ASCUS and AGUS and LGSIL in >30 years old

Dr Trudy Smith
Wits Donald Gordon Medical Center
SHCOOL
Who decided on what to do?

Professional societies, national and international health organizations meet in Bethesda, Maryland

Revised in 2006.

Last updated in 2012.

Used the KPNC analysis of abnormalities of 1,4 million women to come up with their strategies.
Strategies

• Immediate colposcopy and management if risk of having a CIN 2 or greater lesion exceeds 5%
• 6 to 12 month return if risk 2-5%
• 3 year return if 0,1-3%
• 5 year return if less than 0.1%
Terminology and histology of cervical intraepithelial neoplasia

<table>
<thead>
<tr>
<th>LAST System ![1]</th>
<th>Cytology</th>
<th>LSIL</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>LSIL</td>
<td>p16 staining should be performed*</td>
<td>HSIL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bethesda Classification System ![2]</th>
<th>Cytology</th>
<th>LSIL</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>CIN 1</td>
<td>CIN 2</td>
<td>CIN 3</td>
</tr>
</tbody>
</table>

| Previous terminology | Mild dysplasia | Moderate dysplasia | Severe dysplasia | Carcinoma in-situ |

| Histologic images | ![Image](image1) | ![Image](image2) | ![Image](image3) | ![Image](image4) |

Terminology regarding cytologic and histologic precancerous changes of the uterine cervix. The corresponding terminology from the previous classification systems is shown. Images of the histologic correlates for each category are also shown.

LAST: lower anogenital squamous terminology; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; CIN: cervical intraepithelial neoplasia.

* CIN 2 that is p16-positive is classified as HSIL. CIN 2 that is p16-negative is classified as LSIL.
Lower Anogenital Squamous Terminology (LAST) Project

- This classification appears in some literature
- The evidence is not robust so should not be used
- Use p16 on high grade lesions and if the lesion was p16 negative it is deemed a low grade lesion
I’m 20

I’m 41
<table>
<thead>
<tr>
<th>Triage strategy</th>
<th>Percent sensitivity for detection of CIN 3 or higher (95% CI)</th>
<th>Percent women referred for colposcopy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 23 to 28 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV testing</td>
<td>96 (91 to 100)</td>
<td>65 (62 to 69)</td>
</tr>
<tr>
<td>Repeat cytology for ASC-US</td>
<td>88 (79 to 97)</td>
<td>64 (60 to 68)</td>
</tr>
<tr>
<td><strong>Age ≥29 years</strong></td>
<td></td>
<td></td>
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<tr>
<td>HPV testing</td>
<td>94 (86 to 100)</td>
<td>31 (28 to 34)</td>
</tr>
<tr>
<td>Repeat cytology for ASC-US</td>
<td>91 (81 to 100)</td>
<td>50 (47 to 54)</td>
</tr>
<tr>
<td><strong>All ages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV testing</td>
<td>96 (93 to 100)</td>
<td>54 (52 to 56)</td>
</tr>
<tr>
<td>Repeat cytology for ASC-US</td>
<td>86 (80 to 92)</td>
<td>59 (57 to 61)</td>
</tr>
</tbody>
</table>

HPV: human papillomavirus; ASC-US: atypical squamous cells of unknown significance; CI: confidence interval.  
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>AGC</th>
<th>Prevalence (%)</th>
<th>HSIL</th>
<th>Prevalence (%)</th>
<th>LSIL</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All histopathologies</td>
<td></td>
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<tr>
<td>All ages</td>
<td>198</td>
<td>1.35</td>
<td>1633</td>
<td>2.49</td>
<td>428</td>
<td>0.18</td>
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<tr>
<td>23-29</td>
<td>18</td>
<td>1.22</td>
<td>197</td>
<td>0.82</td>
<td>78</td>
<td>0.08</td>
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<tr>
<td>30-39</td>
<td>75</td>
<td>2.29</td>
<td>663</td>
<td>2.84</td>
<td>155</td>
<td>0.23</td>
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<td>40-49</td>
<td>70</td>
<td>1.30</td>
<td>489</td>
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<td>124</td>
<td>0.24</td>
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<td>50-59</td>
<td>35</td>
<td>0.78</td>
<td>284</td>
<td>5.01</td>
<td>71</td>
<td>0.23</td>
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<tr>
<td>Adenocarcinoma</td>
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<td></td>
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<tr>
<td>All ages</td>
<td>145</td>
<td>0.99</td>
<td>163</td>
<td>0.25</td>
<td>49</td>
<td>0.02</td>
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<td>23-29</td>
<td>11</td>
<td>0.75</td>
<td>16</td>
<td>0.07</td>
<td>8</td>
<td>0.01</td>
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<tr>
<td>30-39</td>
<td>51</td>
<td>1.55</td>
<td>71</td>
<td>0.30</td>
<td>12</td>
<td>0.02</td>
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<tr>
<td>40-49</td>
<td>54</td>
<td>1.00</td>
<td>50</td>
<td>0.40</td>
<td>20</td>
<td>0.04</td>
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<td>50-59</td>
<td>29</td>
<td>0.65</td>
<td>26</td>
<td>0.46</td>
<td>9</td>
<td>0.03</td>
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<tr>
<td>Squamous cell cancer</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All ages</td>
<td>44</td>
<td>0.30</td>
<td>1418</td>
<td>2.16</td>
<td>368</td>
<td>0.15</td>
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<tr>
<td>23-29</td>
<td>6</td>
<td>0.41</td>
<td>173</td>
<td>0.72</td>
<td>68</td>
<td>0.07</td>
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<tr>
<td>30-39</td>
<td>20</td>
<td>0.61</td>
<td>569</td>
<td>2.44</td>
<td>141</td>
<td>0.21</td>
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<tr>
<td>40-49</td>
<td>14</td>
<td>0.26</td>
<td>429</td>
<td>3.44</td>
<td>100</td>
<td>0.19</td>
</tr>
<tr>
<td>50-59</td>
<td>4</td>
<td>0.09</td>
<td>247</td>
<td>4.36</td>
<td>59</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Percentage of prevalent cancer among women with abnormality.
Atypical glandular cells
Terminology

• Atypical glandular cells (AGS) has replaced Atypical glandular cells of undetermined significance
• Can be divided into AGS-NOS, AGS-endometrial
• Atypical glandular cells favor neoplasia
• Endocervical adenocarcinoma in situ (AIS)
• Adenocarcinoma
Risk of malignant disease

• Occurs more commonly in women over 40
• Risk of malignancy is nearly 30%
• Approximately half of women with AGC have a coexisting squamous cytologic abnormality
• The risk of malignancy in women with AGC increases with age

The histological significance of atypical glandular cells on cervical cytology: Experience at Groote Schuur Hospital, Cape Town, South Africa

L D Ho man,1 MSc; H-T Wu,2 MB BCh, MMed, FCPath, FRCPath

Fig. 1. Histological diagnosis by age band in women with a cytological diagnosis of AGC. (Ca. = carcinoma; Poly. = polynomial regression.)
Recommendation for AGUS after 30

- HPV NOT NECESSARY
- Colposcopy
- Hysteroscopy
- Endometrial sampling
- Endocervical sampling
- +/- Biopsy
- LLETZ/ Cone if colposcopy inadequate
Inadequate verses Insufficient EC component- Inadequate

• Inadequate implies there is lack of cellularity of any source
• Insufficient implies good cellularity but no endocervical component
• Higher in older women
• HPV testing preferred. If HPV negative repeat pap smear
Cytology NILM but EC/TZ Absent/Insufficient

Ages 21-29*

HPV negative

HPV testing (Preferred)

Routine screening

Age ≥30 years

HPV unknown

Repeat cytology in 3 years (Acceptable)

HPV positive

Cytology+ HPV test in 1 year

Genotyping

Manage per ASCCP guideline

HPV positive

or

Genotyping
Unsatisfactory cytology

• If co tested and HPV positive then colposcopy
• If patient has had 2 unsatisfactory Pap smears in a row then colposcopy
• If HPV negative and unsatisfactory pap smear repeat smear in 2 to 4 months
Unsatisfactory Cytology

- HPV unknown (any age)
- HPV negative (age ≥30)
- HPV positive (age ≥30)

Either is acceptable

Repeat Cytology after 2-4 months

- Abnormal: Manage per ASCCP guideline
- Negative: Routine screening (HPV-/unknown) or Cotesting @ 1 year (HPV+)
- Unsatisfactory: Colposcopy
ASCUS verses ASC-HG

- Atypical squamous cells of undetermined significance (ASC-US) – Cells that display abnormalities more marked than simple reactive changes but do not display a squamous intraepithelial lesion (SIL).

- Atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesion (ASC-H) – Cells that likely consist of a mixture of true high-grade SIL and other findings that mimic such lesions
Risk of cervical neoplasia with abnormal cervical cytology results in women ages 30 to 64

<table>
<thead>
<tr>
<th>Cervical cytology*</th>
<th>Incidence (percent)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIN 2+</td>
<td>CIN 3+Δ</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Negative</td>
<td>0.68</td>
<td>0.26</td>
<td>0.025</td>
</tr>
<tr>
<td>Atypical squamous cells of undetermined significance (ASC-US)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-positive</td>
<td>6.9</td>
<td>2.6</td>
<td>0.18</td>
</tr>
<tr>
<td>HPV-negative</td>
<td>18</td>
<td>6.8</td>
<td>0.41</td>
</tr>
<tr>
<td>HPV-positive</td>
<td>1.1</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>HPV-negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>16</td>
<td>5.2</td>
<td>0.16</td>
</tr>
<tr>
<td>HPV-positive</td>
<td>19</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>HPV-negative</td>
<td>5.1</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Atypical squamous cells: cannot exclude a high-grade squamous intraepithelial lesion (ASC-H)</td>
<td>35</td>
<td>18</td>
<td>2.6</td>
</tr>
<tr>
<td>High-grade intraepithelial lesion</td>
<td>69</td>
<td>47</td>
<td>7.3</td>
</tr>
<tr>
<td>Atypical glandular cells</td>
<td>13</td>
<td>8.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Squamous cell cancer</td>
<td>84</td>
<td>84</td>
<td>68</td>
</tr>
</tbody>
</table>

HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia.
* Results alone, unless testing for high-risk subtypes of HPV is specified.
Δ Includes adenocarcinoma in situ.
◊ Includes squamous cervical cancer and cervical adenocarcinoma.

Data from:
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology

- **Repeat Cytology @ 1 year Acceptable**
  - Negative: **Routine Screening***
  - ≥ ASC: **Colposcopy***
    - Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others
    - HPV Positive (managed the same as women with LSIL)
    - HPV Negative: **Repeat Cotesting @ 3 years**
- **HPV Testing Preferred**
  - HPV Positive: **Repeat Cotesting @ 3 years**
  - HPV Negative: **Manage per ASCCP Guideline***

*Management options may vary if the woman is pregnant or ages 21-24.  
*Cytology at 3 year intervals*
Persistent ASCUS- HPV +ve

Negative colpo

• Endocervical sampling should be performed
• Insure colposcopy is adequate
• If not adequate LLETZ sampling the entire transformation zone
Persistent ASC-US- HPV negative

- Atrophy or inflammation
- Post menopausal women use estrogen
- PV
- Repeat co testing in 1 year
Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)

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

- **LSIL with negative HPV test**
  - Preferred: Repeat Cotesting @ 1 year
    - Cytology Negative and HPV Negative
    - Repeat Cotesting @ 3 years

- **LSIL with no HPV test**
  - Acceptable: Colposcopy
    - Non-pregnant and no lesion identified
    - Inadequate colposcopic examination
    - Adequate colposcopy and lesion identified
      - Endocervical sampling “preferred”
      - Endocervical sampling “preferred”
      - Endocervical sampling “acceptable”

- **LSIL with positive HPV test**
  - Non-pregnant and no lesion identified
  - Inadequate colposcopic examination
  - Adequate colposcopy and lesion identified
    - Endocervical sampling “preferred”
    - Endocervical sampling “preferred”
    - Endocervical sampling “acceptable”

- No CIN2,3
  - Manage per ASCCP Guideline

- CIN2,3
  - Manage per ASCCP Guideline

* Management options may vary if the woman is ages 21-24 years (see text)

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A systematic review of p16/Ki-67 immuno-testing for triage of low grade cervical cytology

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Accepted 31 July 2014. Published Online 11 September 2014.
Conclusion

• p16/Ki-67 testing cannot be recommended for triage women with ASCUS or LSIL cytology due to insufficient high-quality evidence.

• Further studies on test performance and the impact of p16/Ki-67-based triage on health outcomes are needed for a definitive evaluation of its clinical utility.
Screening for Cervical Cancer Precursors With p16/Ki-67 Dual-Stained Cytology: Results of the PALMS Study
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women 18–65 y (n = 25 577; 181 CIN2+, 100 CIN3+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pap cytology</td>
<td>68.5 (61.2 to 75.0)</td>
<td>95.4 (95.1 to 95.6)</td>
</tr>
<tr>
<td>Dual-stained cytology</td>
<td>86.7 (81.1 to 90.9)</td>
<td>95.2 (94.9 to 95.4)</td>
</tr>
<tr>
<td>Women 18–29 y (n = 6372; 70 CIN2+, 37 CIN3+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pap cytology</td>
<td>71.9 (59.8 to 81.5)</td>
<td>92.6 (92.0 to 93.3)</td>
</tr>
<tr>
<td>Dual-stained cytology</td>
<td>89.4 (80.2 to 94.6)</td>
<td>92.0 (91.2 to 92.6)</td>
</tr>
<tr>
<td>Women 30–65 y (n = 19 205; 111 CIN2+, 63 CIN3+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pap cytology</td>
<td>65.9 (56.5 to 74.3)</td>
<td>96.3 (96.0 to 96.5)</td>
</tr>
<tr>
<td>Dual-stained cytology</td>
<td>84.7 (76.8 to 90.3)</td>
<td>96.2 (95.9 to 96.5)</td>
</tr>
<tr>
<td>HPV</td>
<td>93.3 (85.9 to 96.9)</td>
<td>93.0 (92.6 to 93.4)</td>
</tr>
</tbody>
</table>
CYTOLOGY PRIMARY SCREENING – SA HIGH RESOURCE SETTINGS (TO BE PHASED OUT):

SCREEN CYTOLOGY

- Negative LOW RISK
  - SCREEN

- ASCUS or LSIL
  - MEDIUM RISK
    - TRIAGE TEST *
      - NEG
        - FOLLOW
      - POS
        - COLPOSCOPY/BIOPSY
          - TREAT IF POS
          - FOLLOW

*HPV test or cytology stain
IF ALL ELSE FAILS, HUG YOUR DOG.

OR KITTY

Hello there

Hi pal