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
Conflict of Interest Disclosure

- Ritu Nayar, MD
  Professor of Pathology
  Medical Director, Cytopathology
  Northwestern University, Feinberg School of Medicine, Chicago.

- I have no COI to declare except that I am a practicing cytopathologist.
Session Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speakers</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of Meeting Process and Guideline Development</td>
<td>Dr. Ritu Nayar</td>
<td>15 minutes</td>
</tr>
<tr>
<td>2012 Cervical Cancer Screening and Prevention Guidelines</td>
<td>Dr. David Wilbur Dr. Tom Cox Dr Ann Moriarty</td>
<td>45 minutes</td>
</tr>
<tr>
<td>BREAK</td>
<td>9:05-9:50</td>
<td>45 min</td>
</tr>
<tr>
<td>The Lower Anogenital Squamous Terminology (LAST) Standardization Project</td>
<td>Dr Teresa Darragh Dr Tom Cox Dr Michael Henry Dr David Wilbur</td>
<td>60 minutes</td>
</tr>
</tbody>
</table>

American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer

J Low Genit Tract Dis 2012.

PICSM - background

- The Practice Improvement in Cervical Screening and Management (PICSM) committee
  - Formed in 2008 under the sponsorship of the ASCCP
  - Cervical cancer experts from major scientific and professional society organizations with various health care perspectives.

- Focus is to
  - Develop and encourage adoption of consensus, evidence-based guidelines
  - Identify areas where current practice may need to be reconsidered based on scientific/clinical advances in the field
PICSM: contd.

- June 2009 PICSM Symposium

- 2009 idea to hold symposium on role of molecular testing

- Merged with ACS plan to revise Cervical Cancer Screening Guidelines
  – ACS became the lead organization with ASCCP and ASCP as co-sponsors

Guidelines committee structure

- Steering Committee
  - Developed meeting principles
  - Identified scope of effort
  - Developed and implemented a detailed COI policy

- Data/Writing Groups

- 6 Working Groups (60 members)
  - Work Groups were instructed to propose evidence-based screening strategies that best serve women - balancing benefits and harms of screening - without regard to cost

GRADE System for Guideline Development

- “EVIDENCE BASED” and “TRANSPARENCY”

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)
  – Formal process for guidelines development aimed at
    - Systematic approach to evaluating evidence
    - Transparency in communicating criteria used to evaluate evidence and formulate recommendations
    - Clarity in communication about confidence in quality of evidence
**GRADE Guideline Development Process**

1. Formulate specific “key question(s)”
   - Patient, Intervention, Comparator, Outcome Timeline (PILOT)

2. Evaluating Evidence
   - Identify important outcomes for every question
   - Summarize and grade evidence for critical outcomes

3. Going from Evidence to Recommendations
   - Decide on balance of benefits and harms
   - Formulate and grade strength of recommendation(s)

**GRADE: Evaluation of Evidence Quality**

- **HIGH**: Randomized controlled trials (RCTs), or observational studies with overwhelming evidence
- **MODERATE**: RCTs with important limitations, or exceptionally strong evidence from observational studies
- **LOW**: RCTs with notable limitations, or observational studies
- **VERY LOW**: RCTs or observational studies with important limitations, or clinical experience and observations

* Special Consideration-modelling studies (not addressed in GRADE):

**Quality of Evidence**

- Overall quality of evidence graded as:

<table>
<thead>
<tr>
<th>GRADE</th>
<th>IMPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>Further research unlikely to change estimate of effect</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Further research may change estimate</td>
</tr>
<tr>
<td>LOW</td>
<td>Further evidence likely to have impact</td>
</tr>
<tr>
<td>VERY LOW</td>
<td>Estimate of effect is very uncertain</td>
</tr>
</tbody>
</table>
Considerations for Formulating Recommendations

<table>
<thead>
<tr>
<th>Key Factors</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence type for benefits and harms</td>
<td>The higher the confidence in the estimated effect the more likely is a <strong>strong</strong> recommendation.</td>
</tr>
<tr>
<td>Balance between benefits and harms</td>
<td>The larger the difference between the benefits and harms, the more likely is a <strong>strong</strong> recommendation. The smaller the net benefit and the lower certainty for that benefit, the more likely is a <strong>weak</strong> recommendation.</td>
</tr>
<tr>
<td>Values</td>
<td>The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely is a <strong>weak</strong> recommendation.</td>
</tr>
<tr>
<td>Health economic data (e.g., cost-effectiveness)</td>
<td>The lower the cost-effectiveness, the more likely is a <strong>weak</strong> recommendation.</td>
</tr>
</tbody>
</table>

Two Levels of Recommendation

**Strong Recommendation**
- Confident desirable effects of an intervention outweigh undesirable effects (strong recommendation for an intervention) or the converse, undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention).
- A strong recommendation implies, that **most or all individuals will be best served** by the recommended course of action.

**Weak Recommendation**
- Desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists.
- A weak recommendation implies, that **not all individuals will be best served** by the recommended course of action; consider more carefully than usual individual patient’s circumstances, preferences, and values.

GRADE: Wording of Recommendations

**Recommendation categories**

- **STRONG**
  Use words like “recommend,” “recommend against,” “should,” “should not”

- **WEAK**
  Use words like “may,” “suggest against”
GRADE: Key Point

- GRADE separates the evaluation of evidence quality from the strength of the recommendations
  - Allows some judgment on the part of the group making the recommendations.

- There could be consistent "high quality" data from RCTs that a particular chemotherapy regimen improved overall survival by 8 months, but with more severe side effects.
  - Given that patients might have different views on the tradeoff between survival and quality-of-life, this might result in a weak recommendation for the regimen despite high quality evidence.

- Alternatively, only "moderate-low quality" evidence for the benefit of cervical cancer screening compared to no screening
  - Consistency of the evidence that does exist and the difficulties of doing a "high quality" study are such that a strong recommendation for screening is justified.

Evaluating Evidence

- Making Recommendation

GRADE PROCESS

- Periodic review of evidence
- Assessment of patient/provider uptake
- Assessment of feasibility/cost issues

Working Groups

1. Optimal Cytology Screening Intervals
2. Screening Strategies for Women 30 Years and Older: Co-testing
3. Management of discordant combinations of cytology and HPV results
4. Exiting Women from Screening
5. Impact of HPV Vaccination on Future Screening Practices
6. Potential Utility of Molecular Screening: HPV Alone
Meeting Process

- WG draft recommendations/supporting data posted on ASCCP website for pre-meeting public comment period
  - 10,000 titles; 700 publications considered
- 25 “stake holder” organizations, 100 representatives attended November 2011 working consensus meeting
  - WG presented revised draft recommendations rationale, followed by open discussion
- Consensus Process
  - Vote: 66% in favor = passed
  - Major concerns remanded to Breakout
  - Most recommendations passed with >90% approval

Recommendations: 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.

Acknowledgements

- PICSM /Guidelines Meeting Process
  - Debbie Saslow, PhD
  American Cancer Society
  - Diane Solomon, MD
  National Cancer Institute
- GRADE slides
  Evan R Meyers, MD, MPH
  Duke University Medical center
Selected Topics

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Strategies for Women 30 Years and Older: Co-testing</td>
<td>Dr. David Wilbur (Dr Mark Stoler)</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Management of Discordant Combinations of Cytology and HPV results</td>
<td>Dr. Tom Cox</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Potential Utility of Molecular Screening: HPV Alone</td>
<td>Dr. Ann Moriarty</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Q&amp;A</td>
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</tbody>
</table>

2012 ACS ASCP ASCCP Joint Screening Guidelines for Ages 20-29 and 30-65

Mark H. Stoler, MD
University of Virginia Health System

Disclosure of COI - Stoler

- Consultant: Merck, Roche, BD, Qiagen, Gen Probe
- Member of PICS, DG and WG1
- Practicing Cytopathologist

Wilbur
Merck – shareholder (<$10,000)
American Cancer Society, American Society for Cervical Cancer Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer

Debbie Sutliffe, PhD,1 Diane Solomon, MD,1,2 Herschel W. Landry, MD,3,4 Marston Killian, MD,5,6 Nabil I. Kaldany, MD,7 Joanne Carus, MD,7 Francesco A. R. Ginetti, MD, MPH,7 Ann T. Monistere, MD,8 Alex O. Westman, MD, MPH,8 David G. Wilson, MD,9,10 Nicolas Wettig, MD, PhD, MS,11 Levi S. Doupe, Jr, MD,12 Mark Spitzer, MD,13,14 Anna-Branka Moscicki, MD,14,15 Eduardo L. Franco, DrPH,15,16 Mark H. Snider, MD,17 Mark Schiffman, MD,18 Phyllis E. Castle, PhD, MPH,19 and Evan R. Myers, MD, MPH20

J Low Genit Tract Dis 2012.

"WE" ALL AGREE!

ASCP
ACS
ASCCP
USPSTF
IOM
ACOG
NCCN

Balance
Best for Patient
Regardless of Cost

"The fundamental goal of cervical cancer screening is to prevent morbidity and mortality from cervical cancer. The optimal screening strategy should identify those cervical cancer precursors likely to progress to invasive cancers (maximizing the benefits of screening) and avoid the detection and unnecessary treatment of transient HPV infection and its associated benign lesions that are not destined to become cancerous (minimizing the potential harms associated with screening)."
Detection of ≥CIN3 involves a trade-off

Seeking Optimal Balance Among Surrogate Measures

Preventing all cancer by screening is unrealistic

- 50% of the current 12,000+ cancers in the US are in women who have not been screened
- ~10% are in women who have been screened, but not in the last 5 years
- Cancer is rare (<~1/million) in <20 age population
- Cytology alone is a benchmark of screening performance
- Women at similar risk for ≥ CIN3 should be managed similarly
Cervical cancer: The impact of screening

<table>
<thead>
<tr>
<th>Region</th>
<th>Study</th>
<th>FN* smear (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scandinavian countries</td>
<td>Rylander, 1976</td>
<td>44.8</td>
<td>41.6–48.2</td>
</tr>
<tr>
<td></td>
<td>Stenkvist, 1996</td>
<td>20.0</td>
<td>16.8–23.8</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>32.0</td>
<td>23.6–40.2</td>
</tr>
<tr>
<td>UK</td>
<td>Walker, 1983</td>
<td>23.1</td>
<td>21.2–25.2</td>
</tr>
<tr>
<td></td>
<td>Choyce, 1990</td>
<td>54.4</td>
<td>47.7–62.2</td>
</tr>
<tr>
<td></td>
<td>Sasieni, 1996</td>
<td>26.7</td>
<td>24.6–28.8</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>32.1</td>
<td>29.1–36.7</td>
</tr>
<tr>
<td>US</td>
<td>Berkowitz, 1979</td>
<td>55.5</td>
<td>46.0–66.9</td>
</tr>
<tr>
<td></td>
<td>Brown, 1982</td>
<td>36.6</td>
<td>32.5–41.3</td>
</tr>
<tr>
<td></td>
<td>Sung, 2005</td>
<td>28.0</td>
<td>26.9–29.9</td>
</tr>
<tr>
<td></td>
<td>Leydan, 2005</td>
<td>32.0</td>
<td>31.0–33.0</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>35.5</td>
<td>32.6–41.2</td>
</tr>
</tbody>
</table>

*FN* = false-negative

Cytology-based screening alone has limited sensitivity

- Cytology alone is a benchmark of screening performance
  - q2-3 year cytology is consistent in current guidelines and generally accepted as US standard of care
  - Strategies that improve the balance between benefits and harms over cytology alone will be favored
  - Conventional and LBC are substantially equivalent

Women at similar risk for ≥ CIN3 should be managed similarly
Harmonizing Management According To Risk

Considerations about HPV Testing

- Compared to Cytology, HPV testing is ~20-40% more sensitive than cytology
- ≥ 90% sensitive for CIN3+
- But only 5-10% less specific
- CLINICALLY VALIDATED
- Reproducible and Robust

No Annual Screening

“Over time, growing evidence and the improved understanding of the natural history of cervical cancer have led to growing recognition that earlier recommendations for annual screening were excessive and led to an increased rate of harms. Today, there is little evidence to support the annual screening of women at any age by any screening test, method, or modality.”

“Women at any age should not be screened annually by any screening method; rather, recommended screening intervals for women are based on age and clinical history.”
Age to Begin Screening

- Not before 21
- Cancer rate in adolescents is ~1/million
- 40 years of screening adolescents has not changed cancer rate
- Balance favors harm
- Focus on vaccination
- No HPV testing


Women 21-29

- “For women aged 21 to 29 years, screening with cytology alone every 3 years is recommended.”
- “For women aged 21 to 29 years with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (i.e., more than 3 years).”
- “HPV testing should not be used to screen women in this age group, either as a stand-alone test or as a co-test with cytology.”

Relationship of Screening Interval to Cancer Risk in Women <30

<table>
<thead>
<tr>
<th>Screening Interval</th>
<th>Lifetime Risk (%) of Cervical Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screening</td>
<td>3.5</td>
</tr>
<tr>
<td>Every 5 years</td>
<td>2.5</td>
</tr>
<tr>
<td>Every 3 years</td>
<td>1.5</td>
</tr>
<tr>
<td>Every 2 years</td>
<td>1.0</td>
</tr>
<tr>
<td>Every year</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Women 30-65

- “Women aged 30 to 65 years should be screened with cytology and HPV testing ("cotesting") every 5 years (preferred) or cytology alone every 3 years (acceptable).”

- “There is insufficient evidence to change screening intervals in this age group following a history of negative screens.”

Rationale For Co-testing

- Co-testing increases prevalently detected CIN3+ (in comparison to cytology) in the initial screening round and results in decreased CIN3+ in subsequent rounds
- Co-testing significantly reduced the invasive cancer rate in the second screening round in one RCT
- A negative co-test has a high negative predictive value for CIN3+ and cancer in subsequent 5 to 6 years.
- Screening at short intervals leads to unnecessary procedures and potentially harmful treatment of lesions destined to clear without intervention
Real World Performance

Katki et al., Lancet Oncol, 2011

Cumulative Incidence of CIN3+

Years Since Enrollment

HPV & Pap Individually

HPV & Pap Combined

3-yr risk for Pap- = 0.17%
5-yr risk for HPV- = 0.17%
5-yr risk for HPV-/Pap- = 0.16%

Dillner et al., BMJ, 2008

CIN3+ Risk Following a Negative Test

Time since initial testing (mos.)

Cytology negative/HPV positive
Cytology ASC-US/HPV negative

2012 Management Guidelines for women with Discordant cytology/HPV results

2012 Cervical Screening Guidelines

Guidelines are increasingly taking into account the balance between Harms vs. Benefits


2012 Cervical Screening Guidelines

Management of NILM/HPV +


ACS/ASCCP/ASCP and ACOG 2012 Guidelines

Management of discordant results: HPV positive/cytology normal

<table>
<thead>
<tr>
<th>HPV positive/cytology normal</th>
<th>Option 1: Repeat cotest in 12 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Option 2: Test for HPV16/18</td>
</tr>
<tr>
<td></td>
<td>if HPV16 and/or 18 positive refer to colposcopy</td>
</tr>
<tr>
<td></td>
<td>If HPV 16 and 18 negative, repeat cotest in 12 months</td>
</tr>
</tbody>
</table>

ATHENA Trial: Cotesting
NILM population mean age and hrHPV prevalence by genotype

<table>
<thead>
<tr>
<th>Total number of women</th>
<th>32,260</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>44.9 yrs</td>
</tr>
</tbody>
</table>

hrHPV infection at baseline
- hrHPV HPV Negative: 93.3%
- hrHPV HPV Positive: 6.7%

Initial and F/U Pap Management for women >30 with a NILM Pap and HPV + test

- Cytology NILM + HPV (+)
- Two options:
  - Pap & HPV 12 mo
  - HPV 16/18 genotyping

Absolutie Risk of CIN in Normal Cytology
ATHENA Study: Women >30 Years

<table>
<thead>
<tr>
<th>HPV Status</th>
<th>CIN 2+</th>
<th>CIN 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>hrHPV (-)</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>hrHPV (+)</td>
<td>6.3%</td>
<td>4.1%</td>
</tr>
<tr>
<td>16/18 (+)</td>
<td>11.7%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Other 12 hr (+)</td>
<td>4.7%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>


CIN 2+ risk for women > 30 with a NILM Pap by HPV status

![Graph showing CIN 2+ risk for women > 30 with a NILM Pap by HPV status.](image)


Initial and F/U Pap Management for women >30 with NILM Pap and HPV + test: Option 1

- Cytology Negative
- HPV (+)
- Pap & HPV 12 mo


Risks of human papillomavirus (HPV) persistence and progression.

![Graph showing risks of human papillomavirus (HPV) persistence and progression.](image)

Schiffman M et al. JNCI J Nat Cancer Inst 2011;103:368-383
Clinical Responses Based on Risk of CIN 2,3

<table>
<thead>
<tr>
<th>Risk that CIN 2,3 is Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1%</td>
</tr>
<tr>
<td>1%</td>
</tr>
<tr>
<td>5%</td>
</tr>
<tr>
<td>10%</td>
</tr>
<tr>
<td>50%</td>
</tr>
<tr>
<td>80%</td>
</tr>
</tbody>
</table>

- HPV neg Normal Pap
- 1% Normal Pap
- 5% ASC-US HPV+/cyto-
- 10% LSIL HPV+ CIN1/18+
- 50% ASC-H AGC
- 80% HSIL

Initial and F/U Pap Management for women ≥30 with NILM Pap and HPV + test

- Cytology Negative + HPV (+)
  - Pap & HPV 12 mo
  - Both neg WNL & HPV +
  - Rescreen 3-5 yrs
  - ≥ASC-US HPV +/−
  - ASC-US HPV +
  - Colposcopy

Initial and F/U Pap Management for women ≥30 with Pap and HPV test: Option 2

- Cytology Negative + HPV (+)
  - HPV 16/18 genotyping

Between 2003 and 2009 forty-four cervical cancers were diagnosed following at least one cytology/HPV+ result:
- 26 had one cytology-/HPV+ before diagnosis
- 15 had two
- 3 had three

Cancer types:
- 16 squamous
- 1 small cell
- 24 adenocarcinomas
- 2 adenosquamous carcinomas

AdenoCA comprises about 20% of cervical cancers:
- Cytologic screening has been ineffective in reducing the incidence of adenoCA
- Incidence of adenoCA in women <40 has been increasing
- Stage for stage survival for women with adenoCA is significantly less than for squamous cancer
- 85-90% of adenoCA is due to HPV 16,18, much higher than the approximately 70% for squamous cancers

HPV Type: Percent of cervical squamous and cervical adenocarcinoma due to HPV 16 or 18

- Squamous cell carcinoma: 70% HPV 16 or 18 vs 30% all other types
- Adenocarcinoma: 86% HPV 16 or 18 vs 14% all other types
Cumulative incidence of CIN3+ in women with initial normal cytology over the subsequent 10 yrs. by hrHPV status at baseline


Danish follow-up study: Absolute risk of ≥CIN3 development over 12 years in women with NILM cytology and a persistent* HPV infection


ATHENA Trial: NILM population mean age and hrHPV prevalence by genotype

CIN 2+ risk for women > 30 with a NILM Pap by HPV status

Clinical Responses Based on Risk of CIN 2,3

Initial and F/U Pap Management for women >30 with Pap and HPV test
**Initial and F/U Pap Management for women >30 with Pap and HPV test**

- **Cytology Negative** + **HPV (+)** → **Colposcopy**
- Any Pos HPV or ASC-US HPV+ → **16/18 genotyping**
- 16/18 (-) → **Pap & HPV 12 mo** → **Colposcopy**
- Neg/Neg Or ASC-US HPV neg → **Cotest 5 yrs**


---

**Cumulative incidence rate for CIN3+:**

According to baseline test results in first 72 months of follow-up

- **HPV positive**
- **HPV negative**

*Dillner J et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ. 2009*

---

**Safely extending to an “optimal screening interval”**

- Many trials confirm that:
  - Prolonged screening intervals are safe in HPV negative women
  - Short intervals should be discouraged as they will identify too many recently HPV infected women without giving time for resolution between screens
  - Intervals between 5-7 years seem ideal with HPV testing as a primary screen and may be more specific than cytology at 3 yr. intervals (i.e., the # of false positives from two rounds of cytology may be more than one round of HPV testing)

2012 Cervical Screening Guidelines

Management of ASC-US HPV -


CIN 2+ risk for women ≥ 30 with ASC-US cytology by HPV status


Clinical Responses Based on Risk of CIN 2,3

Risk that CIN 2,3 is Present

0.1% 1% 5% 10% 50% 80%

HPV neg Normal Pap

ASC-US HPV+ cytology

ASC-AS

HPV 16/18+ Cytology

HSIL AGC

ASC-H HSIL

LEEP

Reoccur 3 or 5 Yr

Follow-up

Biopsy

LEEP
Reflex HPV DNA testing in women with ASC-US cytology

- Repeat cytology (6 and 12 months)
- HPV DNA testing (preferred if LBC)
- Positive: Colposcopy
- Negative: Repeat cytology (12 months)

Women with ASC-US


Positive
Negative

Repeat cytology (12 months)

Colposcopy

CIN 2+ risk with Negative HPV and NILM or ASC-US

Reflex HPV DNA testing in women with ASC-US cytology


Positive

Negative

Repeat cytology 3 yrs
or cotest 5 (3?) yrs

HPV DNA testing
(prefered if LBC)

≥ ASC

Repeat cytology (6 and 12 months)

ASC

Colposcopy

Women with ASC-US

2012 Cervical Screening Guidelines

2012 ASCCP Consensus Conference for the Management of Women with Abnormal Cervical Cytology and Cervical Neoplasia

2012 Consensus Guidelines

Proposed Pre-Conference: Not necessarily final recommendations

• WG 1: Does a report of “unsatisfactory or “absent/insufficient endocervical/TZ zone” require more intensive screening?
• WG 2: Update on management of abnormal cervical cytology
• WG 3: Management of CIN 1 on ECC
• WG 4: When to return to routine screening
• WG 5: Extending “adolescent” guidelines to age 25
Screening with HPV alone

Ann T. Moriarty
AmeriPath Indiana

Conflict of interest

• I have no conflict of interest to declare.

WG 6: Looking to the Future:
Potential Impact of Molecular Screening

Ann T. Moriarty, MD, Co-chair
Francisco A. Garcia, MD, MPH, Co-chair
Terence J. Colgan, MD
Mark H. Einstein, MD
Michael R. Henry, MD
L. Stewart Massad, MD
Kate Simon, PhD
Patti Gravitt, PhD, DG liaison
Debbie Saslow, PhD ex-officio
Cervical Cancer Screening Tests

- Cervical cancer morbidity/mortality decline
  - Pap test
  - Opportunistic screening
- Prevalence has fallen and will continue to decline
  - Screening and intervention
  - Vaccination
- Cervical cancer screening is repetitive
  - Multiple opportunities for patient interface
  - Prolonged natural history of pre-invasive lesions

New Cervical Cancer Screening Tests

- Substantial burden of new strategies
  - Substantial investment in Pap testing
  - Degree of patient acceptability
  - Degree of provider acceptability
  - Low rate of cancer in the population

Cervical Cancer Screening Tests

- New screening strategies must show either
  - Superior disease detection without increasing harms due to identification and treatment of self limited disease
  - Equivalent accuracy with prolonged intervals to reduce harms associated with screening
Key Questions

Key Q1: Can we issue a multi-society statement supporting the use of HPV DNA testing alone for women?
   - Based on the trade-offs between potential benefits and harms
   - For the general population

Key Q2: Should women who test HRHPV positive be triaged to cytology (or another triage strategy such as genotyping)?

Key Q3: For women with 2 or more consecutive negative HPV results, should the interval be increased further?

What we found

—High-quality evidence
   • Superior sensitivity of primary HRHPV testing.
—Low quality evidence
   • Specificity
   • Relative harms associated with this strategy
—Data are limited
   • Women over the age of 30 years
   • Derived primarily from studies outside of the United States.
     • Centralized/single testing platforms
—Most appropriate
   • Organized screening programs
   • Referral of women
   • Specialized centers for evaluation, management, and treatment.

• In single round screening RCT
   — HPV testing more sensitive for CIN2+
     • Pap
     • Pap+HPV
   — HPV testing is less specific
   — Lack of longer term study limits comprehensive comparison

• In 2 or more rounds RCT
   — HPV detects more CIN2+ earlier
   — Pap testing detects CIN2+ later but prior to invasion
   — No difference in CIN 2+ detection between strategies after 3 rounds (ARTISTIC)
**Recommendation 1**

*In most clinical settings* in the United States, we recommend against the use of high risk HPV testing as a primary screening strategy (even with defined follow up triage).

*(weak recommendation)*

**What about triage?**

HPV+ requires triage to avoid harm

- **Colposcopy**
  - Reduction of cervical cancers (Ronco et al; 2010)
  - Sensitivity only 50% in HPV+/cytology negative (Porras et al; 2011)
  - Low specificity
  - Twice the rate of cytology referral

- **Cytology**
  - High specificity in detecting CIN2+
  - Modeling finds it efficient (Myrand et al; 2007)

- **Molecular/Biomarkers**
  - Limited studies: cross sectional, small scale retrospective, archival
  - No large scale prospective studies with interval testing

**Recommendation 2**

There is no evidence to support the superiority of any single testing method for the triage of women with a positive HPV test when used as a primary screening modality.
What about interval?

- Negative predictive value of a HPV is high
  - Baseline: CIN3+ detected by cytology 0.02% at 3 years
    - (Ronco)
  - 5 year cumulative CIN3+ rate was 0.87%
    - (Katki et al. 2011)

- One negative HPV test may suffice to lengthen interval

- Requires further study
  - Impact on compliance
  - Cost effectiveness

Goal to increase interval

Reduce screening burden in low risk women in an effort to redirect resources to unscreened and rarely screened populations or those who are at higher risk for cervical cancer

Recommendation 3

Screening intervals may be extended to 5 years if HPV testing is used for primary screening, among women aged 30 and over and the HPV test results are negative.

*(weak recommendation)*
HPV Testing in the United States

- HPV tests are not identical
- FDA approved Tests (4)
- Off label use
  - Different media
  - Requires validation
- Laboratory Developed Tests
- Variety of Sites
- Non regulated provider use

Considerations for HPV tests

- Group of high-risk HPV genotypes
  - Clinically validated performance
- Increased analytic sensitivity
  - Unlikely to improve clinical sensitivity for CIN3+
  - May increase harms due to poor specificity
- Performance may vary between laboratories

- Laboratories testing for HPV should:
  - Use FDA approved tests in the manner in which they were intended
  - Have a robust quality assurance program
  - Participate in proficiency testing or interlaboratory comparison program