Updated ASCCP Consensus Guidelines For Managing Diagnosed Cervical Cancer Precursors

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Faculty Disclosure

- No, nothing to disclose
- Yes, please specify
Goals of Screening (& Management)

• Prevent morbidity and mortality from cervical cancer
  – Not find abnormal cytology
  – Not find HPV infection
  – Not find lesions

• Prevent overzealous management of precursor lesions likely to regress or disappear for which the risks of management outweigh the benefits
Why isn’t “finding lesions” the goal of screening?

- Don’t know which lesions will progress
- Need to place emphasis on:
  - **Persistent** HPV infections
  - **CIN3** (no margin for error)
  - **CIN2** in older women (no risk to pregnancies)
  - Persistent CIN2 and CIN2/3 in young women
2012 Guidelines Are Risk Based

• Based on large numbers of clinical observations over 8+ years
• Risk analysis of 1.4 million women from KPNC*
  • More than 1 million women ≥ age 30 with cotesting
    – 440 cancers; 3,231 CIN3+; 7,581 CIN2+
  • Almost 400,000 women < age 30 with ASC-US cytology results and HPV triage
    – 26 cancers; 1,231 CIN3+; 4,193 CIN2+

*Kaiser Permanente Northern California Health System
Risk Analysis of KPNC* Data

- Allows precise risk estimation for various test results & combinations
  - "What are immediate and future (5yr) risks after X?"
- Uses CIN2+ risk for rare events
- Assesses if cancer risk is high even when CIN2,3 risk is relatively low, as after AGC cytology

*Kaiser Permanente Northern California Health System
KPNC* Data Limitations

• Cannot define management of rare events
  – e.g. HPV-/ASC-US x 3

• May not be generalizable to all women
  – US or worldwide

• No 6 month follow up assessments, so utility of short-interval testing unclear

• No conization/LEEP margin status recorded

• 8+ years of follow up data (2003-2010)
  – Cannot guide longer term management
  – Cannot define long term attainment of risk low enough for “routine screening” in all situations

*Kaiser Permanente Northern California Health System
≤CIN1 Diagnosis After Lesser Abnormalities

- Lesser abnormalities include:
  - Pap NILM / HPV 16/18+
  - Pap NILM / Persistent HPV+
  - ASC-US → NOT ASC-H or AGC!
  - LSIL
≤CIN1 Diagnosis After Lesser Abnormalities

- Risk of abnormality is always higher after an initial abnormal result than after a negative cotest result
  - Difficult to get to “routine screening” even if one subsequent cotest is negative
- 5 yr CIN3+ risk after 2 consecutive cytology-/HPV+ cotests is 7.4%—higher than after baseline LSIL
  - 5 yr CIN2+ risk is 16%
- Genotyping results not available in KPNC dataset
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
  - Cytology Negative and HPV(-)
    - Age appropriate* retesting 3 years later
      - Cytology Negative +/- HPV(-)
        - Routine screening*
  - ≥ ASC or HPV(+)
    - Colposcopy
      - If persists for at least 2 years
        - Manage per ASCCP Guideline
      - No CIN
      - CIN2,3
      - CIN1
        - 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.
Follow-up without Treatment

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      - No CIN
      - CIN2,3
        - Manage per ASCCP Guideline
      - CIN1
        - If persists for at least 2 years
          - **Follow-up or Treatment** †

- ≥ ASC or HPV(+) → **Colposcopy**
  - No CIN
  - CIN2,3
  - CIN1

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ASCP
Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by “Lesser Abnormalities”*  

Follow-up without Treatment

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Cotesting at 12 months

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Cytology Negative and HPV(-)

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Age appropriate retesting
3 years later

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Cytology Negative +/- HPV(-)

2nd

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Routine screening*

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≥ ASC or HPV(+)

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Colposcopy

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No CIN

CIN2,3

CIN1

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If persists for at least 2 years

Follow-up or Treatment†

Manage per ASCCP Guideline

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        - CIN1
          - Follow-up or Treatment ‡

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≤CIN1 After ASC-H/HSIL

- 5 yr risk of disease remains high after ASC-H/HSIL cytology results despite no high-grade lesion on colposcopy
  - Sensitivity of colposcopy is limited
  - Sensitivity improves with increasing number of colposcopically directed biopsy up to 4
- Risk of CIN2+ after HSIL is 24% at 5 years despite colposcopy/biopsy result of Negative/CIN1
• After colposcopy/biopsy result of negative/CIN1, risk rises rapidly
• AGC is of special concern for cancer risk

Katki H et al. JLGTD 2013;17:S69-S77
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

Or

**Diagnostic Excision Procedure^**

- HSIL at either visit

Or

**Review of cytological, histological, and colposcopic findings**

Manage per ASCCP Guideline for revised diagnosis

* 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

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≤CIN1 in Women Ages 21-24

• Near-zero cancer risk in this age group
  – Missed CIN unlikely to result in harm
  – Overtreatment may harm future pregnancies
• Potential for harm to future pregnancies means “more conservative (not similar) management than for similar risks” in women 30-64yo
• 5 yr CIN3+ risk after ASCUS/LSIL = 3%
  – Risk must be lower after prevalent lesions found
• 5 yr CIN3+ risk after ASC-H =16% & HSIL=28%
Management of Women Ages 21–24 with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1)

After ASC-US or LSIL

Cytology Alone
Management of Women Ages 21–24 with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1)

After ASC-US or LSIL

1st
Repeat Cytology
@ 12 months

< ASC-H or HSIL

≥ ASC-H or HSIL

Repeat Cytology
@ 12 months

Negative

≥ ASC

Colposcopy

Routine Screening
Management of Women Ages 21–24 with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1)

After ASC-H or HSIL

Observation with colposcopy & cytology @ 6 month intervals for up to 2 years

2 consecutive double negatives
- Routine Screening

HSIL persists for 24 months with no CIN 2/3
- Diagnostic Excisional Procedure

High grade colposcopic lesion or HSIL persists for 12 months
- Biopsy
Management of CIN2,3

Natural history:

- Untreated CIN2
  - 43% will regress
  - 35% will persist
  - 22% will progress

- Untreated CIN3
  - 32% will regress
  - 56% will persist
  - 14% will progress

Management of CIN2,3

- RCTs show similar outcomes (~10% failure risk) for women with CIN2,3 after ablation or excision
  - Excision provides histologic specimen
  - CKC requires operating room but provides best specimen margins
  - LEEP can be performed in office, has less bleeding than CKC, but more margin artifact
  - No ablation unless cancer excluded: -ECC, adequate colpo, no cancer by cytology or colpo
  - Excise if prior treatment (risk of skip lesions)

Management of CIN2,3

1-2% of CIN 2/3 Biopsies assoc. w/ Invasive Cancer

- 3/1000 Invasive Cancer
  - Excision Only
    - 7% Invasive Cancer
    - Unsatisfactory Colpo
      - (+) ECC
      - TSD
  - Unsatisfactory Colpo
    - Satisfactory Colpo
      - (-) ECC
      - No prior Treatment
      - Ablation or Excision
Management of CIN2,3

Rationale for follow-up after treatment

• Most recurrences present within 24 months
  • Among 2,240 women followed after treatment of CIN, 75% of recurrences occurred in the first 24 months
• Recurrences seen 20+ years after treatment

→ Intensive surveillance initially, but some surveillance continued long term

Persad VL et al. Low Genit Tract Dis, 2001;5:199-203
Hellberg and Nilsson. Gynecol Oncol 1990;38:166-9
Kalliala et al BMJ 2005;331:1183-5
Risk of Disease Recurrence of CIN2+ After Treatment Among Women ≥ Age 25

- HPV+/ASC-US or LSIL antecedent
- AGC, ASC-H, or HSIL+ antecedent

Cumulative risk of CIN2+ after treatment (%)

- Years since first follow-up test after treatment for CIN2, CIN3, or AIS
- Years since first follow-up test after treatment for CIN2, CIN3, or AIS
# Post-treatment Utility of HPV Testing

**Treatment failure rates**

<table>
<thead>
<tr>
<th>Study</th>
<th>N (%) HPV-</th>
<th>N (%) HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraskevaidis (2001)</td>
<td>3 (7%)</td>
<td>38 (93%)</td>
</tr>
<tr>
<td>Zielinski (2003)</td>
<td>1 (17%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Debarge (2003)</td>
<td>5 (19%)</td>
<td>22 (81%)</td>
</tr>
<tr>
<td>Alonso (2006)</td>
<td>1 (3%)</td>
<td>35 (97%)</td>
</tr>
<tr>
<td>Verguts (2006)</td>
<td>0</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Kreimer (2006)</td>
<td>3 (9%)</td>
<td>29 (91%)</td>
</tr>
</tbody>
</table>
Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2 and 3 (CIN2,3)*

- Adequate Colposcopy
  - No Previous Treatment of CIN2,3 and Endocervical sampling negative
  - Either Excision† or Ablation of T-zone*
  - Cotesting at 12 and 24 months
  - 2x Negative Results
  - Repeat Cotesting in 3 years
  - Routine Screening

- Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3
  - Diagnostic Excisional Procedure†
  - Any Test Abnormal
  - Colposcopy With endocervical sampling

* 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 4–6 mo is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.

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Diagnostic Excisional Procedure†

Colposcopy With endocervical sampling

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Managing CIN2,3 in “Young Women”

Young women are:

“Those women who, after counseling by their clinician, consider the risks from managing the abnormalities from treating cervical abnormalities to outweigh the risks from observation of those abnormalities. No specific age threshold is intended.”

Massad LS et al. JLGTD 2013;17:S1-S27

- A 23yo after tubal sterilization may not be young
- A 38yo being treated for infertility may still be young
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**

@ 6 month intervals for 12 months

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

- Colposcopy worsens or High-grade Cytology or Colposcopy persists for 1 year
  - Repeat Colposcopy/Biopsy Recommended
  - Treatment Recommended

**Treatment using Excision or Ablation of T-zone**

CIN3 or CIN2,3 persists for 24 months

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

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**Treatment using Excision or Ablation of T-zone**

- CIN3 or CIN2,3 persists for 24 months
  - Treatment Recommended

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Managing AIS At Excision

- Exclude cancer by cone
  - Cold knife or large loop aiming for intact specimen with interpretable, preferably clear margins
  - Not top hat LEEP
- May occur deeper within canal
- Difficult to see colposcopically
- Risk of persistent AIS after cone with clear margins = 10%
- (-) HPV test a strong predictor of clearance
Among 1,101 women undergoing hysterectomy after conization for AIS:
- 55% with positive margins had persistent disease
- 23% with negative margins had persistent disease
- Risk of positive margin less after cold knife cone than after LEEP

AJOG 2007;197:195.3a-195.e8
Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure

**Hysterectomy — Preferred**

**Conservative Management**
Acceptable if future fertility desired

- **Margins Involved or ECC Positive**

- **Re-excision Recommended**

- **Re-evaluation**
  @ 6 months — acceptable

- **Margins Negative**

  - **Long-term Follow-up**

* Using a combination of cotesting and colposcopy with endocervical sampling
Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure

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- Re-evaluation* @ 6 months — acceptable

Margins Negative

Cotesting at 12 & 24 months
Then continued Follow-up

* Using a combination of cotesting and colposcopy with endocervical sampling

Long-term Follow-up
Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure

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      - **Re-evaluation***
        - @ 6 months — acceptable
      - **Long-term Follow-up**

* Using a combination of cotesting and colposcopy with endocervical sampling
Managing Biopsy Reports Of LSIL/HSIL Using LAST* Terminology

- Terminology developed under LAST*
  - Eliminates diagnosis of CIN2 considered equivocal
  - CIN3 is HSIL
  - p16 stain positive CIN2 now considered HSIL
  - P16 stain negative CIN2 now considered LSIL
  - CIN1 is LSIL – no p16 staining of CIN1 specimens

- No clinical evidence for determining long-term management using this terminology

- Consider guidance to be an interim solution until more data are available

*Lower Anogenital Squamous Terminology Project
Interim Guidance for Managing Reports using the Lower Anogenital Squamous Terminology (LAST) Histopathology Diagnoses

**Low Grade Squamous Intraepithelial Lesion (LSIL)**

- Manage like CIN1

**High Grade Squamous Intraepithelial Lesion (HSIL)**

- Manage like CIN2,3

*Histopathology Results only.*
Changes from 2006 guidelines

- Pathway to long-term follow-up of treated and untreated CIN2+ more clearly defined by incorporating cotesting
- More strategies incorporate cotesting to reduce follow-up visits
  - Cytology-only strategies now limited to women <30yo, but cotesting in certain settings is expanded even to women ages <30
- Women ages 21-24 years are managed more conservatively
  - Low risk of invasive cervical cancer
  - Lower risk of progression of precursor disease
Caveats

- Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view recommendations as dictates. Even strong recommendations based on high-quality evidence will not apply to all circumstances and all patients.
Caveats

- Users of guidelines may reasonably conclude that following some strong recommendations based on high quality evidence will be a mistake for some patients. **No clinical practice guideline or recommendation can take into account all of the often compelling unique features of individual patients and clinical circumstances.** Thus, nobody charged with evaluating clinician’s actions, should attempt to apply recommendations in rote or blanket fashion.
For More Information

- Explanatory text available at J Lower Genit Tract Dis 2013;17:S1-S27
- Algorithms are available for free download (read only) at www.asccp.org/consensus2012
ASCCP Guideline Booklets available in both English & Spanish!
ASCCP Updated Guidelines
Algorithm App

ENGLISH Language Version
& SPANISH Language Version

Available for iPhone, iPad, & Android
Ahora Disponible ...

Aplicacion con los Algoritmos y Guias de Manejo de la ASCCP Actualizadas - en Español

Adquierala para su iPhone, iPad, & Android
THANK YOU!