What Would George Think?
The Future of Cervical Cancer Screening

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Disclosures

Consultant (Non-paid): Roche Molecular Systems.
Scientific Advisory Board: Merck (V503)
Objectives

✓ To review the benefits and known limitations of cervical cytology
➢ To review the scientific evidence in support of HPV testing as a primary screening test
➢ To review the role of cervical cancer screening in the era of HPV vaccination

Topics to cover

✓ Cytology screening as the paradigm of cervical cancer control: Glory for some, failure for many.
➢ Rationale and burden of proof for HPV DNA testing in primary screening for cervical cancer.
➢ Post-HPV vaccination era: need for a paradigm change that combines primary and secondary prevention.

It started here... Village of Kimi, Island of Evia, Greece
George Nicholas Papanicolaou (1883-1962)

May 13, 2008: Celebration of 125 years of the birth of Papanicolaou, the developer of the oldest medical test
How good is Pap cytology in cervical cancer screening?

• Duke Report (Nanda et al., 2000): sensitivity 51%, specificity: 98%

• Pooled analysis of European and Canadian studies (Cuzick et al., 2006): sensitivity 53%, specificity 96%

• Cytology screening programs have to compensate for the low sensitivity by requiring 2-3 annual Pap tests before screening can be done less frequently

• Approximate program sensitivity for:
  2 consecutive annual Pap tests: 51% + 51% of 49% = 76%
  3 consecutive annual Pap tests: 76% + 51% of 24% = 88%

Other Issues to Consider with Cytology

• Highly subjective test: substantial inter-laboratory (as well as intra-laboratory) variability and limited reproducibility

• Unable to identify those women who are at future risk of developing cervical cancer precursors

• Unclear how cytology will perform as HPV vaccination rates increase in the US
Cumulative incidence of CIN3+ according to baseline test results in European sites (excluding Denmark and Tubingen)

Time since initial testing (mos.)

Cumulative incidence of CIN3+ (per 10,000)

- Cytology
- HPV
- Cytology+/HPV-

“…The child is grown, the dream is gone. I have become comfortably numb.”

David Gilmour & Roger Waters

HPV testing in cervical cancer screening

(for DNA of high oncogenic risk types)

- Approaches already implemented or being evaluated:
  - Serial: Cytology screening followed by HPV testing to triage ASC-US (approved by many professional societies in North America, FDA)
  - Parallel: Cytology and HPV cotesting (approved by some professional societies in North America, FDA)
  - Serial: HPV testing followed by cytologic triage (aka, Primary HPV Screening)
Women who have sex with HPV-infected men

- HPV infection (within weeks to months some will develop)
- Persistent HR-HPV infection (within months some will develop)
- HG cervical lesions (within months to years some will develop)
- Cervical cancer

<table>
<thead>
<tr>
<th>Pap Cytology</th>
<th>HR-HPV Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected with low sensitivity</td>
<td>Detected with high sensitivity</td>
</tr>
<tr>
<td>Detected with low sensitivity</td>
<td>Perceived as cause of low specificity</td>
</tr>
</tbody>
</table>

The Central Goal in Cervical Cancer Screening

“All zoogles are boogles. You saw a boogle. Is it a zoogle?”

Question in an SAT exam (Nassim Nicholas Taleb in “The Black Swan”)

- All cervical cancers are caused by HR-HPV infection. If a woman is positive on screening for HR-HPV DNA is precancer or cancer present or imminent?
- Of all screening technologies, HPV DNA testing is the one with greatest sensitivity and negative predictive value;
- Most important point: a negative result provides long-term confidence that a lesion is not present.

Why is HPV DNA testing an attractive option for cervical cancer screening?

- More sensitive and reproducible than the Pap test
- More “upstream” in the carcinogenic process, thus enabling a longer safety margin for screening intervals
- Assesses future risk (and not just the presence of current disease)
- Can be automated, centralized, and be quality-checked for large specimen throughput
- May be more cost-effective than cytology if deployed for high volume testing, such as in primary screening
- A more logical choice for screening women vaccinated against HPV infection
Performance of Cervical Cytology
Sensitivity for ≥CIN2

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number</th>
<th>Method</th>
<th>Sensitivity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petry</td>
<td>2003</td>
<td>8,466</td>
<td>Conv</td>
<td>44%</td>
<td>(30-58%)</td>
</tr>
<tr>
<td>Coste</td>
<td>2003</td>
<td>3,080</td>
<td>Conv</td>
<td>65%</td>
<td>(50-80%)</td>
</tr>
<tr>
<td>Taylor</td>
<td>2005</td>
<td>3,114</td>
<td>LBC</td>
<td>71%</td>
<td>(58-81%)</td>
</tr>
<tr>
<td>Ronco</td>
<td>2006</td>
<td>22,760</td>
<td>LBC</td>
<td>74%</td>
<td>(62-84%)</td>
</tr>
<tr>
<td>Mayrand</td>
<td>2007</td>
<td>10,153</td>
<td>Conv</td>
<td>57%</td>
<td>(34-78%)</td>
</tr>
</tbody>
</table>

RCTs of HPV testing in screening

- POBASCAM study: The Netherlands (Meijer et al., Int J Cancer 2004; Bulkmans et al, Lancet 2007)
- Indian Trial (Osmanabad) (Sankaranarayanan et al. NEJM 2009)
- ARTISTIC trial: UK (Kitchener et al. Lancet Oncol 2009)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006; JNCI 2006)
- SWEDESCREEN: Swedish trial (Elfgren et al. AJOG 2005; Nauber et al., NEJM 2007; JNCI 2009)
- Finnish RCT (Kotaniemi et al., BJC 2005; Eur J Cancer 2008; IJC 2008; Leinonen et al., JNCI 2009)
- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Ogilvie et al, BJC 2012)
- ATHENA Trial: United States

CCCaST Study: First Screening Round Results*

<table>
<thead>
<tr>
<th>Indices</th>
<th>Screening test</th>
<th>Estimate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Pap</td>
<td>55.4 (33.6-77.2)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>94.6 (84.2-100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>Pap</td>
<td>96.8 (96.3-97.3)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>94.1 (93.4-94.8)</td>
</tr>
<tr>
<td>PPV</td>
<td>Pap</td>
<td>7.1 (4.8-10.3)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>6.4 (5.0-8.0)</td>
</tr>
<tr>
<td>NPV</td>
<td>Pap</td>
<td>99.8 (99.7-99.9)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>100 (98.6-100)</td>
</tr>
</tbody>
</table>

* 10,171 women in Montreal and St. John’s, aged 30-69 years, randomized to Pap or HPV as primary screening method; detection of CIN2+; estimates corrected for verification bias (Mayrand et al. NEJM 2007)
Influence of laboratory performing the test on Pap and HPV testing performance (CCCaST Study)

(PAP laboratory 1)
(PAP laboratory 2)
(PAP laboratory 3)
(HPV laboratory 1)
(HPV laboratory 2)

(Mayrand et al., unpublished data)

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

Figure 3: Efficacy of HPV-based screening for prevention of invasive cervical cancer.

(Mayrand et al., unpublished data)

The NEW ENGLAND JOURNAL OF MEDICINE

HPV Screening for Cervical Cancer in Rural India

Site: Osmanabad district, India.
Cluster-randomized trial: 131,746 women aged 30-59 years randomly assigned to 4 groups of 13 clusters each.
Groups: screening by HPV testing, cytology, VIA, control (standard care).
Those with positive screening results underwent colposcopy and biopsies; treatment given to those with precancerous lesions or cancer.
Control Cytology VIA HPV Testing

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cytology</th>
<th>VIA</th>
<th>HPV Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cancers</td>
<td>118</td>
<td>132</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>Person-years</td>
<td>247,895</td>
<td>250,523</td>
<td>267,326</td>
<td>268,185</td>
</tr>
<tr>
<td>Rate per 100,000</td>
<td>47.6</td>
<td>60.7</td>
<td>54.7</td>
<td>47.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1 (ref)</td>
<td>1.30</td>
<td>(0.99–1.82)</td>
<td>1.02 (0.77–1.43)</td>
</tr>
<tr>
<td>Advanced cancers</td>
<td>82</td>
<td>58</td>
<td>66</td>
<td>39</td>
</tr>
<tr>
<td>Person-years</td>
<td>247,895</td>
<td>250,523</td>
<td>267,326</td>
<td>268,185</td>
</tr>
<tr>
<td>Rate per 100,000</td>
<td>33.1</td>
<td>23.2</td>
<td>32.2</td>
<td>14.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1 (ref)</td>
<td>0.75</td>
<td>(0.51–1.10)</td>
<td>1.04 (0.72–1.49)</td>
</tr>
<tr>
<td>Deaths</td>
<td>54</td>
<td>54</td>
<td>56</td>
<td>14</td>
</tr>
<tr>
<td>Person-years</td>
<td>251,144</td>
<td>253,144</td>
<td>267,917</td>
<td>268,674</td>
</tr>
<tr>
<td>Rate per 100,000</td>
<td>21.5</td>
<td>24.9</td>
<td>22.9</td>
<td>12.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1 (ref)</td>
<td>1.10</td>
<td>(0.80–1.52)</td>
<td>0.52 (0.33–0.83)</td>
</tr>
</tbody>
</table>

Osmanabad Cluster-RCT: Summary of Findings
(Sankaranarayanan et al., NEJM 2009)

Risk of cervical cancer or precancer among 330,000 women undergoing concurrent HPV testing and Pap testing in routine clinical practice

Rate of cervical cancer following a negative HPV test or normal Pap test

1. For all women with normal Pap test:
   7.5 cervical cancers per 100,000 women / year

2. For all women HPV-negative:
   3.8 cervical cancers per 100,000 women / year

3. For all women HPV-negative who also had a normal Pap test:
   3.2 cervical cancers per 100,000 women / year
HPV testing finds more women at high 5-year risk of cancer or precancer

<table>
<thead>
<tr>
<th>Test Result</th>
<th>5-year Risk</th>
<th>Excess Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV+</td>
<td>7.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>HPV-</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Pap+</td>
<td>4.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Pap-</td>
<td>0.4%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test Result</th>
<th>5-year Risk</th>
<th>Excess Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV+ Pap+</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>HPV+ Pap-</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>HPV- Pap+</td>
<td>0.9%</td>
<td>0.7%</td>
</tr>
<tr>
<td>HPV- Pap-</td>
<td>0.2%</td>
<td></td>
</tr>
</tbody>
</table>

Addressing the Need for Advanced HPV Diagnostics (ATHENA trial)
- 47,000 women enrolled
- Roche Cobas 4800: FDA approval for ASC-US triage and cotesting
- Unanimous approval for candidate primary HPV screening algorithm (13-0) on March 12, 2014

FDA NEWS RELEASE
FDA approves first human papillomavirus test for primary cervical cancer screening

The U.S. Food and Drug Administration today approved the first FDA-approved HPV DNA test for women 25 and older that can be used alone in lieu of a health care professional's exam for women for nearly all additional diagnostic testing for cervical cancer. The labels do not contain claims about the value of testing for increasing survival rates in outcomes.
Use of Primary High Risk Human Papillomavirus Testing for Cervical Cancer Screening

Interim Clinical Guidance

Walter E. Hub, MD, Kevin A. Ault, MD, David Chudacoff, MD, Diane D. Davey, MD, Robert A. Goodman, MD, Frances A. J. Garcia, MD, DVM, Walter K. Kinney, MD, L. Stewart Marshall, MD, Edward J. Meyers, MD, Debbie Salinas, MD, Mark Schiffman, MD, MPH, Nii Addo-Quaye, MD, PhD, Howard W. Laserson, MD, and Michael H. Ensz, MD, PhD

Addressing the Need for Advanced HPV Diagnostics (ATHENA trial)

3-Year Cumulative Risks for 2CIN3 Primary Screening Population (225 Years)

From 3/12/2014 FDA Panel Materials

The ‘Candidate’ Algorithm

Candidate Screening Algorithm

HPV with M18 Genotyping and Reflex Cytology

Follow-up in 12 months

From 3/12/2014 FDA Panel Materials
The ‘Candidate’ Algorithm - Why?

Performance of Screening Strategies in ATHENA in ≥25 Yrs vs ≥30 Yrs

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Total Detected</th>
<th>Detected in 1st Yr</th>
<th>Detected in 2nd Yr</th>
<th>Total Detected CIN 1+</th>
<th>No. Screen Fail</th>
<th>No. Undetected</th>
<th>Total Detected CIN 2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology only</td>
<td>173</td>
<td>173</td>
<td>26</td>
<td>199</td>
<td>199</td>
<td>199</td>
<td>199</td>
</tr>
<tr>
<td>Exfoliation only</td>
<td>78</td>
<td>69</td>
<td>4</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>HPV with genotyping</td>
<td>271</td>
<td>186</td>
<td>128</td>
<td>414</td>
<td>210</td>
<td>177</td>
<td>177</td>
</tr>
<tr>
<td>HPV with reflex cytology</td>
<td>175</td>
<td>148</td>
<td>27</td>
<td>175</td>
<td>135</td>
<td>135</td>
<td>135</td>
</tr>
<tr>
<td>HPV with reflex cytology &amp; HPV</td>
<td>254</td>
<td>197</td>
<td>97</td>
<td>294</td>
<td>268</td>
<td>268</td>
<td>268</td>
</tr>
</tbody>
</table>

Why Start at 25 years of Age?

≥CIN3 by Age Group

ATHENA

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage of CIN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-24</td>
<td>16</td>
</tr>
<tr>
<td>25-29</td>
<td>25</td>
</tr>
<tr>
<td>30-34</td>
<td>27</td>
</tr>
<tr>
<td>35-39</td>
<td>17</td>
</tr>
<tr>
<td>40-44</td>
<td>3</td>
</tr>
<tr>
<td>≥45</td>
<td>1</td>
</tr>
</tbody>
</table>

Why Start at 25 years of Age?

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

ATHENA

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Proportion of NILM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29</td>
<td>62.2</td>
</tr>
<tr>
<td>25-29</td>
<td>43.3</td>
</tr>
<tr>
<td>30-34</td>
<td>61.7</td>
</tr>
<tr>
<td>35-39</td>
<td>72.2</td>
</tr>
<tr>
<td>40-44</td>
<td>57.3</td>
</tr>
<tr>
<td>≥45</td>
<td>44.7</td>
</tr>
</tbody>
</table>
Is Screening Needed After Vaccination?

Yes!!!

– Vaccines protect against HPVs 16 and 18 which cause at most 75% of all cervical cancers
– Vaccination is for pre-exposure prophylaxis; most women will continue to rely on screening

But How?

Perfect political storm in 2006

• qHPV vaccine approved by the Therapeutics Goods Administration.
• Australian vaccine with an iconic inventor.
• National Immunisation Program initially rejected it.
Perfect political storm in 2006

- qHPV vaccine approved by the Therapeutics Goods Administration.
- Australian vaccine with an iconic inventor.
- National Immunisation Program initially rejected it.
- Election year, with a budget surplus.
- Health Minister with a dubious reputation in women’s health.
- First Lady with cancer of the cervix.
  - De-stigmatized the disease
  - Influenced husband
Community program

What are Vaccination Rates in the US and Worldwide
Are we making a Difference?

- One of the highest HPV vaccination rates in the world: ~75% for the 3rd dose in 12-13 year olds
- From 2007 to 2011 - Women <21 years old, 93% reduction in genital warts!
- Women 21-30 years old, 73% reduction in genital warts
- No significant decline in women >30 years old


What are Vaccination Rates in the US and Worldwide
Are we making a Difference? What About Men?

- From 2007 to 2011 - Substantial decline in warts in men, 50-80%, depending on age group (i.e., herd immunity)
- No real decline seen in men (>30 years old)

Loss of Pap screening performance due to vaccination

- As successive cohorts of women are vaccinated:
  - Reduction in prevalence of cytological abnormalities
  - **End result:** decrease in positive predictive value of cytology
  - Increase in false positive rates will lead to non-rigorous diagnostic work-up
  - Impact on cytotecnhician training and quality assurance

Huh et al, Gyn Onc. 2010; Franco et al., Vaccine 2006

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Possible qualitative changes in Pap cytology performance

- **Sensitivity will be negatively affected:**
  - Today’s typical case load: ~10% of all smears contain abnormalities that are serious enough to merit slide review
  - Reduction in lesion prevalence → smears may not be read as thoroughly → more false negatives
  - **End result:** further decline in the PPV of cytology
  - Some of the lowest estimates of Pap sensitivity are in frequently screened, low risk populations of developed countries

Huh et al, Gyn Onc. 2010; Franco et al., Vaccine 2006
Need for a paradigm change in screening following vaccination

- Pap cytology will not be the same if left as primary test
- **Potential solution:** HR-HPV DNA testing as primary screening test followed by cytologic triage:
  - HPV testing more sensitive and reproducible
  - HPV testing less likely to vary in sensitivity and specificity
  - Cytology will perform better in the artificially high lesion prevalence when triaging HPV+ women

Huh et al., Gyn Onc, 2010; Franco et al., Vaccine 2006

High-risk HPV testing in the US

<table>
<thead>
<tr>
<th>Use of test</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever used</td>
<td>70</td>
</tr>
<tr>
<td>Not as recommended</td>
<td>54</td>
</tr>
<tr>
<td>At patient’s request</td>
<td>60</td>
</tr>
<tr>
<td>ASC-US</td>
<td>81</td>
</tr>
<tr>
<td>ASC-H</td>
<td>77</td>
</tr>
<tr>
<td>LSIL</td>
<td>62</td>
</tr>
<tr>
<td>HSIL</td>
<td>60</td>
</tr>
<tr>
<td>Adjust to cytology</td>
<td></td>
</tr>
<tr>
<td>Ever used</td>
<td>21</td>
</tr>
<tr>
<td>Women &lt;30</td>
<td>45</td>
</tr>
<tr>
<td>Women ≥50</td>
<td>33</td>
</tr>
</tbody>
</table>

HR HPV testing has been used by 70% of providers but not always as advised in the ASCCP guidelines


Primary HPV Screening: **Recommendations**

- A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative pap (cytology) result.
- Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to cytology based cervical cancer screening.
Primary HPV Screening-Benefits

- More reproducible than Pap cytology
- Negative test (and most women will test negative) associated with very low risk of developing pre-cancer/invasive cancer (also, a much better predictor)
- More sensitive than cytology (lower FN rate): picks up most women with pre-cancers

Primary HPV Screening-Concerns

- Three screening options: more patient and provider confusion
- Unknown screening interval
- Comparison to co-testing?
- Over-treatment of women 25-29 years of age
- Missing cases where there is abnormal cytology yet a negative HPV result

Other Thoughts to Consider

- Data limited to women >30 years of age
- Primary screening is most appropriate for organized screening programs that allow for referral of women to specialized programs that offer specific evaluation and treatment programs
- What is the best test to reflex to? Cytology, genotyping, biomarkers?
- Most studies are from Europe- one US specific study (will be at least 4-5 years until the next one)
What Women (and Clinicians) Really Think about the Recent Guideline Changes

- Too confusing….WT*
- Too many changes at once
- This is all about $$$
- Paps are going away…
- I am worried about increasing the screening intervals
- I cannot believe you are taking my pap away…

So, what would he think???

Thank you!
Questions?