Applying Cervical Cancer Screening Guidelines to Clinical Practice

Association of Reproductive Health Professionals www.arhp.org
Acknowledgment

• This session is made possible through an educational grant from Roche.
# Expert Medical Advisory Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Disclosure</th>
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<tr>
<td>Lee Shulman, MD (Chair)</td>
<td>Dr. Shulman is a speaker and/or consultant for Actavis, Teva, Merck, Bayer, Shionogi, Sequenom, Natera, Quest, Roche Labs.</td>
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<td>Northwestern University</td>
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<tr>
<td>Nancy R. Berman, MSN, ANP-BC, NCMP (Planner)</td>
<td>Ms. Berman is a speaker for QIAGEN and consultant for Hologic.</td>
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<td>Millennium Affiliated Physicians</td>
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<td>Division of Michigan Healthcare Professionals</td>
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<td>Farmington Hills, Michigan</td>
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## ARHP Consultants and Staff

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<th>Name</th>
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<tr>
<td>Diane W. Shannon, MD (Medical Writer)</td>
<td>Nothing to disclose.</td>
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<tr>
<td>Rana Suliman, MPH (Planner)</td>
<td>Nothing to disclose.</td>
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</table>
Which of the following is true about the management of women age 30 or older with Pap negative/HPV positive results?

A. Genotyping is recommended for use only in women less than age 25.
B. Either reflex or immediate genotyping for HPV 16 and 18 is an option for triage in this population of women.
C. Genotyping is unnecessary; women in this population should proceed immediately to colposcopy, regardless of the genotype result.
D. None of the above is true.
Learning Objectives (continued)

• Describe the elements of an annual well woman visit that does not include an annual Pap test.
• Apply knowledge of cervical cancer screening to the management of various test results.
• Explain how the Affordable Care Act may increase the opportunities for women to receive screening for cervical cancer.
The Impact of HPV
HPV-Associated Disease

• Anogenital cancers
  ▪ Cervical
  ▪ Anal
  ▪ Vulvar and vaginal
• Other cancers
  ▪ Oral cavity, pharynx, larynx
  ▪ Skin
  ▪ Conjunctiva
• External genital warts
• Laryngeal papillomatosis

Munoz N. *Vaccine*. 2006; Lacey CJN. *Vaccine*. 2006.
HPV and Cervical Cancer

• Virtually all cervical cancers are associated with persistent infection with high-risk HPV types

• Data from a variety of studies have confirmed that certain HPV types are associated with cervical cancer:
  ▪ 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59

• Others are probably associated, including:
  ▪ 26, 53, 66, 68, 73, 82

Annual Impact of HPV

- 12,000 cases in US
- 4,000 deaths in US
- 275,000 deaths worldwide
- $3.4 billion for screening

HPV and the Natural History of Cervical Cancer
High Lifetime Risk of HPV Infection

• 6.2 million new infections
• Approximately 20 million people in US currently are infected with HPV
• By age 50, 80% of sexually active women will have acquired genital HPV infection

Risk Factors for HPV Infection

- Sexual Activity
- Multiple Partners
- Younger age at sexual debut
- Lack of condom use

HPV Transmission

• Virus transmitted via sexual intercourse and direct genital contact
• Primarily through male-to-female penetrative intercourse
• Can also be transmitted by:
  ▪ Receptive anal intercourse
  ▪ Non-penetrating sexual activities
  ▪ Oral-genital contact

Transformation Zones and HPV Infection

• HPV infection causes cancer most often within “transformation zones”
  ▪ Area where one type of epithelium contacts and gradually replaces another through process of metaplasia
  ▪ Cervix, anus, and tonsils are all areas with transformation zones

• Less often, HPV can also cause cancer on mature squamous epithelium
  ▪ Vulva, vagina, penis

Moscicki AB. *Vaccine*. 2006.
Cervical Transformation Zone

Role of Persistent Infection

- Average episode 4 to 20 months
- About 90% cleared by immune system
- **Persistent** infection is required for progression
- Type 16 is more likely to persist
Natural History of HPV and Cervical Cancer

Persistence

Normal Cervix → Infection ↔ Clearance → HPV Infection → Progression ↔ Regression → Pre-cancer → Invasion → Cancer

Courtesy of M. Schiffman, National Cancer Institute.
HPV Vaccination

- Before HPV exposure
- Boys and girls age 11 to 12
- Catchup vaccination to age 26

Available Screening Tests
Cytology: Pap Tests

• Conventional and liquid-based acceptable

• Liquid-based facilitates:
  ▪ Reflex testing: adding HPV test after Pap results known
  ▪ Co-testing: ordering Pap and HPV at time of sampling
  ▪ Ordering tests for gonorrhea and chlamydia

HPV Testing Rationale

- Stratifies for risk
- Allows for less frequent testing, due to its high sensitivity
- Identifies women who need increased surveillance

HPV Testing is **NOT** Appropriate:

- For STI screening
- For HPV status before vaccination
- For triage, except for
  - ASC-US
  - LSIL in postmenopausal women
- With cytology for screening women:
  - < 30 years old
  - Status post total hysterectomy

# HPV Tests

<table>
<thead>
<tr>
<th>Available Tests</th>
<th>HPV Types Detected</th>
<th>Identifies HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hybrid Capture 2</td>
<td>High and low risk panels (request high risk only)</td>
<td>No</td>
</tr>
<tr>
<td>Cervista HPV HR</td>
<td>High risk</td>
<td>No (add on test for 16 and 18)</td>
</tr>
<tr>
<td>cobas HPV Test</td>
<td>High risk</td>
<td>Yes for 16 and 18</td>
</tr>
<tr>
<td>APTIMA HPV mRNA assay</td>
<td>High risk</td>
<td>No (add on test for 16, 18, and 45)</td>
</tr>
</tbody>
</table>

ASCCP. *Educate the Educators: HPV and the HPV Vaccines*. 2006.
Current Screening Recommendation: Rationale and Clinical Implications
Goals of Screening

1. Identify and treat high-grade precursors
2. Avoid potentially hazardous evaluations and treatment
3. Minimize costs to the health care system
Increase Benefit and Decrease Harm!
Cervical Cancer Screening Timeline

- Rec. frequency reduced
- HPV test approved
- Co-testing approved
- Algorithms updated
- Stand alone test approved age 25-65

- 1980
- 2000
- 2003
- 2013
- 2014

Key Points in ASCCP Guidelines

Include:

- Screening intervals
- Co-testing women 30 and older: genotyping in Pap/neg, HPV/+ 
- Approach to screening and managing young women

www.asccp.org
Algorithms

Mobile App: iPhone and Android
Screening Interval

“…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.”

American Society for Colposcopy and Cervical Pathology

### Screening Interval for Combined Pap and HPV Testing in Women 30 and Older: Primary Screening

<table>
<thead>
<tr>
<th>HPV Result</th>
<th>Cytology</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Cotest in 5 years</td>
</tr>
<tr>
<td>Negative</td>
<td>ASC-US</td>
<td>Cotest in 3 years</td>
</tr>
<tr>
<td>Positive</td>
<td>ASC-US</td>
<td>Colposcopy</td>
</tr>
<tr>
<td>Negative</td>
<td>Pap ≥ LSIL</td>
<td>Repeat cotesting in 1 year preferred; colposcopy acceptable</td>
</tr>
<tr>
<td>Positive</td>
<td>Pap ≥ LSIL</td>
<td>Colposcopy</td>
</tr>
<tr>
<td>Any</td>
<td>HSIL</td>
<td>Colposcopy or immediate loop electrosurgical excision</td>
</tr>
</tbody>
</table>
| Positive   | Negative     | Option 1: Cotest in 12 months  
Option 2: Reflex to genotyping for HPV 16/18. If positive, colposcopy. If negative, cotest in 12 months |

Management of Repeat Testing After HPV +, Cytology - Results

<table>
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<tr>
<th>HPV Result</th>
<th>Cytology</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Repeat cotesting in 3 years</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Perform colposcopy</td>
</tr>
<tr>
<td>Any</td>
<td>Pap ≥ ASC-US</td>
<td>Perform colposcopy</td>
</tr>
</tbody>
</table>

Genotyping to Triage Women >30 with Pap-/HPV+ Results

- Genotyping
  - Positive for 16 or 18
    - Immediate colposcopy
  - Negative for 16 and 18
    - Co-testing in 12 months
FDA NEWS RELEASE

For Immediate Release: April 24, 2014
Media Inquiries: Susan Laine, 301-796-5349, susan.laine@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

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 to help a health care professional assess the need for a woman to undergo additional diagnostic testing for cervical cancer. The test also can provide information about the patient’s risk for developing cervical cancer in the future.
# Athena Trial of Primary HPV Screening

<table>
<thead>
<tr>
<th>Testing strategy</th>
<th># Screening tests required</th>
<th># Detected CIN2+</th>
<th># Missed CIN2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology with reflex HPV for ASCUS</td>
<td>43,503</td>
<td>270</td>
<td>317</td>
</tr>
<tr>
<td>Cotesting with cytology and HPV</td>
<td>91,822</td>
<td>455</td>
<td>132</td>
</tr>
<tr>
<td>Primary HPV with genotyping and reflex cytology</td>
<td>53,820</td>
<td>473</td>
<td>114</td>
</tr>
</tbody>
</table>

Wright TC. Abstract presented at 2014 Meeting of Society of Gynecologic Oncology.
Management for Women Age 21-24

- Strategy: observation for minor abnormalities
- Use separate algorithm
- No immediate colposcopy for ASC-US and LSIL
- Instead Pap in 12 months
- Strategy allows time for clearance of HPV infection and regression of cellular abnormalities

Factors Indicating Need for More Frequent Screening

- HIV infection
- Immunosuppression
- DES exposure in utero
- Previous treatment for CIN 2, CIN 3, or cancer

Cervical Pre-Cancer Treatment Modalities

• High Grade Squamous Disease
  ▪ Laser excision
  ▪ Cryosurgery in carefully selected cases*
  ▪ LEEP
  ▪ Cold knife conization

• Adenocarcinoma in Situ
  ▪ Hysterectomy is preferred
  ▪ Excisional procedure, followed by careful surveillance, in women desiring to maintain fertility,

*Where excision not available; requires adequate colposcopy, visible upper margin of lesion, and absence of abnormal blood vessels.
Cervical Cancer Management

- Referral to gynecologic oncologist
- Factors affecting treatment choice
  - Stage and location
  - Squamous cell vs adenocarcinoma
  - Age and physical condition
  - Desire to retain fertility

ACS. Treatment options for cervical cancer by stage. 2014;
NCI. Cervical cancer treatment. 2014.
## Cervical Cancer Treatment Modalities

<table>
<thead>
<tr>
<th>Squamous cancer</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hysterectomy with possible lymph node dissection</td>
<td>• Hysterectomy with possible lymph node dissection</td>
</tr>
<tr>
<td>• Trachelectomy*</td>
<td>• Brachytherapy</td>
</tr>
<tr>
<td>• Brachytherapy</td>
<td>• Radiation</td>
</tr>
<tr>
<td>• Radiation</td>
<td>• Chemotherapy</td>
</tr>
<tr>
<td>• Chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

*fertility sparing in young women with early cancer and small tumors*

ACS. Treatment options for cervical cancer by stage. 2014; NCI. Cervical cancer treatment. 2014.
The Updated Well-Woman Visit
Well Woman Visit: Components

- Screening
- Query about risk factors
- Evaluation
- Immunizations
- Counseling

ACOG Committee Opinion #534. 2014.
Implications of Interval Extension

• Clinicians and patients must become comfortable

• Most desirable that previous screening results are available

• Need to educate patients about limits of Pap
American College of Physicians recommends against screening pelvic examination in adult, asymptomatic, average risk, non-pregnant women

ACP's new evidence-based guideline finds that harms of screening pelvic examination outweigh any demonstrated benefits

PHILADELPHIA, July 1, 2014 -- Many women and physicians believe that a pelvic examination should be part of annual well visits, but an analysis of the current evidence by the American College of Physicians (ACP) shows that the harms outweigh any demonstrated benefits.

ACP's new evidence-based clinical practice guideline, “Screening Pelvic Examination in Adult Women,” was published today in Annals of Internal Medicine, ACP's flagship journal. ACP's guideline is based on a systematic review of the published literature on human subjects in the English language from 1946 through January 2014.

“Routine pelvic examination has not been shown to benefit asymptomatic, average risk, non-pregnant women. It rarely detects important disease and does not reduce mortality and is associated with discomfort for many women, false positive and negative examinations, and extra cost,” said Dr. Linda Humphrey, a co-author of the guideline and a member of ACP's Clinical Practice Guidelines Committee. Dr. Humphrey notes that this guideline does not apply to Pap smear screening, only the pelvic examination.

ACP states that when screening for cervical cancer, the recommended examination should be limited to visual inspection of the cervix and cervical swabs for cancer and for some women human papillomavirus (HPV), and does not need to include the bimanual examination. ACP found that the diagnostic accuracy of the pelvic examination for detecting gynecologic cancer or infections is low. ACP advises that the pelvic examination is appropriate for women with symptoms such as vaginal discharge, abnormal bleeding, pain, urinary problems, or sexual dysfunction.

ACP's guideline includes High Value Care advice to help doctors and patients.
ACOG Practice Advisory on Annual Pelvic Examination Recommendations

June 30, 2014

Washington, DC — The American College of Obstetricians and Gynecologists (the College) has reviewed the recommendations from the American College of Physicians about annual pelvic examinations and continues to stand by its guidelines, which complement those released recently by the American College of Physicians.

The College's guidelines, which were detailed in this year's Committee Opinion on the Well-Woman Visit, acknowledge that no current scientific evidence supports or refutes an annual pelvic exam for an asymptomatic, low-risk patient, instead suggesting that the decision about whether to perform a pelvic examination be a shared decision between health care provider and patient, based on her own individual needs, requests, and preferences.

However, the College continues to firmly believe in the clinical value of pelvic examinations, through which gynecologists can recognize issues such as incontinence and sexual dysfunction. While not evidence-based, the use of pelvic exams is supported by the clinical experiences of gynecologists treating their patients. Pelvic examinations also allow gynecologists to explain a patient’s anatomy, reassure her of normalcy, and answer her specific questions, thus establishing open communication between patient and physician.

Of course, pelvic examinations represent just one part of the annual well-woman visit, which can help to identify health risks for women and which can also feature clinical breast examinations, immunizations, contraceptive care discussions, and health care counseling. Importantly, annual well-woman visits help to strengthen the patient-physician relationship.
Well-Woman Care: Assessments & Recommendations

Annual assessments provide an excellent opportunity to counsel patients about preventive care and to provide or refer for recommended services. These assessments should include screening, evaluation and counseling, and immunizations based on age and risk factors. The interval for individual services varies.

These recommendations, based on age and risk factors, serve as a framework for care which may be provided by a single physician or a team of health care professionals. The scope of services provided by obstetrician-gynecologists in the ambulatory setting will vary from practice to practice. The recommendations should serve as a guide for the obstetrician-gynecologist and others providing health care for women and should be adapted as necessary to meet patients’ needs. This information should not be construed as dictating an exclusive course of treatment or procedure to be followed.
Counseling Women about Cervical Cancer Screening
Key Counseling Steps

- Ask about history
- Provide educational messages
- Encourage well woman visits
- Ask about questions and concerns
Utilize Written Materials

Helpful in supporting patient education
Patients can use for later reference
Many are available in additional languages including Spanish

Unbranded materials:
- Center for Disease Control
- American Cancer Society
- American Society for Colposcopy and Cervical Pathology
- Association of Reproductive Health Professionals
Messages about HPV

- HPV is sexually transmitted and very common
- HPV infection usually clears without treatment
- Persistent HPV infection can cause cervical cancer
- Most women with HPV do not get cancer

Messages about HPV Positive Results

- Most women will have HPV at some point
- There is no way of knowing how long HPV has been present
- Having HPV is not a sign of infidelity or promiscuity
Messages about HPV Positive Results (Continued)

- Most women who have HPV do not develop abnormal cells or cancer
- Women who have HPV in their cells a long time are at greater risk for developing abnormal cells or cancer
Health Care Reform and Cervical Cancer Screening
Impact of Increased Access to Screening

“...perhaps the largest immediate gain in reducing burden of cervical cancer incidence and mortality could be attained by increasing access to screening (regardless of the test used) among women who are currently unscreened or screened infrequently.”

COMPILATION OF PATIENT PROTECTION AND AFFORDABLE CARE ACT

[As Amended Through May 1, 2010]

INCLUDING

PATIENT PROTECTION AND AFFORDABLE CARE ACT
HEALTH-RELATED PORTIONS OF THE HEALTH CARE AND EDUCATION RECONCILIATION ACT OF 2010

PREPARED BY THE
Office of the Legislative Counsel
FOR THE USE OF THE
U.S. HOUSE OF REPRESENTATIVES

MAY 2010
Case study: Jennifer

- 43 year teacher
- G1P1
- 9 year old daughter
- Divorced two years ago
- Relationship for 6 months
Case study: Screening
Case study: Results

- Cytology -
- HPV +
Case study: Counseling

- HPV infection does not mean your partner was unfaithful.
- Women who have HPV a long time are at a greater risk for developing abnormal cells or cancer.
- Most women who have HPV do not develop abnormal cells or cancer.
Case Study: Follow Up

• Recommended follow up: Repeat co-testing in 12 months
• If genotyping 16/18 had been positive, immediate colposcopy is recommended
Case Study: Exiting from Screening
Case Study: Exiting from Screening

- Age 65 or older
- Adequate negative prior screening
  - 3 negative Pap tests
  - 2 negative co-tests within last 10 years
- Follow-up after CIN2/3 for 20 years regardless of age
- If Pap ASC-US and HPV negative: continue screening with Pap and HPV in 12 months
Summary
Key Take Home Points

• Cervical cancer is caused by *persistent* infection with high risk HPV
• Intervals for screening have been revised based on accumulated evidence
• Women age 21-24 have a separate algorithm, reflecting the need to minimize invasive testing and overtreatment of transient HPV infection and associated cellular changes

More…
Key Take Home Points

• Genotyping can be used for triage of women age 30 or older with Pap-/HPV+
• Women age 65 or older can exit from screening with adequate negative prior screening