
HPV and Cervical Cancer Prevention Update: Addressing HPV Vaccine Compliance Issues, New Guidelines for Screening and Management of Abnormal Screening Tests

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Disclosures

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Objectives

At the end of this session, the attendee will:

1. Discuss the natural history of HPV and cervical cancer
 2. Describe 2 strategies for increasing uptake of HPV vaccination for age appropriate young men and women
 3. Discuss the age to initiate cervical cancer screening, use triage for the ASC-US Pap and age to discontinue screening
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What's to Know, What's New and What's Changed

HPV Natural History and
Understanding Transformation Zones

HPV-Associated Disease

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

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

HPV Impact: Cervical Cancer

- In the US (2013 estimate):
 - 12,340 cases per year
 - 4,030 deaths per year
- Worldwide (2008 estimate):
 - 530,000 cases per year
 - 275,000 deaths per year
 - 85% of deaths occur in developing countries
- Cervical cancer screening: costs \$3.4 billion annually

HPV and Non-Cervical Cancers

- HPV 16
 - Evidence of causal role in cancer of vagina, vulva, penis, anus, oral cavity, oropharynx; limited evidence for carcinogenicity in the larynx
- HPV 18
 - Limited evidence of carcinogenicity in vagina, vulva, penis, anus, oral cavity, larynx
- HPV 6 and 11
 - Limited evidence of carcinogenicity in vulva, penis, anus, larynx

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

Incidence/Prevalence of HPV in Men

2011 cohort study

- Prevalence of HPV in > 1,100 men was 50%
- Incidence of new genital HPV infection in 12-month period was 39.3%

Oncogenic HPV infection was significantly associated with:

- High number of lifetime female sexual partners
- High number of lifetime male anal-sexual partners

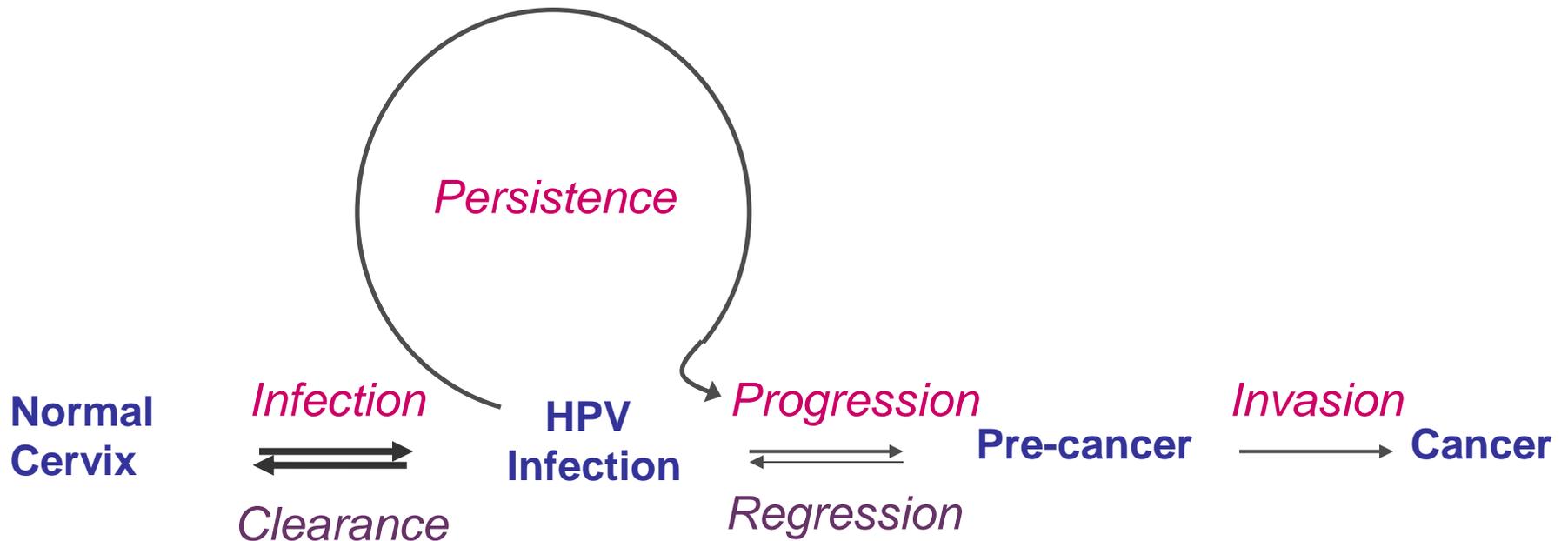
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Incidence/Prevalence of HPV in Men

Median duration of HPV infection

- 7.5 months for any HPV infection
- 12 months for HPV 16
- Clearance of infection decreased with high number of female partners
- Clearance was more rapid with increasing age

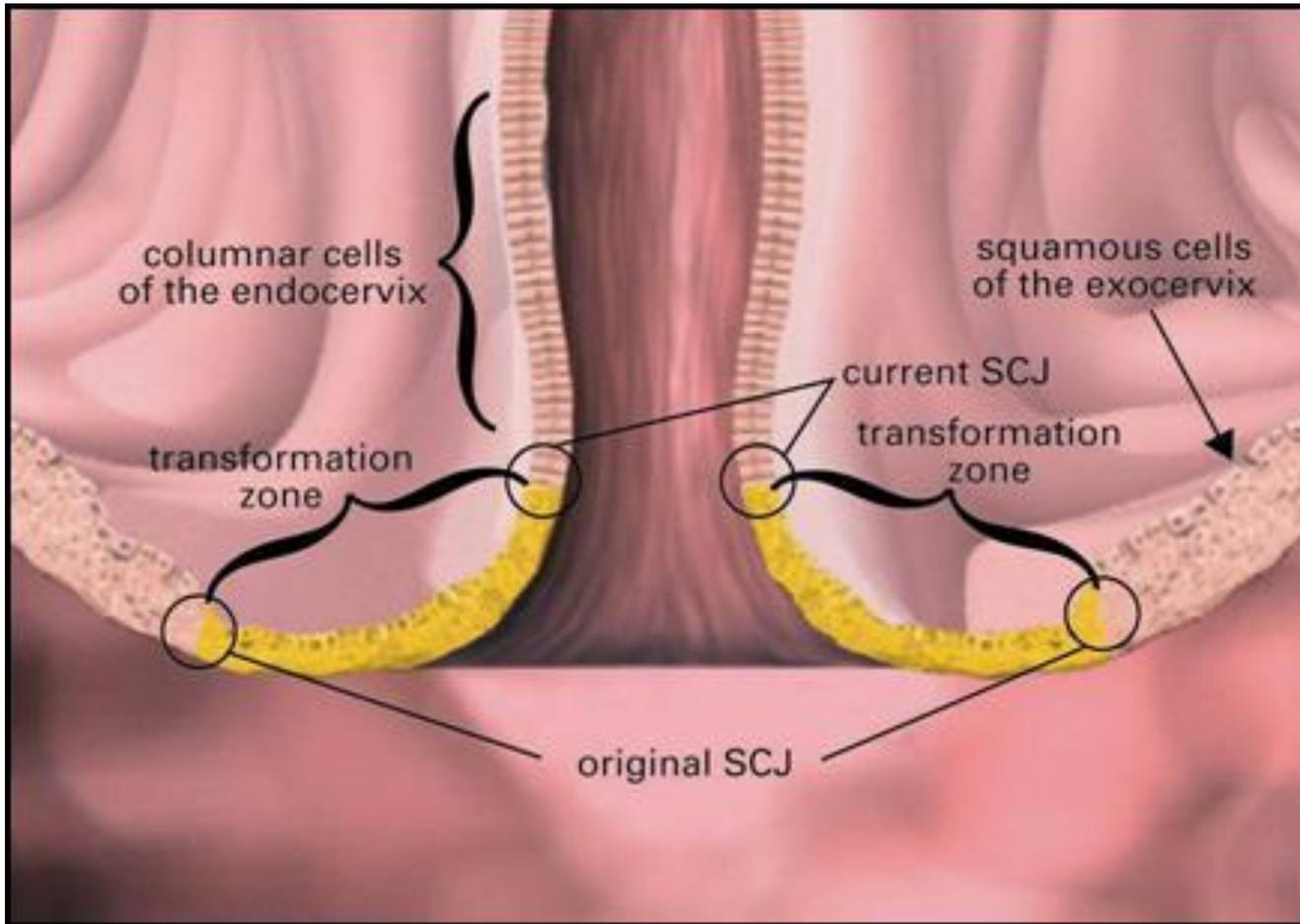
Natural History of HPV & Cervical Cancer



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

Cervical Transformation Zone



Source: <http://www.merckmedicus.com/ppdocs/us/hcp/diseasemodules/hpvd/images/figure25.jpg>

Role of Persistent Infection

- Persistent infection with high-risk types of HPV is necessary for the progression of high-grade lesions to invasive cancer

more...

Role of Persistent Infection (Continued)

- Average episode lasts 4-20 months
- <50% of women have same type 1 year later
- Type 16 has a greater risk of persistence

Prevention of HPV-Related Disease

- Primary prevention
 - Preventing HPV infection
 - Secondary prevention
 - Identifying and treating high-grade precancerous lesions
 - Tertiary prevention
 - Treatment of cervical and other anogenital cancers
-

What's to Know, What's New and What's Changed

Primary Prevention:
HPV Vaccination

Current Status of Prophylactic Vaccines

June 2006:
Merck quadrivalent
HPV vaccine
(Gardasil) approved
by FDA

October 2009
GSK bivalent HPV
vaccine (Cervarix)
approved by FDA

October 2011:
Recommendations
for use in males by
ACIP



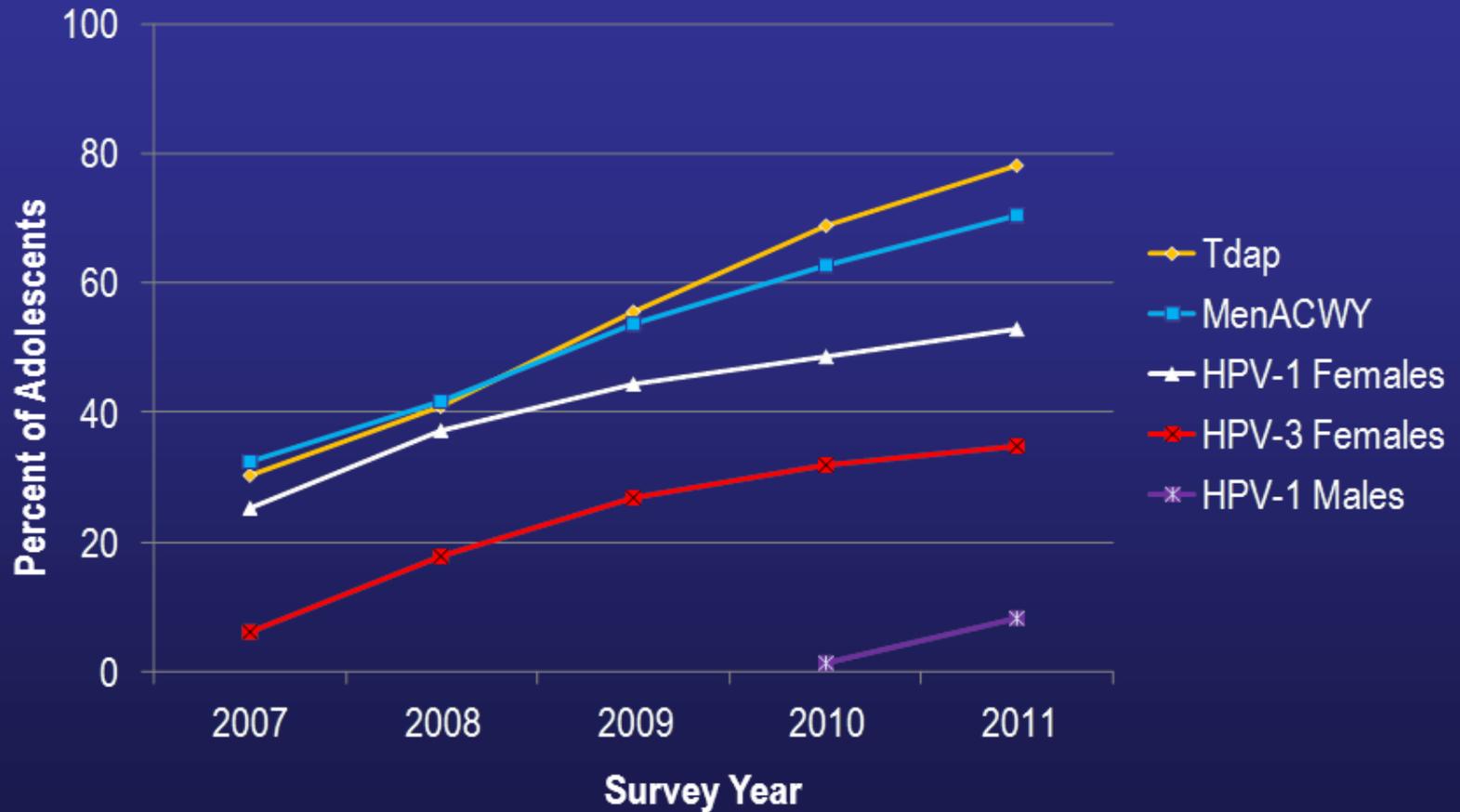
2006:
Recommendations for
use in girls and women
by ACIP and included in
VFC program

2009:
Quadrivalent vaccine
approved for use in
boys & men

HPV Vaccination

- Vaccination rates among adolescent females aged 13 to 17 years failed to increase between 2011 and 2012
- HPV vaccine rates have not kept pace with other vaccines recommended for preteens and teens
- 84% of girls attended a health care visit in which another vaccine was received and the HPV vaccine was not administered

HPV Vaccine Coverage (Age 13-17 Years) is Less Than Other Adolescent Vaccines



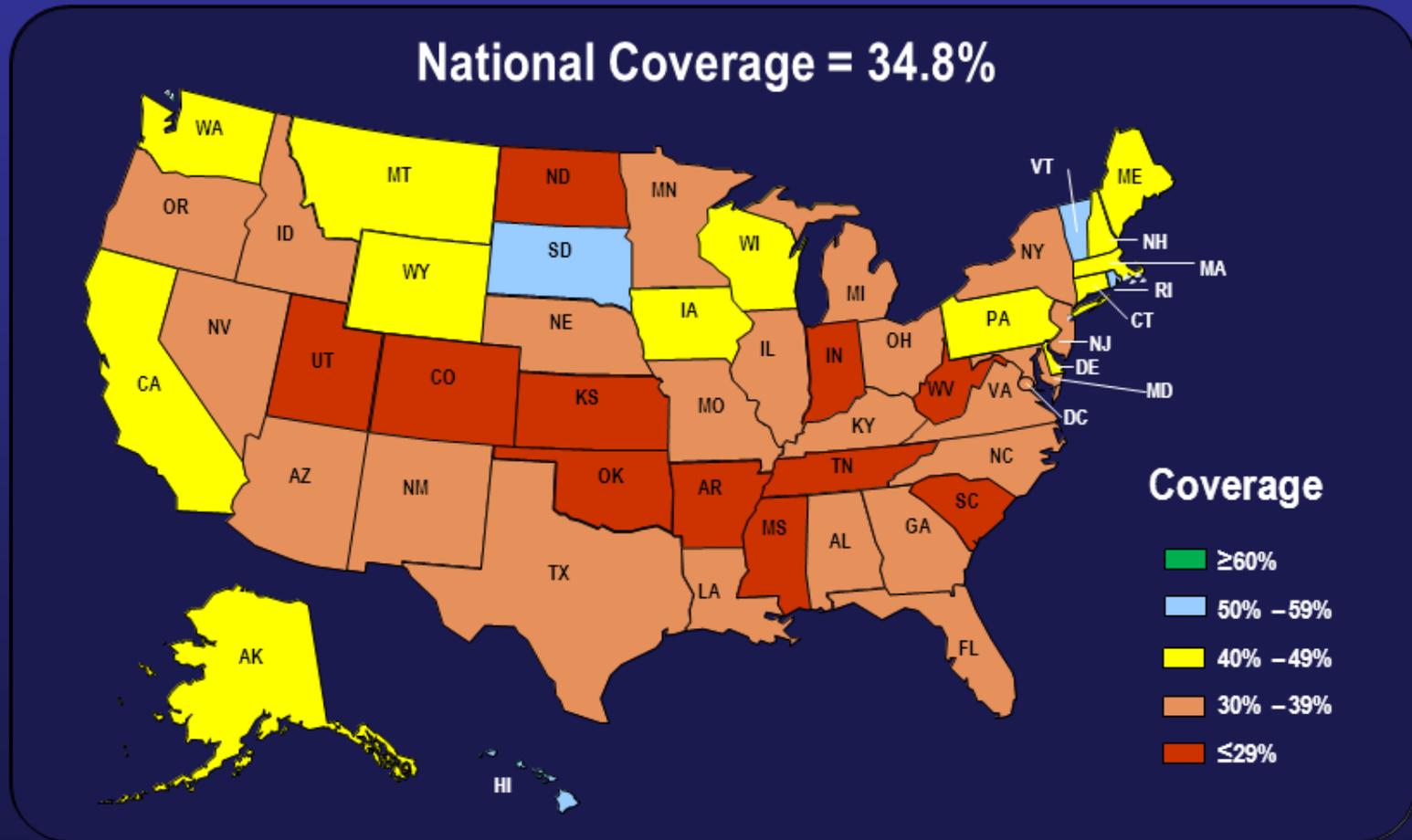
HPV=human papillomavirus; HPV-1=1 or more doses of HPV vaccine; HPV-3=3 doses of HPV vaccine; MenACWY=meningococcal conjugate vaccine (1 or more dose); Tdap=tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (1 or more doses).

1. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep.* 2008;57(40):1100-1103.

2. CDC. *MMWR Morb Mortal Wkly Rep.* 2009;58(36):997-1001.

3. CDC. *MMWR Morb Mortal Wkly Rep.* 2012;61(34):671-677.

Estimated US HPV Vaccine Coverage for Females Aged 13-17 (3 doses), 2011



HPV=human papillomavirus.

1. Centers for Disease Control and Prevention (CDC). *MMWR*. 2012;61(34):671-677.

Potential Strategies to Help Improve Vaccination Rates

Strategies to Improve Vaccination Rates

- Provide clear recommendations
 - Consider appropriate opportunities to vaccinate
 - Pre-school or camp physicals
 - Make use of reminder systems to help ensure series completion
 - Vaccinate in early adolescence when patients are still having regular office visits
-

Make a Strong Recommendation

- Help parents and guardians and young adults make informed decisions about being vaccinated
 - Discuss the safety profile of the vaccine
 - Relay guidance of the ACIP and other societies
 - Understand the strength of your personal recommendation
-

Make a Strong Recommendation

Evidence shows that:

A health care provider recommendation to get vaccinated, is the single most influential factor in determining whether a parent gets an immunization for their child!

Messaging

- Educate women when they are being screened, about the role of HPV infection in cervical cancer
 - You need an HPV test to determine if you have the virus
 - Your son or daughter may be vaccinated to be protected from being infected by the types in the vaccine
-

Utilize Written Materials



30 or Older?
Let's Talk about HPV Testing

You Have HPV, but Your Pap Test is Normal: What Your Results Mean

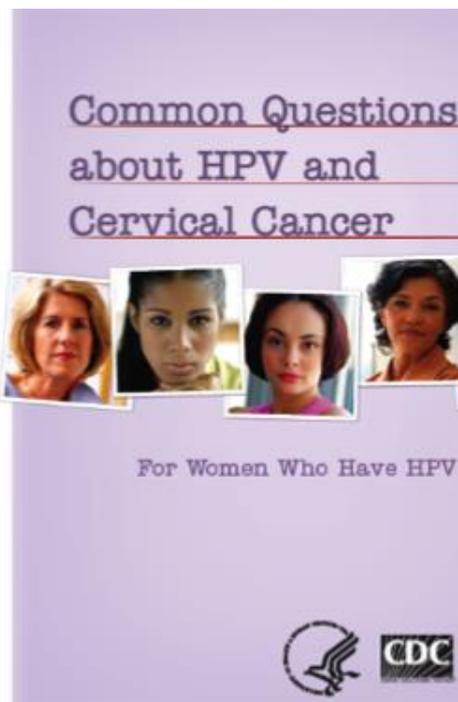
You have just learned that you have HPV. You may feel confused and scared. But once you have all the facts, you'll learn that having HPV is very common. And it's nothing to be afraid of.

First, a few facts:

- HPV – or human papillomavirus – is very common, almost like a cold. ("Papilloma" is pronounced "pap-ah-LO-mah.") In fact, about 8 out of 10 women will have had HPV by the time they're 50.
- The virus is spread through sexual contact. You can get HPV from being intimate with just one partner.

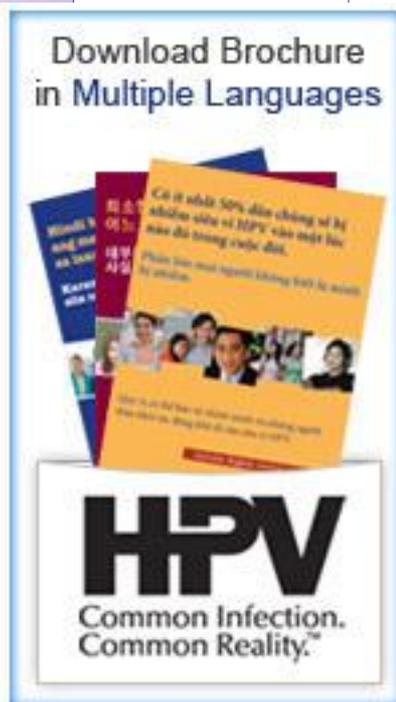
The good news:

- While HPV is common, cervical cancer is not. Most HPV infections go away on their own without causing any problems. It's only when an infection lasts for several years that it can cause abnormal cells to form in the cervix – the kind that can become cervical cancer.



Common Questions about HPV and Cervical Cancer

For Women Who Have HPV



Download Brochure in Multiple Languages



HPV
Common Infection.
Common Reality.™

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

What's to Know, What's New and What's Changed

Secondary Prevention

Identifying and treating high-grade
precancerous lesions

Goal of Cervical Cancer Screening

- Prevent morbidity and mortality from cervical cancer by:
 - Identifying and treating high-grade cervical cancer precursors
 - Avoiding unnecessary and potentially hazardous evaluations and treatment
 - Minimizing costs to healthcare system

Current Approach to Cervical Cancer Prevention

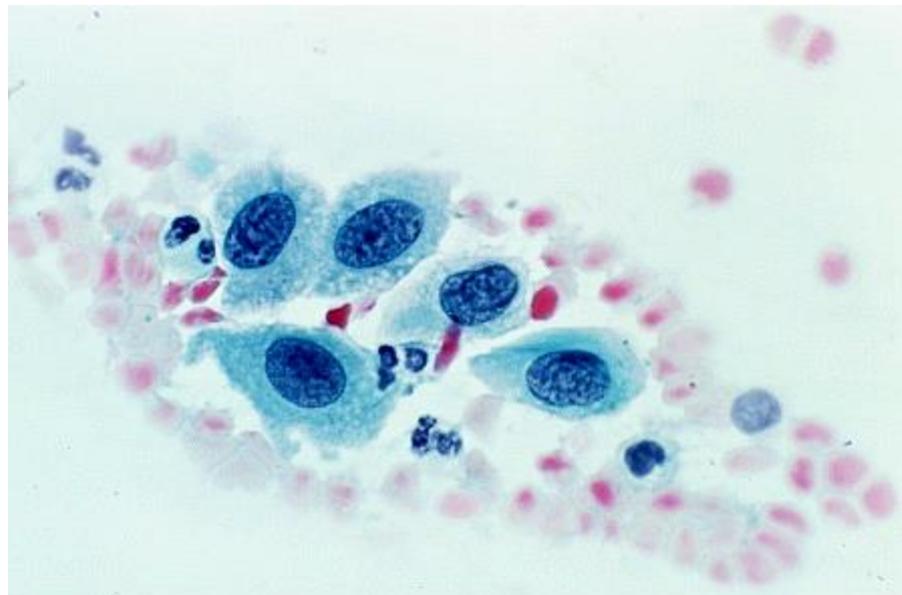
Requires four separate but linked components:

- HPV vaccination
- Screening
 - Cytology with or without HPV testing
- Evaluation of screen-positive women using colposcopy and cervical biopsy
- Treatment of women with biopsy-confirmed high-grade cervical cancer precursors

Cervical Cancer Screening Methods

- Both conventional Pap tests and liquid-based cytology are acceptable
- Similar for identifying high-grade disease
- Most laboratories prefer liquid-based
- Liquid-based cytology facilitates "reflex" HPV testing and can also be used for gonorrhea/chlamydia testing

2012 ACS/ASCCP/ASCP Cervical Cancer Screening Guidelines



Saslow, Solomon, Lawson, et al. JLGTD, March 14, 2012 (online)

Saslow, Solomon, Lawson, et al. CA: A Cancer J for Clinicians, March 14, 2012 (online)

Objectives of Screening

- Prevent morbidity and mortality from cervical cancer
- Prevent over zealous management of precursor lesions
 - That most likely will regress or disappear
 - For which the risks of management outweigh the benefits

Being rarely or never screened is the major contributing factor to most cervical cancer deaths today.

Who are the Rarely and Never Screened?

Descriptions

Minorities

Low SES*

Foreign born

- Living in the US < 10 years

No usual source of health care

Where are the data?

US Census

NCHS § Cervical cancer mortality

BRFSS^μ

NHIS**

* Socio-economic status

§ National Center for Health Statistics, CDC

μ Behavioral Risk Factor Surveillance System, CDC

** National Health Interview Survey, CDC

Age to Start Cervical Cancer Screening

Factors to consider

- HPV infections are common in young women
- Cervical cancer is rare in adolescents/young women
- Evaluation of minor cytological abnormalities:
 - Is expensive
 - Causes anxiety
 - Can lead to unnecessary treatments

Guidelines: Age to Start Cervical Cancer Screening

ACS/ASCCP/ASCP, ACOG, USPSTF agree:

- Start at age 21 regardless of age of sexual debut

Guidelines: Age to Stop Cervical Cancer Screening

- ACS, ASCCP, ASCP, and ACOG
 - Can stop screening in women older than age 65 with no history of CIN2 within the past 20 years and with evidence of adequate negative screening*
 - USPSTF
 - Can stop at age 65 if adequate recent screening with normal Pap tests and are not at high risk for cervical cancer
- * *defined as 3 consecutive normal Pap tests or 2 consecutive negative cotests within preceding 10 years, with the most recent test occurring within the past 5 years.*

Guidelines: Cervical Cancer Screening Interval

ACS/ASCCP/ASCP and ACOG

- Pap testing every 3 years for women ages 21-29
- Preferred for women 30 and older:
Cotesting with Pap and HPV test every 5 years
- Acceptable for women 30 and older: Pap testing alone every 3 years

more...

Guidelines: Cervical Cancer Screening Interval (Continued)

- USPSTF
 - Pap testing every 3 years for women ages 21-65
 - For women ages 30-65, may have Pap test plus HPV test every 5 years to extend screening interval

Guidelines: Screening Post-Hysterectomy

ACS/ASCCP/ASCP, ACOG, USPSTF Guidelines

- Recommend against routine screening if hysterectomy performed for benign disease and no history of high-grade precancer or greater

Interval Extension and Well Woman Visit

- Pap is only one part of the annual well woman exam
- “Unteach” women about annual cervical screening
- Individualized: age, prior screening, HPV status
- Pap only part of visit, and not every year
- The annual exam should include
 - Screening, evaluation, counseling, immunizations per age, risk factors

HPV Testing

HPV Detection with FDA-Approved Tests

- Four tests are currently FDA approved and commercially available in the US
- None are approved for primary, stand-alone screening

more...

HPV Detection with FDA-Approved Tests

- Hybrid Capture 2 High-Risk HPV DNA Test
 - Uses pooled mixture of probes for 13 “high-risk” HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, & 68)
 - Does not identify the specific HPV type
 - Also a low-risk HPV test available
 - No rationale for testing for low-risk HPV types
 - Advise lab to test only for high-risk types
 - Avoid labs that routinely test for low- and high-risk types

more...

HPV Detection with FDA-Approved Tests (Continued)

- Cervista HPV HR
 - Uses 14 “high-risk” HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, & 68)
 - Does not identify the HPV type in an individual clinical sample
 - Can use Cervista HPV 16/18, a genotyping assay, for reflex testing of women with positive HPV results to detect presence or absence of 16 and 18

more...

HPV Detection with FDA-Approved Tests (Continued)

- Cobas HPV Test
 - Provides genotyping for HPV types 16 and 18 concurrently with testing for the presence of 12 other “high-risk” HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, & 68)

more...

HPV Detection with FDA-Approved Tests

- APTIMA HPV mRNA assay
 - Detects 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, & 68)
 - Is not HPV type specific
 - Can use APTIMA HPV 16 18/45 for reflex testing of women with positive HPV results to detect presence or absence of 16 and 18 and/or 45
-

HPV Testing for Screening: Stratifies Risk

- Allows for less frequent testing
- Identifies women who need increased surveillance

HPV Testing is ***NOT*** Appropriate:

- To triage women with Pap results other than ASC-US*
- As adjunct to cytology for screening women:
 - < 30 years old
 - Status post total hysterectomy
- As an STI screen
- To determine HPV status before vaccination

*except postmenopausal women with LSIL

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

HPV Result	Cytology	Recommended Management
Negative	Negative	Cotest in 5 years
Negative	ASC-US	Cotest in 3 years
Positive	ASC-US	Colposcopy
Negative	Pap \geq LSIL	Repeat cotesting in 1 year preferred; colposcopy acceptable
Positive	Pap \geq LSIL	Colposcopy
Any	HSIL	Colposcopy or immediate loop electrosurgical excision
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

Massad LS, et al. *J Low Genit Tract Dis.* 2013. Saslow D. *CA Cancer J Clin* 2012.

Management of Repeat Testing After HPV +, Cytology - Results

HPV Result	Cytology	Recommended Management
Negative	Negative	Repeat cotesting in 3 years
Positive	Negative	Perform colposcopy
Any	Pap \geq ASC-US	Perform colposcopy

ACS/ASCCP/ASCP on HPV Testing

“... health care providers can rely on the negative predictive value of the HPV test to assure women who cotest negative that they are at very low risk for CIN3 and cancer for at least 5 years after negative cotesting.”

What's to Know, What's New and What's Changed

Management of Abnormal Cervical
Cancer Screening Results

Why Are There New Guidelines?

AGAIN??????? !!!!!!!!!!!

Rationale for New Guidelines for the Management of Abnormal Cervical Cancer Screening Tests

- New evidence emerged
 - 2012 review of world literature
 - Analysis of a 7 year database from Kaiser Permanente Northern California Medical Care Plan conducted in collaboration with the National Cancer Institute
- Recognition that cervical cancer prevention entails both benefits and potential harms
 - Potential risk cannot be reduced to zero
 - Attempts to achieve zero risk could result in unbalanced harms, including overtreatment

Managing Abnormal Cervical Cancer Precursors

- Most of the 2006 management guidelines remain valid
- Cervical cancer prevention is a process with benefits and harms
- Similar management strategies were prescribed for similar levels of risk

Managing Abnormal Cervical Cancer Precursors

- Guidelines cannot be developed for all situations
- Clinical judgment should always be applied when applying guidelines to individual patients

Potential Harms From Cervical Cancer Screening

- Anxiety from an abnormal test that the patient might fear to be a sign of cancer
- Stigma from diagnosis of a ubiquitous sexually transmitted infection (HPV)
- Time and patient expense related to screening and management
- Pain and injury from the procedures and treatment
- Increased risk of premature delivery and pregnancy loss

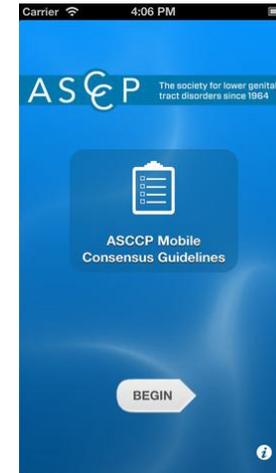
New Guidelines Are Meant to
Increase Benefits and Decrease
Harms!

Complicated?
HELP IS AVAILABLE!

2013 American Society for Colposcopy and Cervical Pathology (ASCCP) Guidelines



www.asccp.org
Download Algorithms



Mobile App: iPhone and Android

What's to Know, What's New and What's Changed

2013 Algorithms: Essential to Know

Introduction to guidelines for some of
the most common cytologic
abnormalities

2013 Algorithms: Essential to Know

Cytology

- Cytology: negative, but lacking endocervical cells can be managed WITHOUT a repeat earlier than when the next cytology is due
 - Cytology: “Unsatisfactory” requires repeat even if HPV if negative
-

2013 Algorithms: Essential to Know

- Reflex genotyping or immediate genotyping when available, is used in the triage of the Pap/negative, HPV/positive woman
 - Genotype positive for HPV 16 or 18 leads to immediate colposcopy
 - Genotype HPV 16/18 negative leads to repeat co-testing in 12 months
-

Management of Young Women

- Annual incidence of cervical cancer in US women ages 21 to 24 = 1.4/100,000
- Almost 55,000 cytology tests run for every cervical cancer diagnosis in this age group
- Justifies need for screening, but suggests observation for minor abnormalities

If an adolescent is screened inappropriately and has an abnormal Pap test, refer to guidelines for women ages 21 to 24.

2013 Algorithms: Essential to Know

- 21 to 24 years old women have a separate algorithm for abnormal results
 - Similar management for similar risk strategies
 - ASC-US, LSIL: no longer go straight to colposcopy
 - Pap follow-up in 12 months, even if there is a triage to HPV and it is positive!
-

2013 Algorithms: Essential to Know

ASC-US Cytology

- Age 25 to 65
 - ASC-US/HPV negative: co-testing at 3 years (routine follow-up after Pap and HPV negative is 5 years)
-

Management of Postmenopausal/Aged 65 and older Women with ASC-US

- Postmenopausal women should be managed in the same manner as women in the general population
- For women 65 and older exiting from screening, HPV-negative/ASC-US results should be considered abnormal. Additional surveillance with cotesting in 12 months is recommended.

LSIL or ASC-US with HPV: Risk of High-Grade Neoplasia

- The ASCUS LSIL Triage Study (ALTS) showed that women with LSIL and women with ASC-US who are high-risk HPV DNA positive have an identical risk of high-grade neoplasia
- ASCCP management guidelines are similar except in special circumstances

2013 Algorithms: Essential to Know

- Co-testing women 30 and older with cytology and HPV as screening, will identify some with HPV/ negative LSIL
- Risk of CIN3+ in HPV negative women with LSIL is low and similar to that of ASC-US without HPV status known

2013 Algorithms: Essential to Know

- Cotesting women 30 and older means that HPV status will be known in many women with an LSIL Pap, *even though HPV testing is NOT recommended for the triage of the LSIL Pap*
- This means that a group of women with LSIL will have their HPV status known, creating multiple management strategies
 - LSIL/Negative HPV: Repeat Cotesting @ 1 year
 - LSIL/ No HPV Test: Colposcopy
 - LSIL/HPV Positive: Colposcopy

What's to Know, What's New and What's Changed

Lower Anogenital Squamous
Terminology Standardization (LAST)

Lower Anogenital Squamous Terminology Standardization (LAST)

In June 2012, a new reporting system was published to standardize reporting for all HPV-associated preinvasive squamous lesions of the lower anogenital tract (LAT).

Goals of new system:

- Align terminology with current understanding of the similar biology and morphology of these lesions
- Improve communication between pathologists making diagnoses and clinicians using these diagnoses
- Create optimal, consistent, and more effective management of patients

more...

LAST (Continued)

- Change from 3-tier cervical intraepithelial neoplasia (CIN) to 2-tier system of reporting pathology of squamous lesions
 - LSIL
 - HSIL
- Integrating the LAST recommendations into the standard practice of pathologists and clinicians is an ongoing task
- More reliable and reproducible results will ultimately lead to improved patient outcomes

What's to Know, What's New and What's Changed

HPV Counseling

Counseling Women Age 30 or Older with HPV and a Negative Pap

- Diligent follow-up is important
- Follow-up options:
 - Return in 12 months for a Pap and HPV test. If HPV is still present, colposcopy will be recommended.

OR

- Test immediately for HPV 16/18, the two most serious types of HPV. If this test is positive, immediate colposcopy will be recommended.

Counseling Women with HPV

Remind your patient that:

- 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.

more...

Counseling Women with HPV

(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.
-

HPV Educational Messages

- HPV is sexually transmitted.
 - HPV is very common.
 - Most women with HPV will not get cervical cancer.
 - HPV infection usually clears without treatment.
 - HPV tests are used to detect the virus that can cause cell changes and cervical cancer.
 - Pap tests are used to detect HPV-related pre-cancers.
- more...*

HPV Educational Messages (Continued)

- Many women who initially test positive for high-risk HPV will not have pre-cancer on further evaluation or be diagnosed with cancer.
- 30% of cervical cancers caused by HPV types are not covered by vaccine.
- Women will continue to need cervical cancer screening even if vaccinated.

Summary

The 2012 Guidelines for cervical cancer prevention

- More benefit with least harm (over screening)
- Identifies low risk women (HPV and Pap negative) and reassures them about safety of longer screening interval
- Identifies truly at-risk women *with persistent HPV ...*
Follow them diligently
- Majority of cervical cancer in U.S. occurs in women who have not been screened or infrequently screened

Improving access to screening for these women will have a great impact on the prevention of cervical cancer!

References

1. Saslow, D. et al. 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. *CA: A Cancer Journal for Clinicians* 2012; 62: 147–172
2. U.S. Preventive Services Task Force. Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2012;156:880-891
3. Castle PE et al. Five-year experience of human papillomavirus DNA and Papanicolaou test co-testing. *Obstet Gynecol* 2009; 113:595-600
4. Rodriguez AC et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *J Natl Cancer Inst* 2008; 100:513-517
5. ACOG Committee Opinion No. 463. Cervical cancer in adolescents: screening, evaluation, and management. *Obstet Gynecol* 2010; 116, 469-472

THANK YOU!

QUESTIONS?
