An Update on Cervical Cancer Screening Algorithms: Should HPV or Cytology be the Primary Test?

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University of Virginia
Disclosure

- Dr. Stoler is a consultant to Roche Molecular Systems, BD Diagnostics, Cepheid, Merck and Hologic
Objectives

• Contrast the relative performance of clinically valid HPV testing compared to cytology

• Compare ATHENA 3 year data to the ex-US long term follow up studies

• Integrate the benefits of using HPV16/18 Genotyping for primary screening

• Differentiate the relative performance of different algorithmic approaches to cervical cancer screening.
For use in the United States, HPV tests should both be FDA approved (for validity) and meet specific criteria for clinical performance as described above.47,48 Other well-validated tests (eg, GP5+/6+ polymerase chain reaction-enzyme immunoassay) are commercially available in Europe, and data using these tests were included in our review,39,40 but these are not approved by the FDA. HPV tests not meeting these standards of performance (including FDA-approved tests) should not be used. The updated guidelines for cervical cancer screening described herein were developed based on HPV tests that have performance characteristics similar to those of the HPV tests used in the supporting evidence. The guidelines cannot be expected to perform as designed (ie, to balance benefits and harms) when using HPV tests with different performance characteristics.

Laboratory-developed tests (LDTs), which are currently exempt from regulatory oversight by the FDA, rarely have undergone the necessary evaluation using clinical endpoints of CIN3+ and CIN2+ in properly designed studies. Therefore, we recommend against the use of LDTs for cervical cancer screening.”
Cytology
*(Cytology With Reflex HPV for ASC-US)*

**Routine screening**
- NILM
- ASC-US
- LSIL/HSIL
- HPV-
- HPV+

**Colposcopy**
- HPV-
- HPV+

**Limitations:** Variability, Sensitivity, Predictive value

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HPV test, high-risk HPV DNA test.
# Variability of Cervical Cytology

## ATHENA Results

<table>
<thead>
<tr>
<th></th>
<th>Lab A</th>
<th>Lab B</th>
<th>Lab C</th>
<th>Lab D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of samples</td>
<td>12,294</td>
<td>4,218</td>
<td>16,979</td>
<td>12,442</td>
</tr>
<tr>
<td>Median age, years</td>
<td>40.9</td>
<td>37.9</td>
<td>39.3</td>
<td>40.1</td>
</tr>
<tr>
<td>≥ASC-US</td>
<td>3.8%</td>
<td>5.2%</td>
<td>8.1%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Sensitivity of cytology*</td>
<td>42.0%</td>
<td>51.0%</td>
<td>60.5%</td>
<td>73.0%</td>
</tr>
<tr>
<td>Sensitivity of HPV*</td>
<td>90.1%</td>
<td>88.2%</td>
<td>88.4%</td>
<td>88.9%</td>
</tr>
</tbody>
</table>

*To detect ≥CIN2.*

Sensitivity of HPV Testing to Detect $\geq$CIN2 is Higher than Cytology in USPSTF Review

Studies performed in developed countries in women aged $\geq$ 30 years

10 Year Cumulative Incidence Rate (CIR) of ≥CIN3 in Women Aged ≥30 Years With NILM Cytology

13,229 women aged ≥30 years, according to oncogenic HPV status at enrollment

Genotyping offers HPV risk stratification


Women 25 years and older verification bias adjusted
Limitations of Cervical Cytology

• Interpretation is quite subjective which results in considerable intra- and inter-laboratory variation

• Relatively low sensitivity for the detection of high-grade cervical cancer precursors

• Identifies individuals with cancer precursors but not women at risk of developing cancer precursors
Co-testing With Cytology and HPV
Used in the United States But Not the Predominant Method

- Routine screening
  - NILM / HPV-
  - ASCUS / HPV-
- Cotesting 12 months
  - NILM / HPV+
  - HPV 16/18 genotyping
- Colposcopy

Cytology

HPV test

- 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 16, 18
Limitations of Co-testing

- **Co-testing is expensive**
  - Requires 2 screening tests every time a woman is screened

- **Co-testing is not logical**
  - Combines a relatively insensitive test with a highly sensitive test

- **Co-testing is complicated**
  - It incorporates cytology as part of the initial screen and cytology-based screening has become incredibly complicated over the last decade...UNINTENDED CONSEQUENCES
ASCCP Consensus Guidelines for Managing Abnormal Screening Results

WHY SCREEN DIFFERENTLY AT DIFFERENT AGES?

- Need for Primary HPV Screening Starting at Age 25 Years
- Current management algorithms are extremely complicated and this confusion potentially results in poor clinical care
- Cytology is not a good solution for identifying the majority of high-grade disease in women aged 25-29 years
≥CIN3 by Age Group

ATHENA

More ≥CIN3 disease in women 25-29 years than in women ≥40 years*

*Population of women ≥40 years of age is 3x that of the 25-29 group.

Proportion of Women with ≥CIN3 Who Have Negative Cytology (NILM)

ATHENA

More than half of the ≥CIN3 cases in the 25-29 age group had falsely negative cytology

Percentages shown are for hrHPV+ women with ≥CIN3, N=252.

Huh et al. 27th IPV, Berlin, Germany, September 17–22, 2011, OP-229
And Wright et al Gynecol Oncol 2015.
HPV 16/18 Genotyping Triages Fewer Women to Colposcopy than ≥ASCUS Cytology

Primary HPV Screening
With HPV16/18 Genotyping and Reflex Cytology in women ≥ 25

Routine screening

HPV−

12 other hrHPV+

16+ 18+

Cytology

≥ ASC-US

NILM

Follow up in 12 months

Colposcopy

hrHPV=high risk HPV
Comparison of the Performance of Cytology vs HPV Primary vs Cotesting* to Detect ≥CIN3

<table>
<thead>
<tr>
<th>Description</th>
<th>≥CIN3</th>
<th>Relative Sensitivity**</th>
<th>Relative Specificity**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>HPV Primary</td>
<td></td>
<td>1.40*</td>
<td>0.99*</td>
</tr>
<tr>
<td>Cotesting*</td>
<td></td>
<td>1.28*</td>
<td>0.99*</td>
</tr>
</tbody>
</table>

The sensitivity of Cotesting ≥30 years decreases due to women aged 25-29 years having cytology screening only

*Cotesting is a hybrid strategy to parallel preferred screening approach in the US; uses cytology only for 25-29 and cotesting for women ≥30yrs

**Calculated as VBA sensitivity or specificity

*Statistically significant

Roche FDA presentation, Spring 2014.
Comparison of HPV Primary vs Cotesting to Detect $\geq$CIN3: Predictive Values and Likelihood Ratios

<table>
<thead>
<tr>
<th>Description</th>
<th>PPV$^1$ %</th>
<th>NPV$^1$ %</th>
<th>PLR$^1$ (Positive Likelihood Ratio)</th>
<th>NLR$^1$ (Negative Likelihood Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotesting</td>
<td>11.04</td>
<td>99.52</td>
<td>12.66</td>
<td>0.49</td>
</tr>
<tr>
<td>HPV primary</td>
<td>12.25</td>
<td>99.58</td>
<td>14.24</td>
<td>0.44</td>
</tr>
<tr>
<td>Difference</td>
<td>1.21*</td>
<td>0.06*</td>
<td>1.58*</td>
<td>-0.05*</td>
</tr>
<tr>
<td></td>
<td>(0.46, 1.96)</td>
<td>(0.01, 0.09)</td>
<td>(0.62, 2.71)</td>
<td>(-0.10, -0.01)</td>
</tr>
</tbody>
</table>

The PPV and NPV of the HPV primary are superior, indicating significantly improved effectiveness and safety over Cotesting.

$^1$ Verification bias adjusted (VBA)

*Statistically significant

Roche FDA presentation, Spring 2014.
Comparison of the Performance of Cytology vs HPV Primary vs Cotesting to Detect ≥CIN3

Cotesting is a hybrid strategy to parallel preferred screening approach in the US; uses cytology only for 25-29 and cotesting for women ≥30yrs

Presented to FDA panel, 12 March 2014.
A women with a negative cobas® HPV Test has one-half the risk of developing ≥CIN3 within 3 Years compared to a women with a negative Pap

The Benefit of Cotesting Over HPV in Reducing the 3 Year Risk of ≥CIN3 is Minimal

ATHENA primary screening population: women ≥25 years

Co-testing adds little benefit
increases the colposcopy rate from 4.6% to 5.4%
&
IT ALSO DOESN’T MAKE SCREENING PERFECT…

* Difference statistically significant

* cobas® HPV Test Package Insert
Focusing on the Screen Positives
Genotyping Identifies Women at theHighest Risk

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16+</td>
<td>17.8%</td>
<td>20.5%</td>
<td>25.2%</td>
</tr>
<tr>
<td>HPV 18+</td>
<td>8.2%</td>
<td>11.0%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Other 12 hrHPV+</td>
<td>3.9%</td>
<td>4.3%</td>
<td>5.4%</td>
</tr>
<tr>
<td>HPV-</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Cumulative Incidence of ≥CIN3(%)
Risk of CIN3+ After Negative Screening Test

ATHENA study; 42,209 women ≥25 yrs

cases of CIN3+ per 10,000 women

- Pap (-)
- HPV (-)
- Pap & HPV (-)

cobas HPV Test – Package Insert
Risk of CIN3+ After Negative Screening Test

*Kaiser N. California; 315,061 women ≥30 yrs*

Katki et al. Lancet Oncol. 2011;12:663
Risk of CIN3+ After Negative Screening Test

7 European follow-up studies; 24,295 women

Dillner et al. BMJ 2009;377
Risk of CIN3+ After Negative Screening Test

_Kaiser N. California; 1,011,092 women ≥30 yrs_

Gage et al. JNCI 2014;106
HPV Testing versus Cytology for the Prevention of Cervical Cancer

Risk of Cancer After Negative Test

*Kaiser N. California; 1,011,092 women ≥30 yrs*

Gage et al. JNCI 2014;106 (8)
### Different Studies, Yet the same result!

<table>
<thead>
<tr>
<th>Population/Study</th>
<th>No. of Women</th>
<th>Negative test at entry</th>
<th>3-year CIN3+ risk</th>
<th>5-year CIN3+ risk</th>
<th>3-year cancer risk</th>
<th>5-year cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser Permanente Northern California</td>
<td>1,011,092</td>
<td>HPV</td>
<td>0.07</td>
<td>0.14</td>
<td>0.011</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>0.19</td>
<td>0.31</td>
<td>0.02</td>
<td>0.031</td>
</tr>
<tr>
<td>ATHENA</td>
<td>42,209</td>
<td>HPV</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>0.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ronco: 4 European trials</td>
<td>176,464</td>
<td>HPV</td>
<td></td>
<td>0.0046</td>
<td>0.0087</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td></td>
<td>0.0154</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Dillner: 7 European studies</td>
<td>24,295</td>
<td>HPV</td>
<td>0.12</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>0.51</td>
<td>0.83</td>
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*Huh et al. (2015). Gynecologic Oncology*

*Huh et al. (2015). Obstet Gynecol*

*Huh et al. (2015). J Lower Gen Tract Dis*
## Performance of Screening Strategies in Women Aged ≥ 25 Years

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<tr>
<th>Strategy</th>
<th>No. of ≥CIN3 Detected</th>
<th>Total Missed ≥CIN3</th>
<th>No. of Screening Tests</th>
<th>No. of Colpos</th>
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<td>Total: 179 At Baseline: 143 Years 1-3: 36</td>
<td>168</td>
<td>45,152</td>
<td>1927</td>
<td>10.8</td>
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<tr>
<td><strong>Cotesting</strong></td>
<td>Total: 240 At Baseline: 143 Years 1-3: 97</td>
<td>107</td>
<td>82,989</td>
<td>3096</td>
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Total ≥CIN3 cases = 347

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Total ≥CIN3 cases = 347  

Summary of ATHENA Data in Support of Primary HPV Screening

• When compared with cytology or co-testing:
  – Primary HPV demonstrates the best sensitivity for detection of ≥CIN3
  – Specificity of primary HPV is at least equal to cytology when 16/18 genotyping and reflex cytology is added to HPV as the primary screen
  – PPV and PLR are 2x those of cytology and significantly greater than those of co-testing
  – NPV and NLR are improved over those of both cytology and co-testing
  – Finds more CIN3 with fewer tests, fewer procedures, and less loss to follow-up than co-testing or cytology alone
Seeking Optimal Balance

≥CIN3

Colposcopies
**MSAC recommendations(1):**

- The Medical Services Advisory Committee (MSAC) has recommended to the Australian Government that a new ‘cervical screening test’ should replace the current Pap smear.
- The new cervical screening test detects human papillomavirus (HPV) infection, which we now know to be the first step in developing cervical cancer.
- Following a comprehensive review of the current evidence for cervical screening, MSAC has recommended for both HPV vaccinated and unvaccinated women that:
  - an HPV test should be undertaken every 5 years;
  - cervical screening should commence at 25 years of age;
  - women should have an exit test between 70 and 74 years of age; and
  - women with symptoms (including pain or bleeding) can have a cervical test at any age.

The MSAC Recommendations(2):

- A HPV test every 5 years is more effective than, and just as safe as, screening with a Pap test every 2 years
- A HPV test every 5 years can save more lives and women would need fewer tests than in the current every other year Pap test program
- Pending policy decisions, it is anticipated that changes would not be implemented prior to 2016
- HPV vaccinated women would still require cervical screening because the HPV vaccine does not protect against all the types of HPV that cause cervical cancer
- Until any changes are implemented women should continue to have a Pap test every 2 years

Further information on the MSAC recommendation may be found at: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/ncsp-renewal#Key-Information
Primary HPV screening guidance

Clinical Commentary

Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance

Warner K. Huh a,*, Kevin A. Ault b, David Chelmow c, Diane D. Davey d, Robert A. Goulart e, Francisco A.R. Garcia f, Walter K. Kinney g, L. Stewart Massad h, Edward J. Mayeaux i, Debbie Saslow j, Mark Schiffman k, l, Nicolas Wentzensen k, l, Herschel W. Lawson l, Mark H. Einstein m

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d University of Central Florida, Orlando, FL, USA
e New England Pathology Associates, Springfield, MA, USA
f Pinellas County Health Department, St. Petersburg, FL, USA
g Kaiser Permanente, Sacramento, CA, USA
h Washington University School of Medicine, St. Louis, MO, USA
i University of South Carolina School of Medicine, Columbia, SC, USA
j American Cancer Society, Atlanta, GA, USA
k National Cancer Institute, Bethesda, MD, USA
l American Society of Colposcopy and Cervical Pathology, Frederick, MD, USA
m Albert Einstein College of Medicine, Bronx, NY, USA
Primary HPV Screening: Interim Guidance

• Primary HPV screening is an alternative to current cervical cancer screening methods due to equivalent or superior effectiveness

• A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative cytology result

• Women 25 and older
  – About 1/3 of all CIN3+ cases found in ATHENA were in women 25-29
  – More than half of CIN3+ cases in women 25-29 were negative by cytology

• Assay Specific
  – Performance characteristics vary between HPV tests so assumptions around test comparability should not be made
  – At this time, only the cobas® HPV Test is FDA-approved for this indication
Multiple, large, prospective multi year trials all show that the safety & efficacy of HPV primary screening is higher than cytology and equivalent or better than cotesting with the added benefit of algorithmic simplicity.

Suggesting there is insufficient data to adopt HPV primary screening overlooks the fact that we have more data for HPV primary screening than we had when either cytology or cotesting was adopted.

Studies may have methodological differences yet all of the studies find the same result.