesion identified, review of all results is recommended (B-III).
  - If HSIL upheld, review not possible or CIN 1 identified, diagnostic excisional procedure is recommended in non-pregnant women (A-II).
  - Ablation is unacceptable (E-II).

Recommended management of HSIL

- Unsatisfactory colposcopy.
  - Omission of endocervical sampling is acceptable when diagnostic excision is planned.
  - When colposcopy suggests a high-grade lesion, initial diagnostic excision is acceptable (B-I).
  - Triage with repeat cytology or HPV DNA testing is unacceptable (E-I).
**HSIL in special circumstances**

- **Pregnant women.**
  - Colposcopy should be performed by experienced clinicians (B-III).
  - Biopsy of high-grade lesions is preferred and biopsy of other lesions is acceptable (B-III).
  - ECC is unacceptable (E-III).
  - Treatment is unacceptable unless invasive cancer is identified (E-II).
  - Colposcopy and cytology no sooner than 6 weeks postpartum (C-III).

- **Young women.**
  - When CIN 2-3 is not identified, observation with cytology and colposcopy at 4-6 month intervals is acceptable.
  - Colposcopy is satisfactory, endocervical sampling is negative and patient accepts risk of potential progression of lesion.
  - If lesion progresses to high-grade or HSIL persists, a diagnostic excision procedure is recommended (B-III).
Algorithm for colposcopy referral

ASC-H  LSIL  HSIL

Colposcopy

AGC

ASC-US