He Said, She Said: HPV and the FDA

Audrey P Garrett, MD, MPH

June 6, 2014
Cervical Cancer Screening: 21\textsuperscript{st} century

- Dr. Papanicolaou
- Cytology
- War on Cancer
- Epidemiology
- a Virus
- a Test
- a Vaccine
Disclosure

- Speaker for Merck
  - Gardasil
- Speaker for Hologic
  - Thin Prep and Cervista
March 12, 2014

• FDA advisory committee released recommendation for HPV primary screening
April 24, 2014

• FDA approved Roche Cobas test
Objectives

• To understand that HPV is important in cervical cancer oncogenesis
• To understand the epidemiology of HPV
• To understand the role of HPV testing in cervical cancer screening
• To explore the potential for early detection of HPV related diseases
• To appreciate the NPV of HPV neg result
Cervical Cancer: Epidemiology

• Prior to the advent of screening, 30-40 cases per 100,000
• Similar to rate of anal cancer in MSM
• Some populations 70-90/100,000
• Previously the most common malignancy in women
• 500,000 cases annually worldwide
Cervical Cancer Statistics

- Approximately 500,000 new cases/year\(^1\)
- Majority are in countries where no screening is possible or offered
- Majority are in countries where no treatment is possible or offered
- Approximately 250,000 deaths/year

US Cervical Cancer Statistics

- Approximately 12,710 new cases/year\(^1\)
- Approximately 4,290 deaths/year\(^1\)
- Approximately 10 million cases of HPV infection without cytologic abnormalities\(^2\)
- Approximately 1 million cases CIN 1\(^2\)
- Approximately 300,000 – 700,000 cases of CIN2/3
- Direct cost of prevention and treatment of cervical cancer is $6 billion annually in the US

Cervical Cancer: Real Disease that happens to Real Women
Pap Smear: History

• 1920s developed technique
  – Hans Hinselmann invented colposcope
• 1941 paper published
• 1946 Ayer’s spatula introduced
• 1950s incorporated into well woman care
• 1965 endorsed by ACS
• Cervical cancer mortality began to drop
• 1971 Nixon declares war on Cancer
Major Advances in Cervical Cancer Screening


1941 Pap Smear

1940s

1970s Research by Harald zur Hausen linking HPV to cervical cancer

1999 Hybrid Capture® 2 HPV Test

1996 ThinPrep® Pap Test

1999 SurePath® Pap Test

1996 ThinPrep® Imaging System

1999

2000s

2006 Gardasil® HPV Vaccine

2003 ThinPrep® Imaging System

2009 Cervista® HPV HR Test and Cervista® HPV 16/18 Genotyping Test

2009 Cervarix® HPV Vaccine

2006 ThinPrep® Receives Glandular Indication

2009 Cervista® HPV HR Test and Cervista® HPV 16/18 Genotyping Test
<table>
<thead>
<tr>
<th>TASKS:</th>
<th>Definitions</th>
<th>Actuals</th>
<th>Targets</th>
<th>Actions</th>
<th>Notes</th>
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**Notes:**

- Task 1.0: Brief description of task 1.0.
- Task 2.0: Brief description of task 2.0.
- Task 3.0: Brief description of task 3.0.
- Task 4.0: Brief description of task 4.0.
- Task 5.0: Brief description of task 5.0.
- Task 6.0: Brief description of task 6.0.
2003 ACOG Guidelines

**< 21 Years**
First screen three years after first intercourse or by age 21

**21-29 Years**
Annual pelvic exam AND annual cytology

**≥ 30 Years**
Screen every 2 to 3 years after testing negative on 3 consecutive annual cervical cytology tests, or screened every 3 years after cervical cytology and an FDA-approved HPV DNA tests for high-risk HPV strains are both negative.

**Hysterectomy**
- If for benign reasons, discontinue screening.
- If CIN2 or CIN3, discontinue screening after 3 consecutive negative vaginal cytology tests.
2009 ACOG Guidelines

- **< 21 Years**
  - No routine speculum exam or cytology; STD testing and counseling on safe sex and contraception as needed

- **21-29 Years**
  - Annual pelvic exam AND biannual cytology

- **30-64 Years**
  - Annual pelvic exam AND cytology\(^a\) OR cytology plus HPV testing (if both are negative, rescreen in 3 years)

- **≥ 65 Years**
  - Annual pelvic exam AND consider discontinuing cytology at 65 or 70 years of age if patient has had 3 or more normal test results in a row, no abnormal test results in 10 years, and lacks other risk factors\(^b\)

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\(^a\) Frequency of screening can be decreased to 2-3 years after 3 normal test results if no history of CIN 2/3, no immuno-suppression, HIV-negative, and no history of DES in utero.

\(^b\) History of cervical cancer or DES in utero, HIV-positive, immunosuppression, or other risk factors for acquiring STDs.

STD = Sexually transmitted disease

USPSTF and ACS/ASCCP/ASCP

2012 Cervical Cancer Screening Guidelines

- No routine speculum exam or cytology regardless of age of onset of intercourse or other risk factors.
- STD testing and counseling on safe sex and contraception as needed.

21-29 Years

- Annual pelvic exam
- Screening with cytology alone every 3 years is recommended

30-65 Years

- Annual pelvic exam AND screening with
- Cytology and HPV testing (“co-testing”) every 5 years (preferred)
  OR
- Cytology alone every 3 years (acceptable) is recommended.

> 65 Years

- Women with three consecutive negative cytology tests
  OR
  - Two consecutive negative co-tests within the last 10 years and with the most recent test in the past 5 years
  AND
  - No history of CIN2+ within the last 20 years

The New York Times

• New guidelines discourage annual pap smears, cervical cancer screenings
• Published: Thursday, March 15, 2012, 11:46 AM
• By The Associated Press
Human Papillomavirus (HPV) Is a Cause of Cervical Cancer

- Over 100 types identified\(^2\)
- 30–40 anogenital\(^2,3\)

- 15–20 oncogenic\(^2,3\) types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58\(^4\)
  - HPV 16 (54%) and HPV 18 (21%) account for the majority of cervical cancers worldwide\(^5\)

- Nononcogenic types include:
  - 6, 11, 40, 42, 43, 44, 54\(^4\)
    - HPV 6 and 11 account for 90% of external genital warts\(^3\)

HPV Facts: Most common STD in the U.S.

Approximately 20 million Americans are currently infected.¹

- Estimated incidence of new cases 6 million per year¹
- 80% sexually active adults in U.S. infected w/ at least one HPV type by age 50¹
- Peak prevalence during adolescence and young adulthood
  - Among sexually active 15-24 year olds:
    - 74% new infections occur in this age group²
    - ~9.2 million currently infected²

¹ Centers for Disease Control & Prevention, Rockville MD: CDC National Prevention Information Network; 2009
Cervical Cancer and HPV

- HPV presents biologic plausibility
  - E6 and E7 interact P53 and RB
- Archival slides demonstrate presence
- Prospective studies link HPV and dysplasia
- 98% cervical cancers test positive
- Vaccine data demonstrates efficacy
Screening Test

- Efficacy of test dependent on epidemiology
  - Prevalence
  - Incidence

- Heavily pre-screened populations
  - Decrease prevalence
  - Stable incidence
  - Smaller incident lesions (lead time bias)

- Altered epidemiology of target lesion
Changing Epidemiology
Cervical Cancer Screening

- Public health concept
- Screening is for ASSYMPTOMATIC pts
- For a sufficiently common disease
- With a sufficiently long pro-drome
- With a sufficiently reasonable potential intervention
Public Health/ Statistics

- True positive
- False negative
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Sensitivity
- Specificity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
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<tr>
<td>+</td>
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<td>-</td>
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Sensitivity = \( \frac{a}{a+b} \)

Specificity = \( \frac{c}{c+d} \)
> 75% of *Squamous Cancers in the United States Are Caused by HPV 16/18

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>Cumulative Prevalence</th>
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<tbody>
<tr>
<td>16 alone</td>
<td>54.7%</td>
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<tr>
<td>16 + 18</td>
<td>76.4%</td>
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<tr>
<td>+ 35</td>
<td>83.7%</td>
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<tr>
<td>+ 31</td>
<td>87.6%</td>
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<tr>
<td>+ 33</td>
<td>91.0%</td>
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<tr>
<td>+ 45</td>
<td>93.6%</td>
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<tr>
<td>+ 52</td>
<td>94.2%</td>
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<tr>
<td>+ 58</td>
<td>94.4%</td>
</tr>
<tr>
<td>+ 59</td>
<td>94.5%</td>
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Proportion of Cancers Associated with HPV Types
Risk Stratification with HPV Types 16 and 18 in Women ≥ 30 Years of Age with Negative Cytology

In women ≥ 30 years of age, 10-year cumulative incidence of ≥ CIN 3 was 20% and 18% for HPV 16 and 18, respectively.

Chocolate Consumption, Cognitive Function, and Nobel Laureates

$r=0.791$
$P<0.0001$

Messerli, NEJM 367;16 October 18, 2012
equal management of equal risks

don’t change risk thresholds for action

risk is a combination of immediate risk and future risk

– 1000 women with LSIL pap

• 24 (2.4%) have CIN3+ at colpo
• 29 (2.9%) have CIN3+ over next 5 years
• cumulative risk 5.3%
Risk Stratification with HPV Types 16 and 18 in Women ≥ 30 Years of Age with Negative Cytology

In women ≥ 30 years of age, 10-year cumulative incidence of ≥ CIN 3 was 20% and 18% for HPV 16 and 18, respectively.

Risk of precancer/cancer for each Pap smear result

Katki et al, J Low Genit Tract Dis, 2013
A “Risk Bar” for the App

Risk for this result: 0.43%

<table>
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<tr>
<th>5-year CIN3+ risk:</th>
<th>0.08%</th>
<th>0.26%</th>
<th>2.6%</th>
<th>5.2%</th>
<th>25%</th>
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</table>

- “Equal Management of Equal Risks” logic needs to be obviously and immediately apparent

- The risk calculation underlying the recommendation is displayed on the continuum

- “Why is the recommendation for HPV-negative/ASC-US a 3-year return?”
  - “Oh, the data say it’s just like a negative Pap. I get it.”
Cumulative incidence of CIN3+ according to baseline test results in European sites (excluding Denmark and Tubingen)

Dillner, J. et al. BMJ 2008;337:a1754

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**HPV testing finds more women at high 5-year risk of cancer or precancer**

<table>
<thead>
<tr>
<th>Test</th>
<th>5-year Risk</th>
<th>Excess Risk</th>
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<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>
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<table>
<thead>
<tr>
<th>HPV Test</th>
<th>Pap Test</th>
<th>5-year Risk</th>
<th>Excess Risk</th>
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<tbody>
<tr>
<td>HPV+</td>
<td>Pap+</td>
<td>12%</td>
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</tr>
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<td>HPV+</td>
<td>Pap-</td>
<td>6%</td>
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<tr>
<td>HPV-</td>
<td>Pap+</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>HPV-</td>
<td>Pap-</td>
<td>0.2%</td>
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Influence of laboratory performing the test on Pap and HPV testing performance (CCCaST Study)

(Mayrand et al., unpublished data)
Influence of prevalence of cervical lesions on the positive predictive value (PPV) and negative predictive value (NPV) of cytology as a primary screening test. Sensitivity and specificity held constant at 70% and 98%, respectively. Gray bands: 95% credibility intervals around median values for 1000 simulations using each of the parameter combinations in hypothetical populations of 10,000 women. (Franco et al., Arch Med Res 2009)
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
- 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
Addressing the Need for Advanced HPV Diagnostics (ATHENA trial)

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

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

Candidate Screening Algorithm
HPV with 16/18 Genotyping and Reflex Cytology

Routine screening
HPV-
Follow-up in 12 months
NILM
≥ASC-US
COLPOSCOPY

12 other hrHPV+
Cytology

HPV16/18+
COLPOSCOPY

cobas® HPV Test
31 33 35 39 45 51
52 56 58 59 66 68
hrHPV=high risk HPV

From 3/12/2014 FDA Panel Materials
Why Start at 25 years of Age?

≥CIN3 by Age Group
Athena

Data not reviewed by FDA

From 3/12/2014 FDA Panel Materials
Why Start at 25 years of Age?

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

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<table>
<thead>
<tr>
<th>Age</th>
<th>≥ASC-US</th>
<th>NILM</th>
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<tbody>
<tr>
<td>25-29</td>
<td>57.3%</td>
<td>42.7%</td>
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<tr>
<td>30-39</td>
<td>46.7%</td>
<td>53.3%</td>
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<tr>
<td>40-49</td>
<td>38.3%</td>
<td>61.7%</td>
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<tr>
<td>≥50</td>
<td>27.8%</td>
<td>72.2%</td>
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Data not reviewed by FDA
Percentages shown are for hrHPV+ women with ≥CIN3, N=252

From 3/12/2014 FDA Panel Materials
Cervical Cancer Prevention: Get with the times...

“This dial phone has always worked for me...”

“My patients would never be able to understand a more modern test...”
Unanswered Questions

• Why do I have HPV and my friend doesn’t?
• Should I have my tonsils out?
• Will it go away?
• Should I divorce my husband?
• Will I still be able to have orgasms after my hysterectomy?
• Will Brazil win the World Cup?
Some Answers

- Risk assessment is here to stay
- HPV testing is more reproducible than cytology
- HPV testing provides more information regarding FUTURE risk of dysplasia or cancer
- HPV negativity provides reassurance for many and allows safe extension of screening intervals