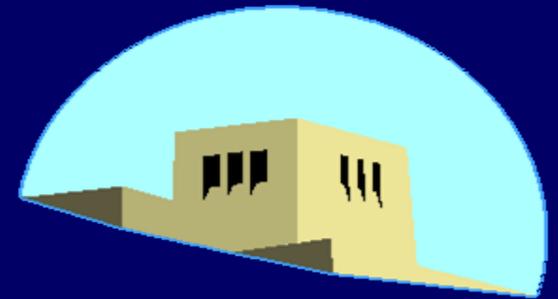


# New Cervical Screening Guidelines – Again!!!

*ACS/ASCCP/ASCP and USPSTF  
Guidelines 2012*

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I have no commercial relationships related to this talk.



**The University of New Mexico**

# Objectives

- Review how recommendations for cervical cancer screening have evolved over the past 50 years.
- Summarize the 2012 USPSTF and ACS/ASCCP/ASCP guidelines for cervical cancer screening.
- Discuss the evidence for co-testing in cervical cancer screening.

Cervical  
screening:  
It's not black  
and white!

# *Pap Wars*

- 1928** Papanicolaou finds malignant cells in vaginal smear
- 1941** Papanicolaou & Traut publish utility of vaginal cytology
- 1957** American Cancer society: “Uterine Cancer Year”
  - *Promotes annual Pap smear*
- 1976** Walton Report in Canada recommends Pap every 3 yrs

# *Pap Wars*

**1980** American Cancer Society recommends Pap every 3 years in women with two negative annual Paps.

- ACOG continues to recommend annual Paps

**1988** ACS and ACOG reach consensus

- Start screening at age 18 or with onset of sexual activity. After 3 or more consecutive satisfactory, negative annual Paps the interval may be extended at the discretion of the provider.

**1995** ACOG: annual Paps in women with risk factors

# *Pap Wars*

## 2002-2003

### ACOG and ACS largely agree

- Start ~ 3 yrs after onset of intercourse or age 21, annually until age 30 (ACOG) / biennially if liquid Pap (ACS), q 2-3 years from age 30 until end of screening (age 70 ACS, not specified by ACOG)
- Co-testing with cytology and HPV “appropriate”

### USPSTF

- Start ~ 3 yrs after onset of intercourse or age 21, then q 3 yrs until age 65 in well screened low risk women. Insufficient evidence to recommend co-testing

# *Pap Wars*

## 2009 ACOG Recommendations revised

- Start screening at age 21
- Liquid or conventional cytology every 2 years until age 29, then every 3 years
- Co-testing an appropriate alternative, if negative repeat no sooner than every 3 years
- OK to discontinue screening at age 65-70

# *Pap Wars*

## November 2011

- USPSTF posts draft of new guidelines
- ASC / ASCCP / ASCP Symposium on “The Role of Molecular Testing” Nov 18-20
  - to inform the American Cancer Society in development of new guidelines.

## March 15, 2012

- Coordinated release of USPSTF and ACS/ASCCP/ASCP

# Evidence Based Practice Guidelines

Where do they come from?

# U.S. Preventive Services Task Force

- Mandated by congress
- Since 1988 under the Agency for Health Research and Quality (AHRQ) U.S. DHHS
- Independent panel of private-sector experts in prevention and primary care.
  - Defines questions and makes final recommendations
  - Contracts with one of 14 Evidence Based Practice Centers for the initial review of literature and grading of evidence.

# American Cancer Society 2012 Guidelines

- ACS/ASCCP/ASCP Consensus Conference on the Role of Molecular Testing
  - Nov. 18-20, 2011 Bethesda, MD
- 25 participating professional organizations
- 40 content experts from various disciplines divided into 6 workgroups with clearly defined questions.
- Systematic Review: 2,000 abstracts reviewed
  - 600 publications considered, sorted and sent to workgroups for further Inclusion/Exclusion review
  - Workgroups addressed questions using GRADE system of evaluation of evidence

Case 1: A 19 year old G0, sexually active for 5 years. She's had five sexual partners. She presents for contraceptive counseling.

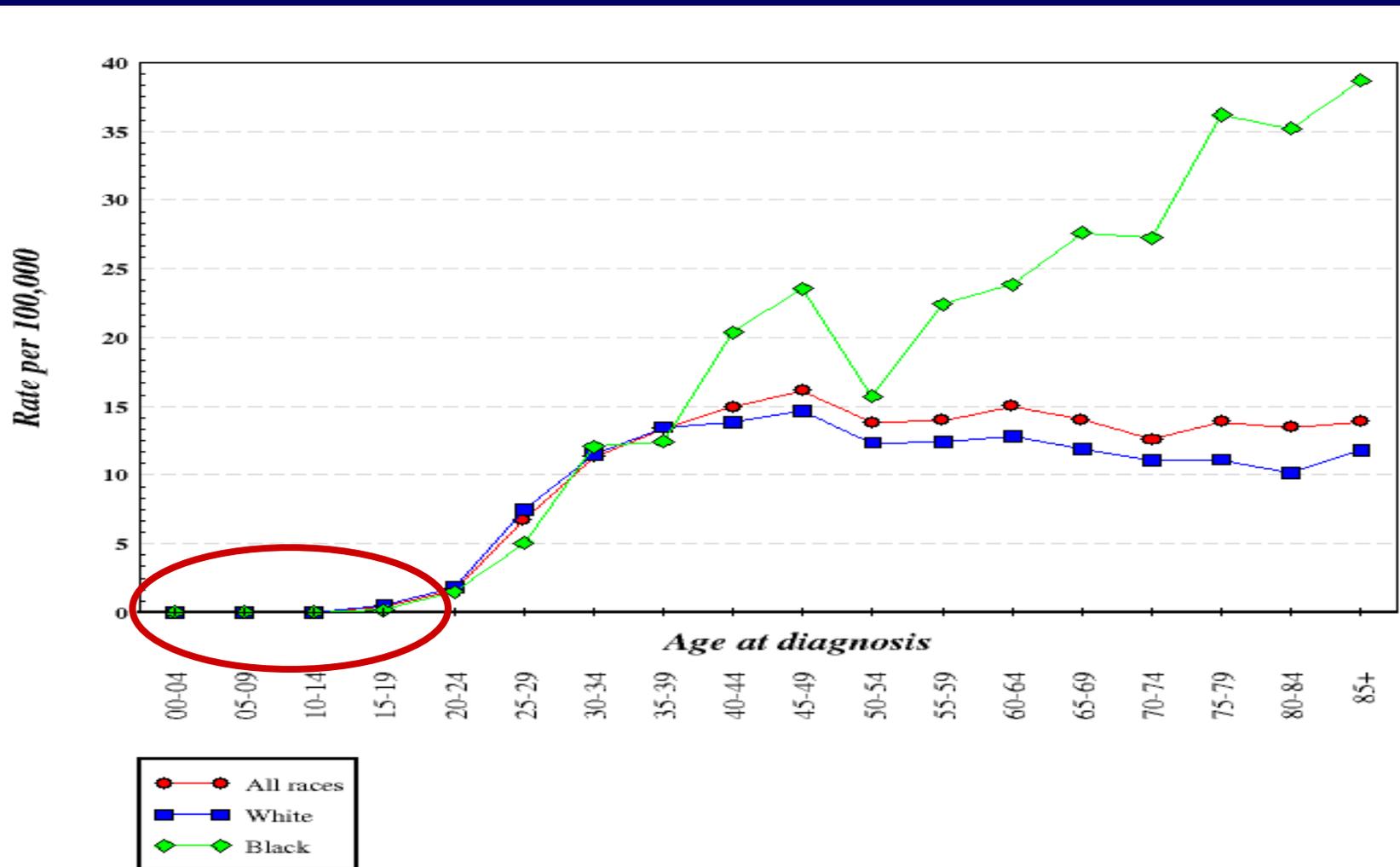
How will you assess her this visit?

- A. Pap test / GC, Chlamydia with Pap / Pelvic exam
- B. Pap test / Pelvic exam / Urine for GC, Chlamydia
- C. No Pap test / Pelvic exam / Urine for GC, Chlamydia
- D. No Pap / No pelvic exam / Urine for GC, Chlamydia

ACS / ASCCP / ASCP 2012 Recommendations:  
Cervical cancer screening should begin at age 21 years. Women under the age of 21 should not be screened regardless of the age of sexual initiation or other risk factors.

USPSTF 2012 Recommendation:  
Do not screen women younger than age 21.  
Screening before age 21 leads to more harms than benefits regardless of sexual history. Grade D

# Invasive Cervical Cancer is Exceedingly Rare in Adolescents



# Invasive Cervical Cancer in Adolescents (Age <21)

- 0.1% of cervical cancers in U.S.
- Rate ~1/ 1,000,000 adolescents
- Ave 14 cases per year in 15-19 year olds.
  - Too rare to report under age 15
  - Rate unchanged between 1973-77 and 1998-2006
    - Recommendation to start screening at age 18 or with onset of intercourse made in 1980s

Case 2: A young woman comes to clinic on her 21<sup>st</sup> birthday.

You should

- A. Bake her a cake
- B. Buy her a drink
- C. Do her Pap test
- D. Do an HPV test

Case 2 continued: Her Pap is negative.  
What do you recommend for her next  
screening

- A. Pap in one year
- B. Pap in three years
- C. Co-testing with Pap and HPV test  
in 3 years
- D. Co-testing with Pap and HPV test  
in 5 years.

## ACS/ ASCCP/ ASCP:

Begin screening for all women at age 21. From age 21– 29 cytology every 3 years.

## USPSTF:

Screen women age 21 – 65 with cytology every 3 years.

But shouldn't women get a Pap  
test every year???

**A PAP TEST FOR EVERY WOMAN EVERY YEAR!**  
-American Cancer Society 1957

# The “annual” Pap test is dead!

~~A PAPER TEST FOR EVERY WOMAN AN EVERY YEAR!  
-American Cancer Society 19~~



# How much protection do we lose by not doing Pap tests every year?

- Percentage reduction in rate of invasive cervical cancer in cohort of women aged 35 - 64 with different frequencies of screening
  - Assumes at least negative Pap prior to age 35
  - Next Pap 1 yr: 93.5%
    - 30 Paps required over 30 years
  - Next Pap 2 yrs: 92.5%
    - 15 Paps required over 30 years
  - Next Pap 3 yrs: 90.8%
    - 10 Paps required over 30 years
  - Next Pap 5 yrs: 83.6%
    - 8 Paps required over 30 years

# What are the harms of abandoning annual screening?

- Markov model based on NBCCEDP data
- Assumed  $\geq 3$  prior consecutive negative Paps
- Cancers prevented by doing Pap annually instead of every 3 years
  - Age 30 – 44: 3 / 100,000 women
  - Age 45 – 59: 1 / 100,000 women
- Additional tests needed to find each incremental cancer
  - Age 30 – 44: 69,665 Paps plus 3,861 colpos
  - Age 45-59: 209,324 Paps plus 11,502 colpos

What about Pap plus  
HPV: “Co-testing” for  
this 21 y.o.?

Co-testing is not recommended for  
women under age 30!

- Not FDA approved.
- Unacceptably high false positive rate in younger women.

# Prevalence of HPV Infection – U.S. Females

Dunne et.al. JAMA 2007;297:813-819

24% of 14-19 y.o. women were HPV positive

17% high-risk HPV positive

Among 20-25 y.o. women, 45% HPV positive

27% high risk HPV positive

Rates declined with age after age 25

Case 3: A 30 year old G2 patient presents for her routine Gyn exam. Her pap test at age 27 was negative. She's never had an abnormal pap.

What will you do in terms of cervical screening this visit?

A. No screening for cervical cancer

B. A pap test liquid or conventional

C. Co-testing with cytology & HPV DNA

D. HPV 16/18 genotyping

## ACS/ ASCCP/ ASCP:

From age 30 – 65, co-testing every 5 years is recommended. If HPV testing not available, continue with cytology alone every 3 years.

## USPSTF:

Screen women age 21 – 65 with cytology every 3 years. For women age 30 – 65 co-testing with cytology and HPV DNA every 5 years is a reasonable alternative for those women wishing to extend the screening interval.

# Why add HPV to the Pap test?

- Compared with Cytology
  - HPV testing is more sensitive
    - Including for AIS
  - Less specific
  - Higher negative predictive value
- Screening with Combined cytology plus HPV
  - Combination is most sensitive
  - Least specific
  - Highest negative predictive value

# Benefits of Co-testing: Studies from U.S. and Europe

- Co-testing leads to earlier diagnosis of CIN 3+ and Cancer
- Incorporating HPV finds more AIS than cytology alone
- Negative cytology plus negative HPV allows spacing screening beyond every three years.

# Follow-up of 5 yrs of Co-testing Kaiser N Cal.

More CIN 3+ diagnosed by HPV than Pap within 2 years – almost doubled by 5 years.

5 yr cumulative CIN 3+ in >300,000 women

Katki, Kinney, et al Lancet oncol.2011;12:663072

# Screening with HPV more effectively prevented Cancer than cytology alone: Italian NTCC Trial

- 94,000 women aged 25-60
- Two screening rounds 3.5 yrs apart - co-test or cytology first round, cytology alone second round

- First round of screening – Cancers detected:
  - Co-testing 7            Cytology alone 9     $p=0.62$
- Second round – Cancers detected:
  - Co-testing 0            Cytology alone 9     $p=0.004$

- Cancers diagnosed In Round 2
  - Disproportionate number adenocarcinoma (44%)
  - 5 squamous cell carcinoma / 4 adenocarcinomas
  - All had negative cytology in round one

# Screening with HPV prevented CIN 2+ in the second round of screening- Italian NTCC Trial

- More CIN 2+ detected in group screened with co-testing or HPV alone compared with cytology alone
- Significantly fewer CIN 2+ found by round 2
  - Fewer CIN 3 /AIS but not statistically significant

	<b>Co-Testing/HPV</b>	<b>Cytology</b>	<b>Rel. Detection</b>
<b>Round 1</b>			
CIN 2, 3, AIS	206 (0.60%)	101 (0.29%)	2.03 (1.60, 2.57)
<b>Round 2</b>			
CIN 2, 3, AIS	16 (0.05%)	32 (0.09%)	0.51 (0.28, 0.93)
<b>Both Rounds</b>			
CIN 2, 3, AIS	221 (0.64)	133 (0.039%)	1.66 (1.34, 2.06)

# Cancer reduction also found in Dutch Study POBASCAM

- 44,938 women randomized to co-testing or cytology
  - Two screening rounds 4-6 years apart
  - Follow-up at 6 months and 18 months.
  - Colposcopy limited to:
    - HSIL+ on initial cytology
    - ASC LSIL X 2: initially and at 6 month follow-up
    - Colposcopy for persistent HPV + over 18 months

## Diagnosis of Cancer in POBASCAM Study

	Co-testing	Cytology	p value
First round	12 (0.06%)	6 (0.03%)	0.166
2 <sup>nd</sup> round	4 (0.02%)	14 (0.07%)	0.031

# Trend toward reduction of pre-cancer in POBASCAM Significant in CIN3+

## Diagnosis of CIN 2+ - 3+ in POBASCAM Study

<b>Baseline screen</b>	<b>Co-testing</b>	<b>Cytology</b>	<b>P Value</b>
CIN 2+	267 (1.34%)	215 (1.07%)	0.015
CIN 3	159 (0.80%)	144 (0.72%)	0.387
CIN 3+	171 (0.86%)	150 (0.75%)	0.239
<b>Second round</b>	<b>Co-testing</b>	<b>Cytology</b>	<b>P Value</b>
CIN 2+	160 (0.82%)	184 (0.93%)	0.234
CIN 3	84 (0.43%)	108 (0.55%)	0.096
CIN 3+	88 (0.45%)	122 (0.62%)	0.023

# Positive HPV diagnoses more AIS and Adenocarcinoma than Cytology alone

331,818 women enrolled in Kaiser N. Cal

Significantly more AIS and Adenoca diagnosed over 5 yrs if initial screen:

- HPV + vs Pap + (p<0.0001)
- HPV + / Pap – vs HPV -- / Pap + (p<0.0001)

	<b>AIS</b>	<b>Adenocarcinoma</b>
Total	70	27
Pap Negative	42 (60%)	23 (85%)
Pap Positive	28 (40%)	4 (15%)
HPV Positive	56 (80%)	21 (78%)
Pap -- / HPV +	31 (44%)	17 (63%)
Pap + / HPV --	3 (4%)	0

Case 4: Our 30 y.o. is screened with co-testing. Both her Pap and HPV test are negative. When should you screen her again for cervical cancer?

- A. One year
- B. Two years
- C. Three years
- D. Five years

# A single negative HPV test confers more protection from CIN 3+ than a single negative Pap.

- Cohort of 20,810 women followed for up to 122 months
- Risk of CIN 3+ after 45 months

Neg Pap alone	0.53%
Neg HPV DNA	0.24%
Neg Pap + Neg HPV	0.16%

A negative HPV DNA test offers better protection after 6 years than a negative Pap does after 3 years.

- Joint European Cohort Study compared HPV testing with conventional Pap in 6 countries
- N=24,295

<u>Rate of CIN 3+ after baseline negative test</u>				
	<u>3 yrs</u>	<u>4 yrs</u>	<u>5yrs</u>	<u>6yrs</u>
Pap –	0.51%	0.69%	0.83%	0.97%
HPV-	0.12%	0.19%	0.25%	0.27%

# NB: All HPV Tests are Not Alike

- Only *FDA approved* and *clinically validated* tests should be used in cervical screening
  - Performance characteristics of FDA approved tests established against clinical endpoints of CIN 2+ and 3+ in large RCTs
- Avoid laboratory developed tests
  - Exempt from FDA oversight
  - Rarely evaluated against defined clinical endpoints

# NB: All HPV Tests are Not Alike

- On March 31, 2003 the FDA approved the Hybrid Capture 2 test (HC2) for triage of ASC-US cytology and for co-testing with cytology in women aged 30 and over.
- Subsequently, two additional products Cervista HPV and Cobas 4800 have been approved based on comparability with HC 2 at a threshold of 1 pg / ml.

Case 5: A 45 y.o. G2P2 is screened with co-testing. You have no records of her last screening. This time the Pap is negative, but the HPV is positive.

How would you manage her?

- A. Repeat Pap and HPV in 1 year
- B. Repeat Pap and HPV in 3 years
- C. Check an HPV 16/18 assay
- D. Colposcopy

# How often is the HPV test positive when the Pap is negative?

- 9 studies in literature
  - Prevalence ranges from 3.4% to 8.2%

Identifying “evidence-based” management of discordant co-testing (cytology negative / HPV +) was a concern at the ACS/ASCCP/ASCP Consensus Conference.

- Studies limited
- No RCTs that directly mirror U.S. Practice
- There is enough data to make moderate to strong recommendations.

# Women screening cytology neg / HPV + should not go to immediate colposcopy

- Immediate colposcopy could double the numbers of colposcopy currently done
  - Cytology -/HPV + 3.7%
  - Cytology LSIL + 3.8%

Katki et. al. Lancet Oncol 2011

- Risk of CIN 3+ in women testing Cytology neg / HPV + remains low within 12 months
  - Range 0.8% to 4.1%
  - Below accepted clinical threshold for colposcopy (10% risk of CIN 3+)

Kahn JNCI 2005, Wright Am J Clin Pathol 2011



5 yr cumulative risk of CIN 3+ in >300,000 women screened with Pap plus HPV cotesting in a prepaid healthcare system.

3.1% of women testing Pap negative / HPV positive at baseline had CIN 3+ by 3 years.

Women who screen cytology - / HPV+ may be triaged with repeat co-testing after 12 months.

If HPV is still positive OR cytology is now abnormal : HPV+/ASC-US or LSIL or higher grade → refer to colposcopy.

# Management with Repeat Co-Testing

Recommendation based largely on experience and modeling data. No good direct clinical trials

- ASCCP Guidelines (2006) recommend repeat co-testing in 12 months
  - Colposcopy if  $\geq$ LSIL or persistent HPV +
  - Not subject to clinical trials
  - Used in Northern California Kaiser study (Katki 2011) and with modification in POBASCAM (Rijkaart 2012)
- Modeling suggests 17% fewer colposcopy referrals and improved cancer prevention with co-testing at 5 yr. intervals
  - Compared with triennial cytology screening
    - Kulasingam 2011

If HPV reverts to negative with normal or ASC-US cytology at 12-month testing → return to routine screening.

A second management option is acceptable:

Women who screen cytology - / HPV+ may be tested with HPV 16 or 16/18 genotyping.

- If positive for HPV 16 or 16/18 →  
refer to immediate colposcopy.

- If negative for HPV 16 or 16/18 →  
repeat co-testing in 12 months

•Cytology negative / HPV 16 or 16/18 positive:  
Risk of CIN 3+ reaches threshold for colposcopy  
comparable to ASCCP Guidelines

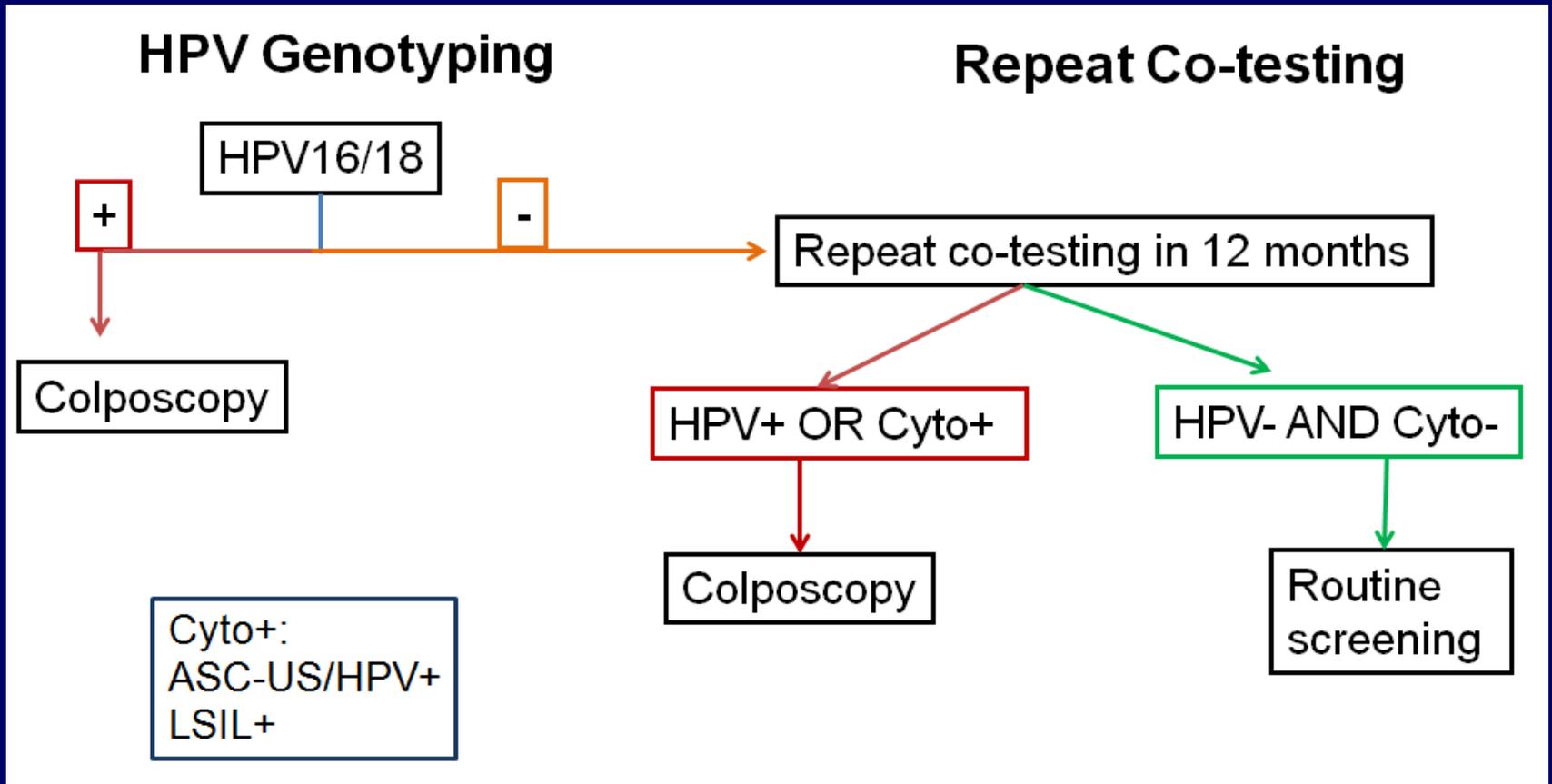
**Cytology neg / HPV 16+**

- 11.7% CIN 3+
  - By 12 wks f/u
    - Wright 2011
- 10% CIN 3+
  - By 12 months f/u
    - Kahn JNCI 2005

**Cytology neg / HPV 18+ or  
16/18+**

- 9.8% CIN 3+ if 16/18+
  - By 12 wks
    - Wright 2011
- 12% CIN 3+ if HPV 18+
  - By 39 months
    - Kahn JNCI 2005

# Recommended Testing Algorithm



Case 6: A 65 year old has a negative Pap and negative HPV. She has never had CIN 2 or worse. Her last two co-tests were negative 5 and 10 years ago. When should she have her next screening for cervical cancer?

A. Never

B. In five years

C. In ten years

D. Never unless she has a new sexual partner.

## ACS/ASCCP/ASCP:

Women with evidence of adequate negative prior screening and no history of CIN 2+ within the past 20 yrs should not be screened. Screening should not be resumed for any reason, even if a woman reports a new sexual partner

## USPSTF:

Recommends against screening in women older than age 65 who have had *adequate* prior screening and are not otherwise at high risk for cancer.

*ACS/ASCCP/ASCP Footnote:*

*Adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative co-tests within the last 10 years before ceasing screening, with the most recent test performed within the past 5 years.*

# Natural History of HPV Disease Not Affected by Age of Infection

- New HPV infection in women aged 55 and older has same risk and rate of progression as in young women
  - Median time course from infection to cancer 15-25 years
    - Age 75-90 for 60 y.o. with new infection
      - » Chen 2011
- Modeling studies: Continued screening Q 3 yrs after age 65 in a woman with previous q 3 yr Paps would prevent 1.6 cancers and 0.5 cancer deaths per 100,000 women by age 90. (Kulasingam 2011)

# Risks of Overscreening in Post-menopausal Women

- 2561 post-menopausal women 1-2 years after negative Pap
- 110 required diagnostic work-ups for abnormal Paps
  - 231 interventions
  - 1 mild-moderate dysplasia

# Some Final Miscelany...

- Both organizations recommend against screening in women who have had a hysterectomy with removal of the cervix provided they have not had CIN 2 or worse
- Following spontaneous regression or treatment of CIN 2+, routine screening should continue for at least 20 years.
  - Even if this extends screening beyond age 65.

# Some Final Miscelany...

- Women immunized with an HPV vaccine should be screened using the same guidelines as the non-immunized population.

Guidelines:

ASCCP.org

<http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm>

<http://journals.lww.com/jlgttd/PublishingImages/ASCCP%20Guidelines.pdf>