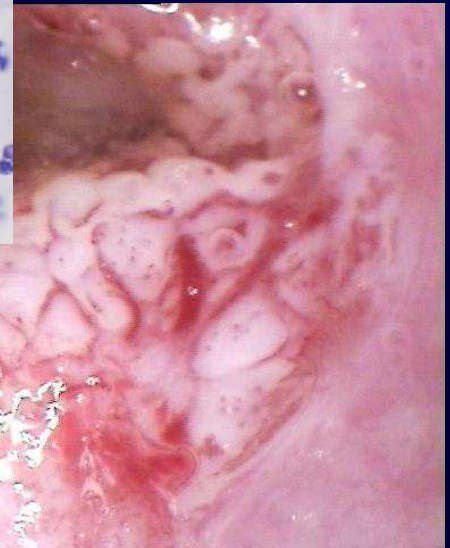
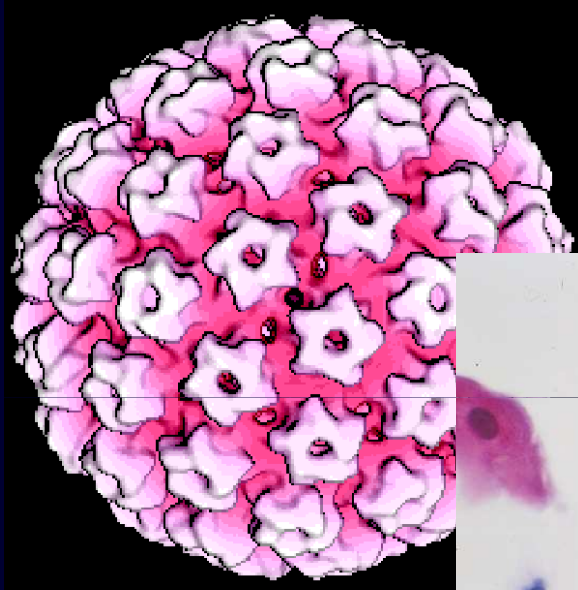
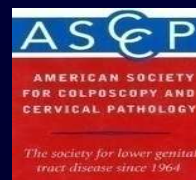


# Cervical Cancer Screening Recommendations, 2012



The American Society for Colposcopy  
and Cervical Pathology

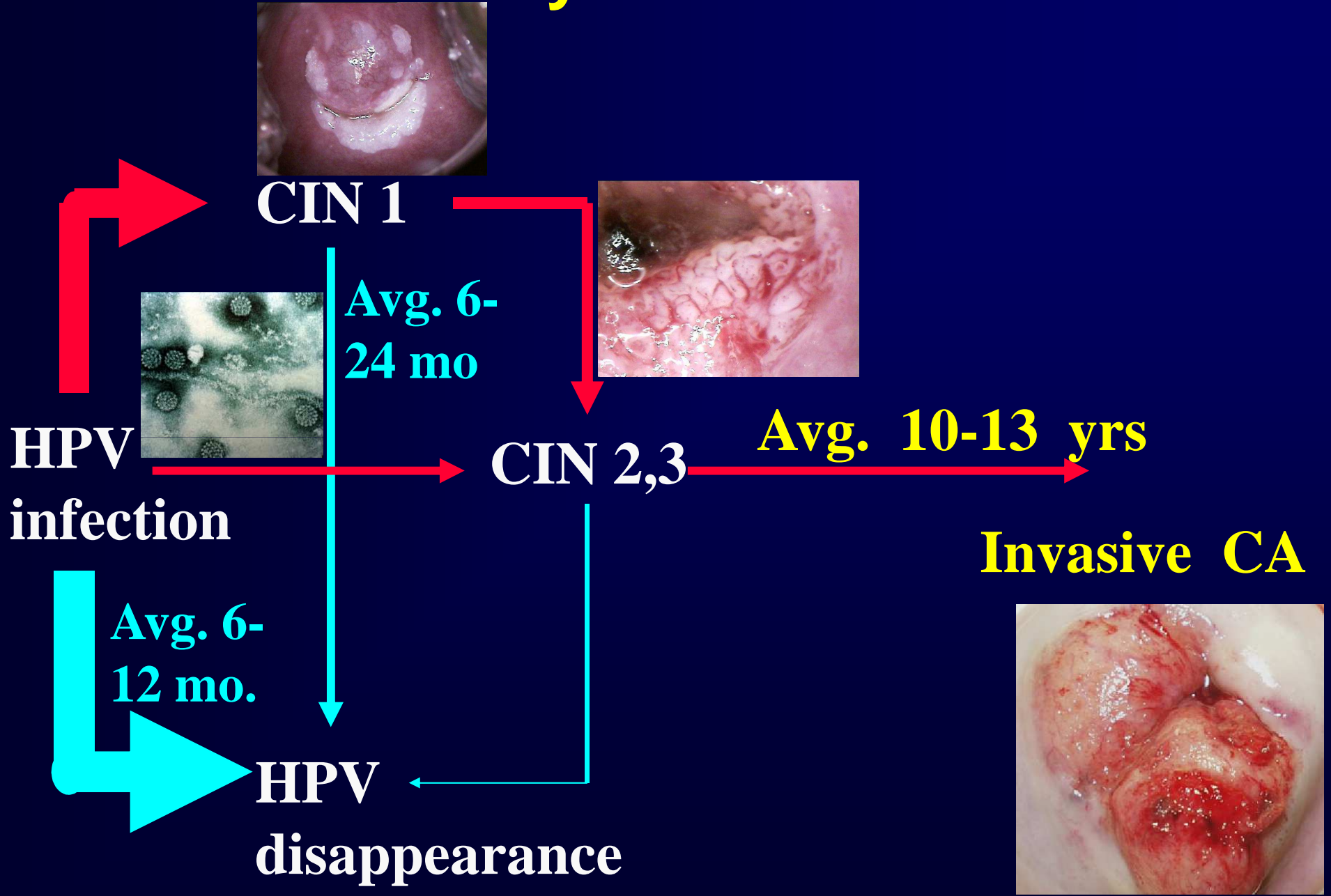


# Objectives of Screening

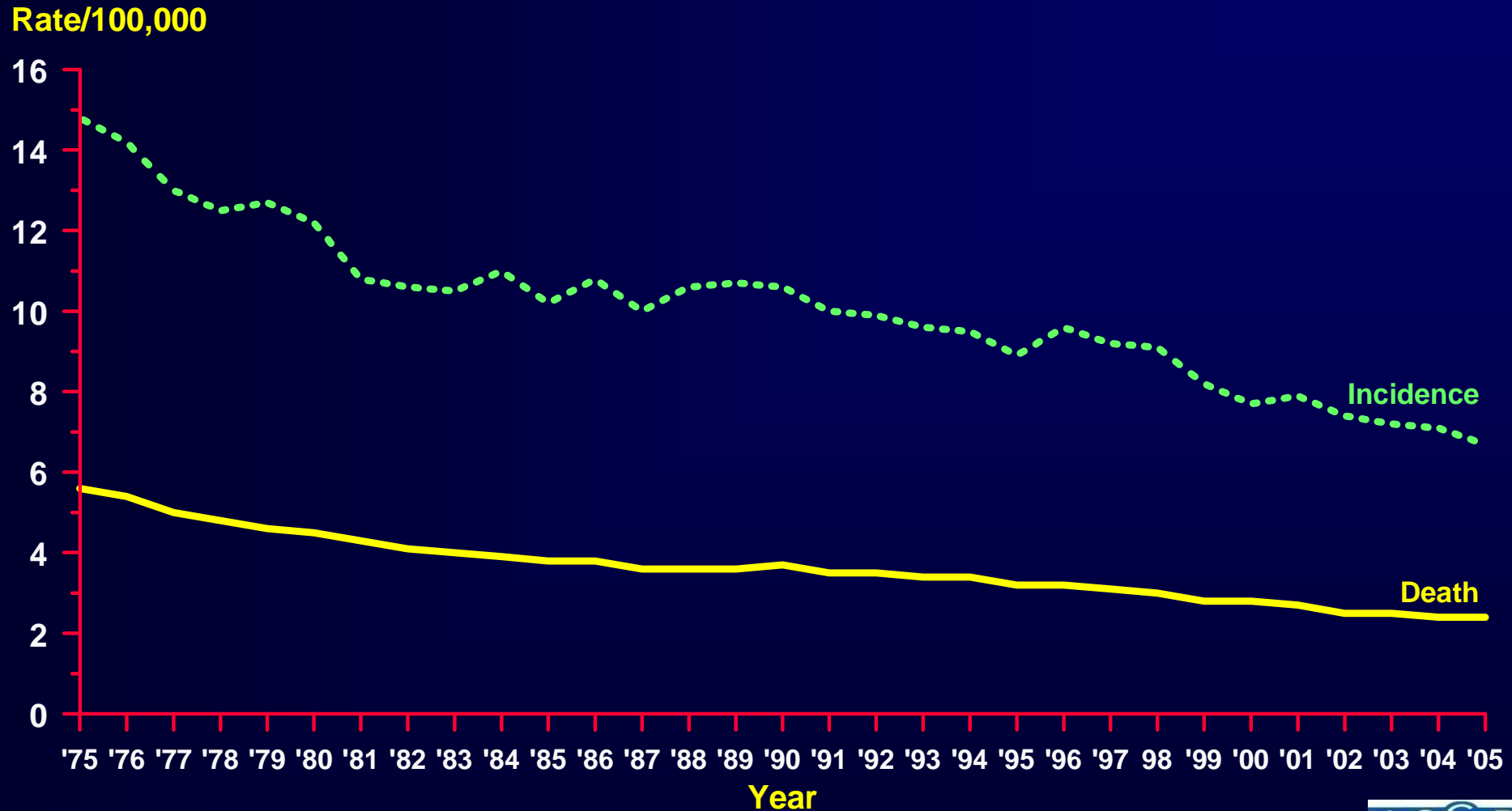
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- Prevent morbidity and mortality from cervical cancer
- Prevent overzealous management of precursor lesions that most likely will regress or disappear and for which the risks of management outweigh the benefits

# Natural History of Cervical Cancer

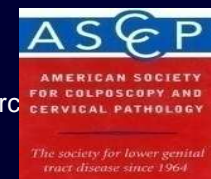


# Cervical Cancer Incidence (SEER) and U.S. Death Rates,\* 1975-2005

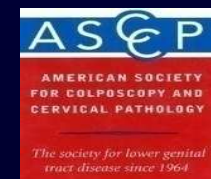


Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Mortality source: US Mortality Files, National Center for Health Statistics, CDC.

\*Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).



**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?

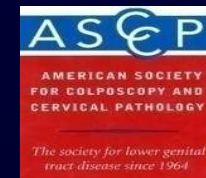
- US Census
- NCHS§ Cervical cancer mortality
- BRFSS<sup>μ</sup>
- NHIS\*\*

\* Socio-economic status

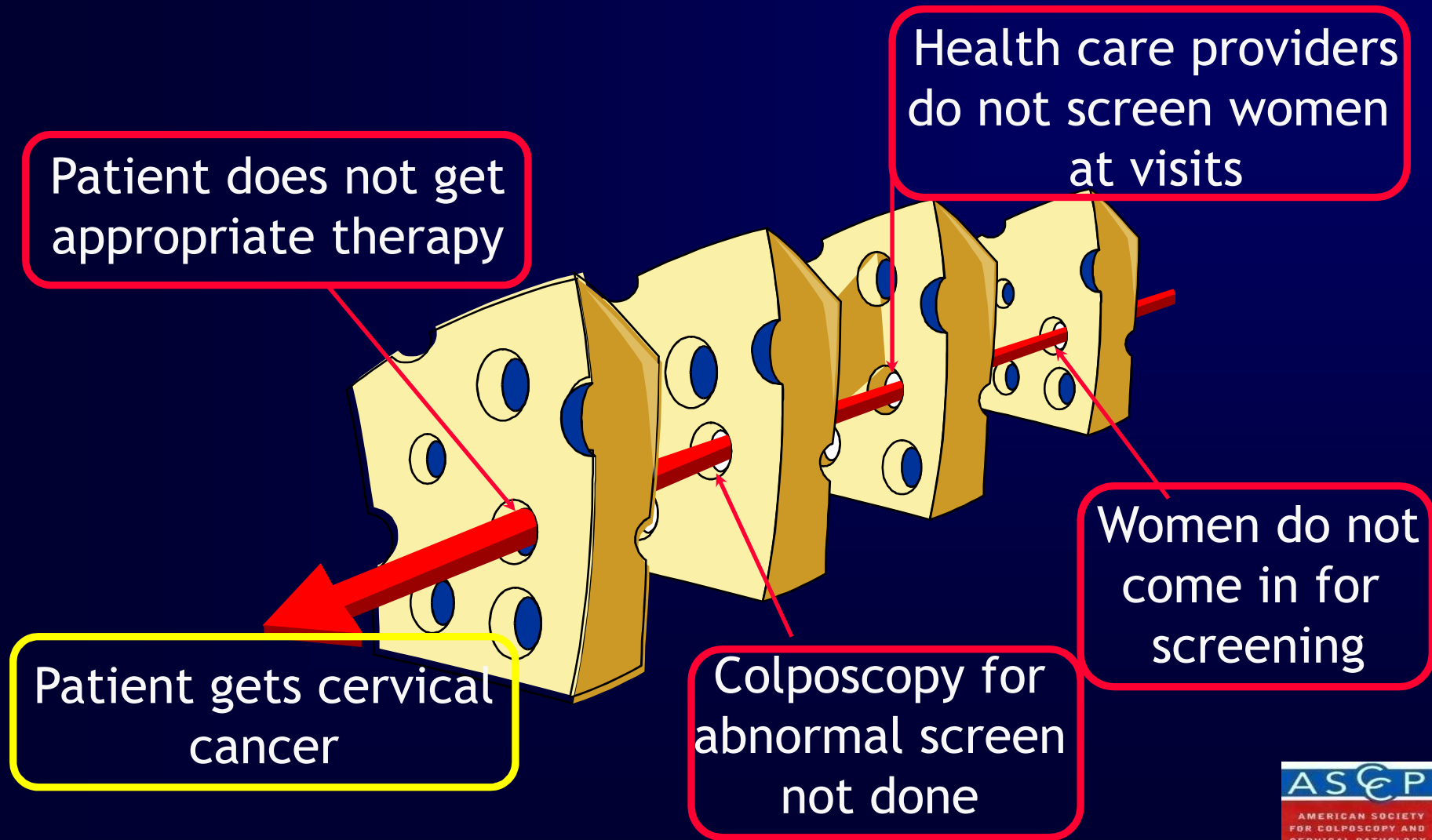
§ National Center for Health Statistics, CDC

μ Behavioral Risk Factor Surveillance System, CDC

\*\* National Health Interview Survey, CDC



# System Failures Leading to Cervical Cancer Diagnosis



Courtesy of Connie Trimble, MD, Johns Hopkins University School of Medicine, Baltimore, MD

# Retrospective Study of Cervical Cancers Diagnosed at Kaiser Northern California

Pap results 3-36 months prior to diagnosis

N=833

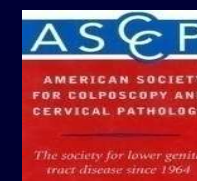
Failure to  
screen  
No Pap  
464 (56%)

Failure in  
detection  
1<sup>st</sup> Pap WNL  
263 (32%)

Failure to  
follow-up  
1<sup>st</sup> Pap abnormal  
106 (13%)

- No visit 19%
- 1-2 visits 18%
- >3 visits 63%

Leyden MA, Manos M, Kinney W et al JNCI 2005;97:67583.



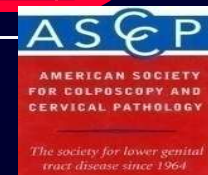


# Proportion of Women Receiving Cervical Cancer Screening, NHIS\*, United States, 2000

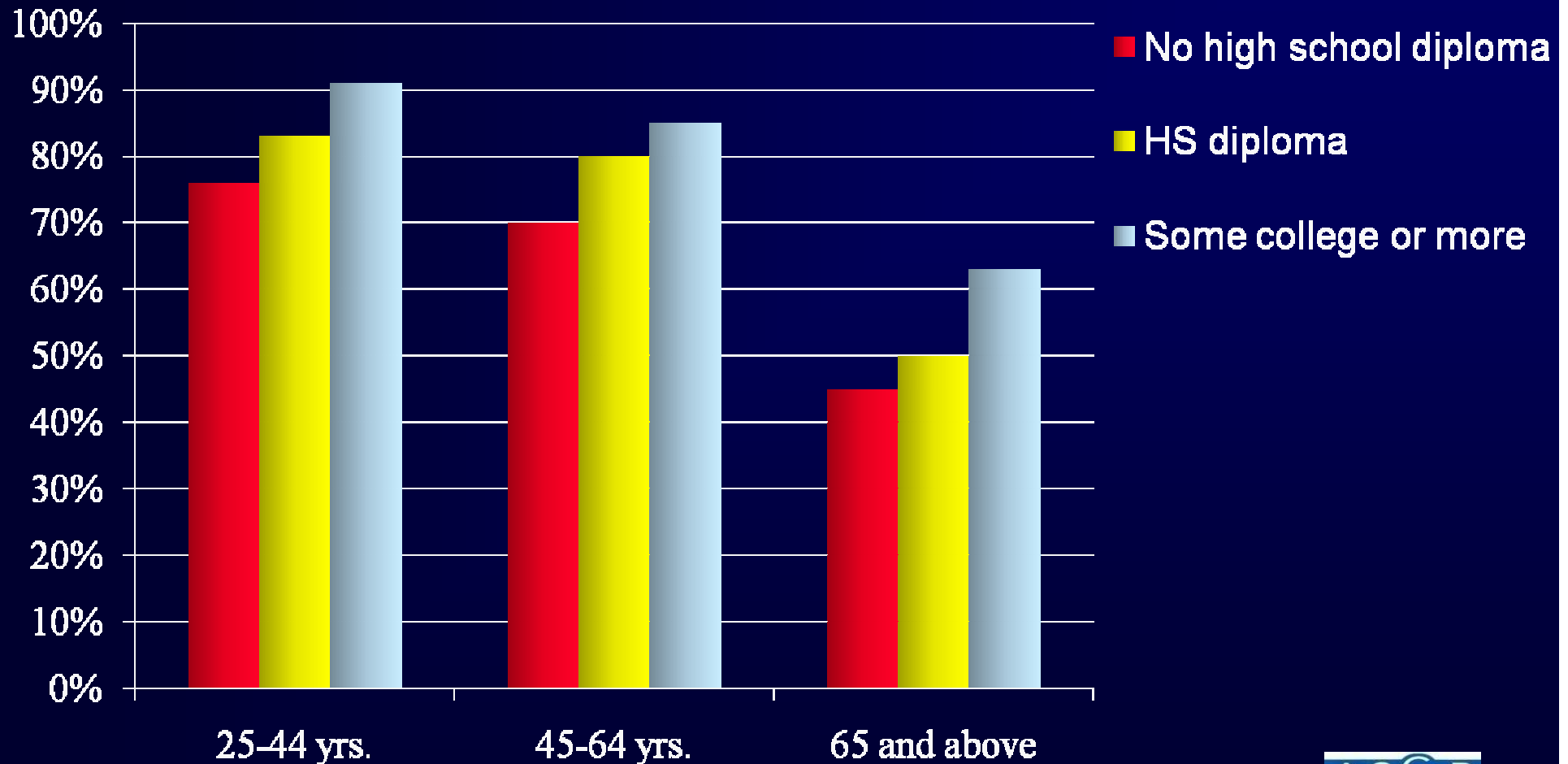
Group	% Pap test past 3 years
All women	82%
Insured	
Yes	85%
No	62%
Country of birth	
US born	83%
Foreign born in U.S. <10 yrs	61%

\*National Health Interview Survey

Swan J, Breen N, Coates RJ, Rimer BK, Lee NC. Progress in cancer screening practices in the United States: results from the 2000 National Health Interview Survey. *Cancer*. 2003;97:1528-40.

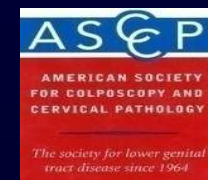


# Prevalence of Pap Tests during last 3 years, by education level, U.S.



<https://www.cdc.gov/nchs/data/hus/hus07.pdf>

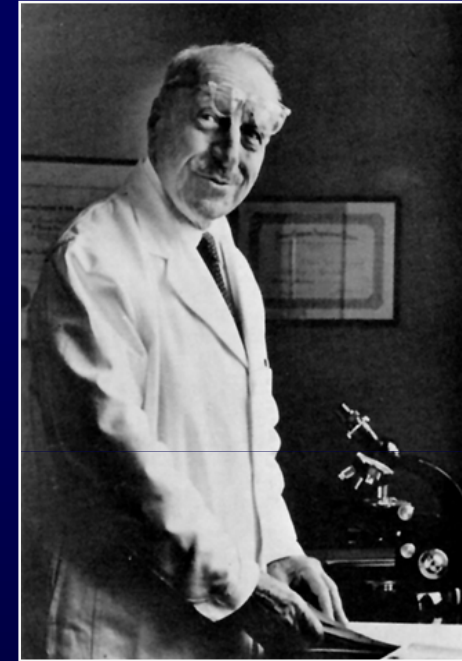
2007. Health US 2007.CDC, National Center for Health Statistics.



# Cervical cancer prevention:

*Where have we been and where are we going?*

Widespread introduction of the Pap begins



Markers

Conventional Pap smear

LBC

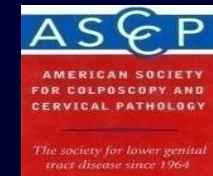
HPV testing

Vaccine

1949

1996

2000's



# Why isn't "finding lesions" the objective of screening?

- Don't know which lesions will progress.
- Need to place emphasis on:
  - **Persistent** HPV infections
  - **CIN 3** (no margin for error)
  - CIN 2 in older women (no risk to pregnancies)
  - Persistent CIN 2 and CIN 2/3 in non-adolescent women

# Consensus Conference

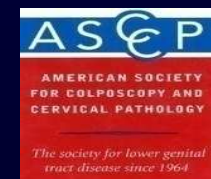
Sponsored by

- American Society of Colposcopy and Cervical Pathology (ASCCP)
- American Cancer Society (ACS)
- American Society of Clinical Pathology (ASCP)



# ACS/ASCCP/ASCP Guidelines Development Process

- 2009-2011 – A steering committee from the 3 organizations created 6 working groups and a data group to direct the evidence evaluation
- **Participating organizations:**  
AHRQ, AAFP, ABOG, ACHA, ACOG, ASHA, ASC, ASCT, CAP, CDC, CMS, FDA, NCI, NCCN, NPWH, PPFA, SCC, SGO, SGOC, AHRQ/USPSTF, VHA



# Guidelines Development Evidence Review

- Used “Grading Recommendations Assessment, Development, and Evaluation” (GRADE) system
- Articles retrieved 1995 to mid-2011
- WGs reviewed and graded evidence as “critical, important, nice to know”
- WGs developed recommendations --“strong” or “weak” depending on the quality of the evidence

# ACS/ASCCP/ASCP Guidelines Development Process

## 6 topic areas identified:

- Optimal screening intervals
- Screening women 30+
- Managing discordant cytology/HPV results
- Exiting women from screening
- Impact of HPV vaccination on screening
- Potential for primary HPV testing (no Pap)



# Guidelines Development Process Assumptions

- Preventing all cervical cancer is unrealistic
  - No screening test has 100% sensitivity
- Reasonable risk is determined by a strategy of performing cytology alone at 2-3y intervals
  - Screening strategies with similar outcomes are acceptable
- Women at similar risk for cancer should be managed the same

# Guidelines Development Process Assumptions

- Conventional and liquid-based cytology perform similarly
- HPV tests should have  $\geq 90\%$  sensitivity for CIN2+ and CIN3+
  - Comparability of all FDA-approved HPV tests cannot be assumed
  - Utility of unapproved/laboratory developed tests is unknown, and tests should not be used in screening

# Guidelines Development Process Assumptions

## Benefits of screening

- Cancer is the ideal endpoint but unrealistic
- CIN3 is a reliable surrogate marker for sensitivity
- CIN2 is equivocal (a combination of CIN1 and CIN3)
  - hard to diagnose—poor inter-rater reliability
  - often regresses
  - a threshold for treatment

# Guidelines Development Process Assumptions

- Screening interval
  - Risk of developing invasive cancer before next screen should be unlikely
  - Earlier detection of CIN3+ is a benefit
    - Even studies with less sensitive tests show similar CIN3 detection--no increased cancer risk during later screening rounds

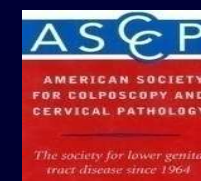
# Guidelines Development Process Assumptions

- Possible harms of screening
  - Anxiety over a positive test
  - Stigma of an STI
  - Pain/bleeding from procedures
  - Treatment-related pregnancy complications
- Number of colposcopies is a marker for harms

# Treatment saves lives, but at what cost?

- Women with LEEP more likely to have
  - Preterm birth (O.R. 1.7)
  - LBW (O.R. 1.8)
  - PPRM (O.R. 2.7)
- Single studies show association with perinatal death, incompetent cervix
- Risk rises with depth and number of LEEPs
- Similar findings after conization or laser treatment
- Absolute risk increase is small

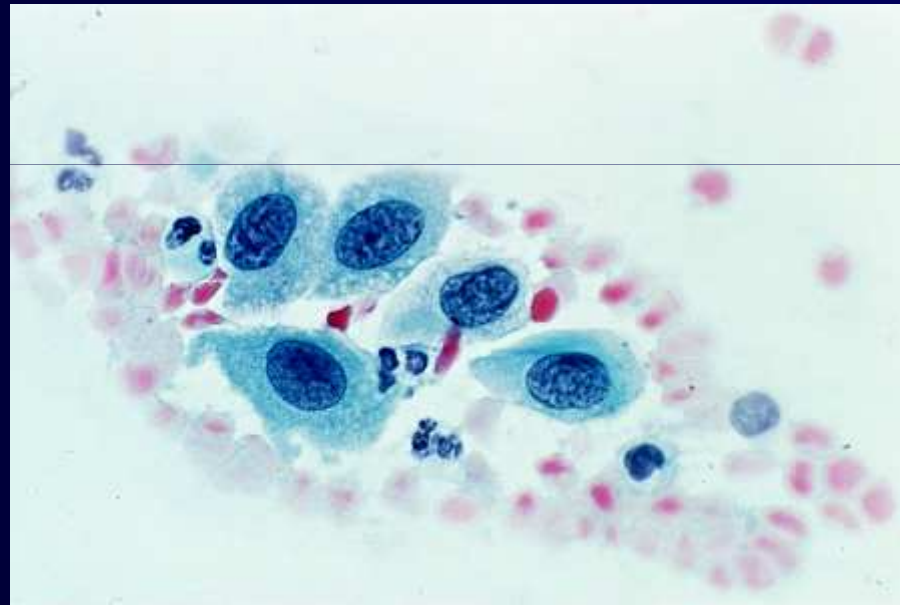
Kyrgiou M et al. *Lancet* 2006;367:489-98  
Bruinsma et al *BJOG* 2007;114:70-80



# Guidelines Development Evidence Review Process

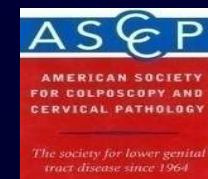
- Recommendations posted to ASCCP website for public comment 10/19-11/9/11
  - Revisions made based on comments as needed
- Consensus conference held 11/17-18/2011
- Discussion of draft recommendations by attendees
- Recommendations approved by at least a 2/3 majority of delegates

# 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)





# New ACS/ASCCP/ASCP Guidelines

## When to begin screening

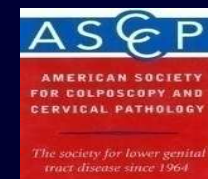
**Cervical cancer screening should begin at age 21.**

**Women < 21 should not be screened  
regardless of age of sexual onset**

❖ Guidelines do not apply to special populations – hx of cervical cancer, DES exposure, & immune-compromise

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)



# Cervical Cancer Incidence by Age Group, USCS\*, 1998-2002

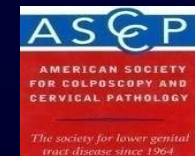
**Age** **Rate per 100,000**

---

0-19	0.1
20-29	4.5
30-39	13.9
40-49	16.5
50-64	15.4
65+	14.6
All ages	9.4

\*United States Cancer Statistics includes data from CDC's National Program of Cancer Registries and NCI's Surveillance, Epidemiology and End Results Program.

Saraiya M et al. *Obstet Gynecol* 2007;109:360-70.



# Adolescent Needs

- Care for contraception and STI screening/treatment.
- No Pap test
- No speculum exam for asymptomatic women
- STI testing can be done using urine

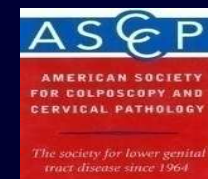
## Screening for ages 21-29

- Cytology alone every 3 years
- HPV testing “should not be used to screen”
  - Not as a component of cotesting
  - Not as a primary stand-alone screen

# Rationale for Longer Pap Screening Intervals

- Sensitivity of single Pap test 50-70%
  - Cancer risk 18mo after 3 neg Paps = 1.5/100,000
  - Cancer risk 36mo after 3 neg Paps = 4.7/100,000
  - 99,997 women screened unnecessarily to help 3
- Risk of HSIL/cancer <3 years after negative Pap not significantly higher than risk after 1year
- Longer Pap screening intervals (e.g., 5y) inappropriate for mobile US population

Sawaya GF et al. Acta Cytol 2005;49:391-7

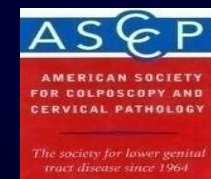


# Rationale for Longer Pap Screening Intervals-2

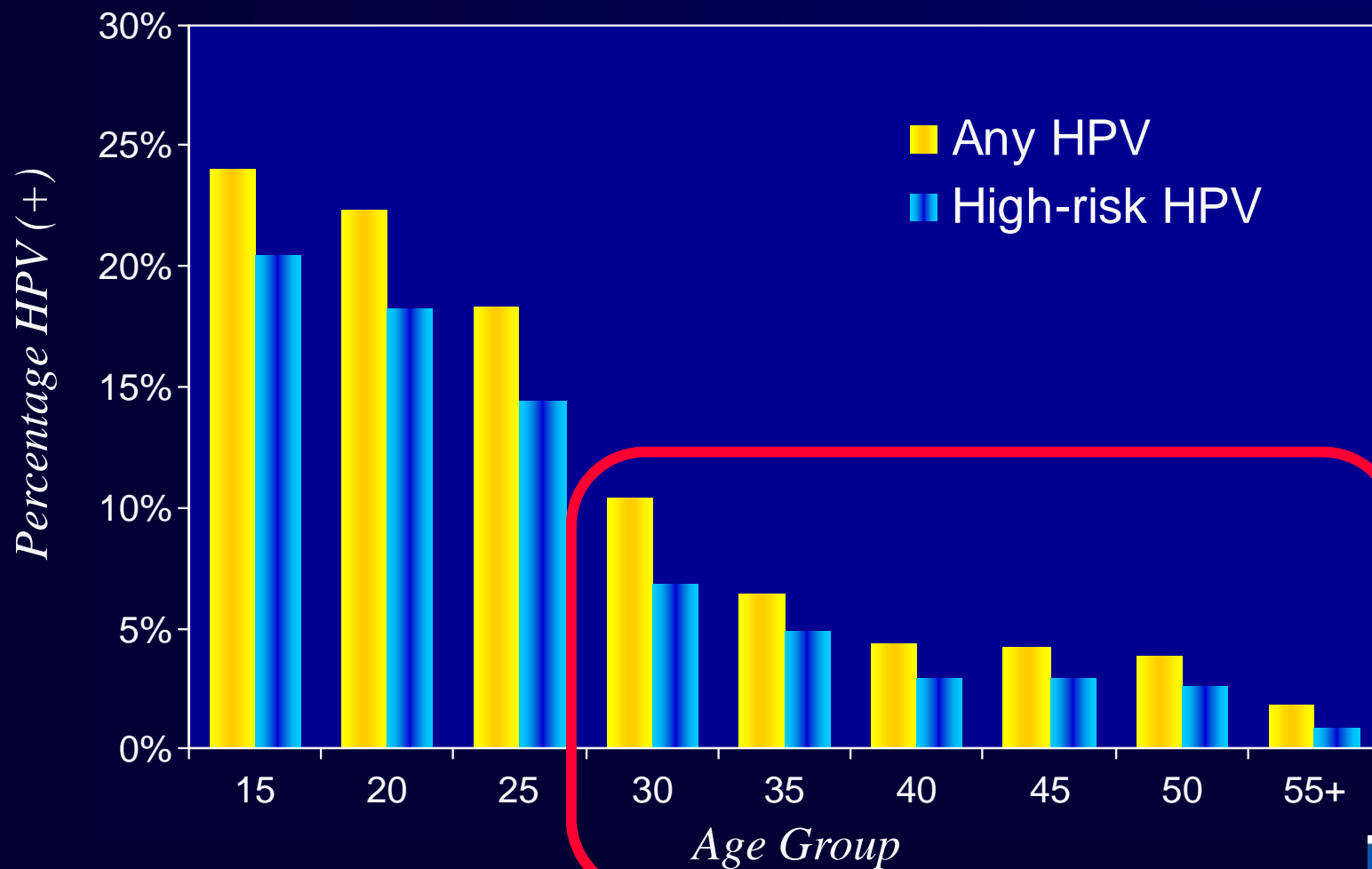
- Screening harms: lifetime risk of colposcopy
  - Screening q3y: 760 colpos/1000 women
  - Screening q2y: 1080 colpos/1000 women
  - Screening annually: 2000 colpos/1000 women

Stout NK et al. Arch Intern Med 2008;168:181.

Kulasingham S et al. 2011. AHRQ Publication No.11-05157-EF-1.

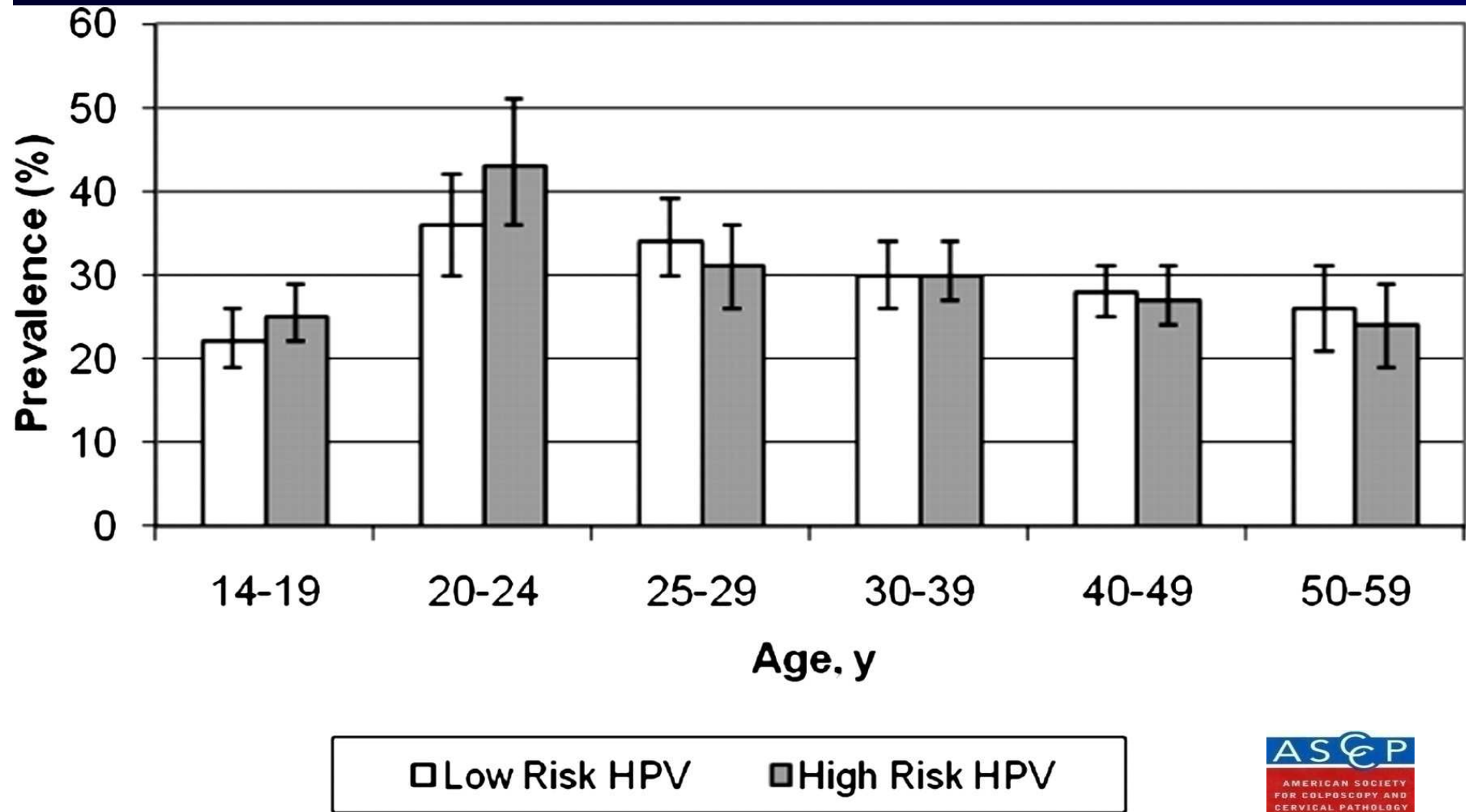


# Prevalence of HPV by Age, Manchester, U.K.



Peto et al Br. J. Cancer (2004;91:942-53)

# Weighted Prevalence of Low-risk and High-risk HPV Types Among US Women 14–59yo, 2007-2010 (NHANES)





# Rationale for Avoiding HPV Tests Among Women Ages 21-29

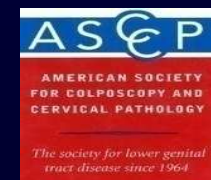
- Prevalence of carcinogenic HPV approaches 20% in teens and early 20s
- Most carcinogenic HPV infections resolve without intervention
- Identifying carcinogenic HPV that will resolve leads to repeated call-back, anxiety, and interventions without benefit

# Screening For Women Ages 30-64

- Cytology + HPV testing (Cotesting) every 5 years is preferred
- Cytology alone every 3 years is acceptable

# Rationale for Cotesting, Ages 30-64

- Increased detection of prevalent CIN3
- Decreased CIN3 in subsequent screening rounds
- Achieves risk of CIN3 equal to cytology alone @ 1-3year intervals
- Enhances detection of adenocarcinoma/AIS
- Minimizes the increased number of colposcopies, thus it reduces harms.



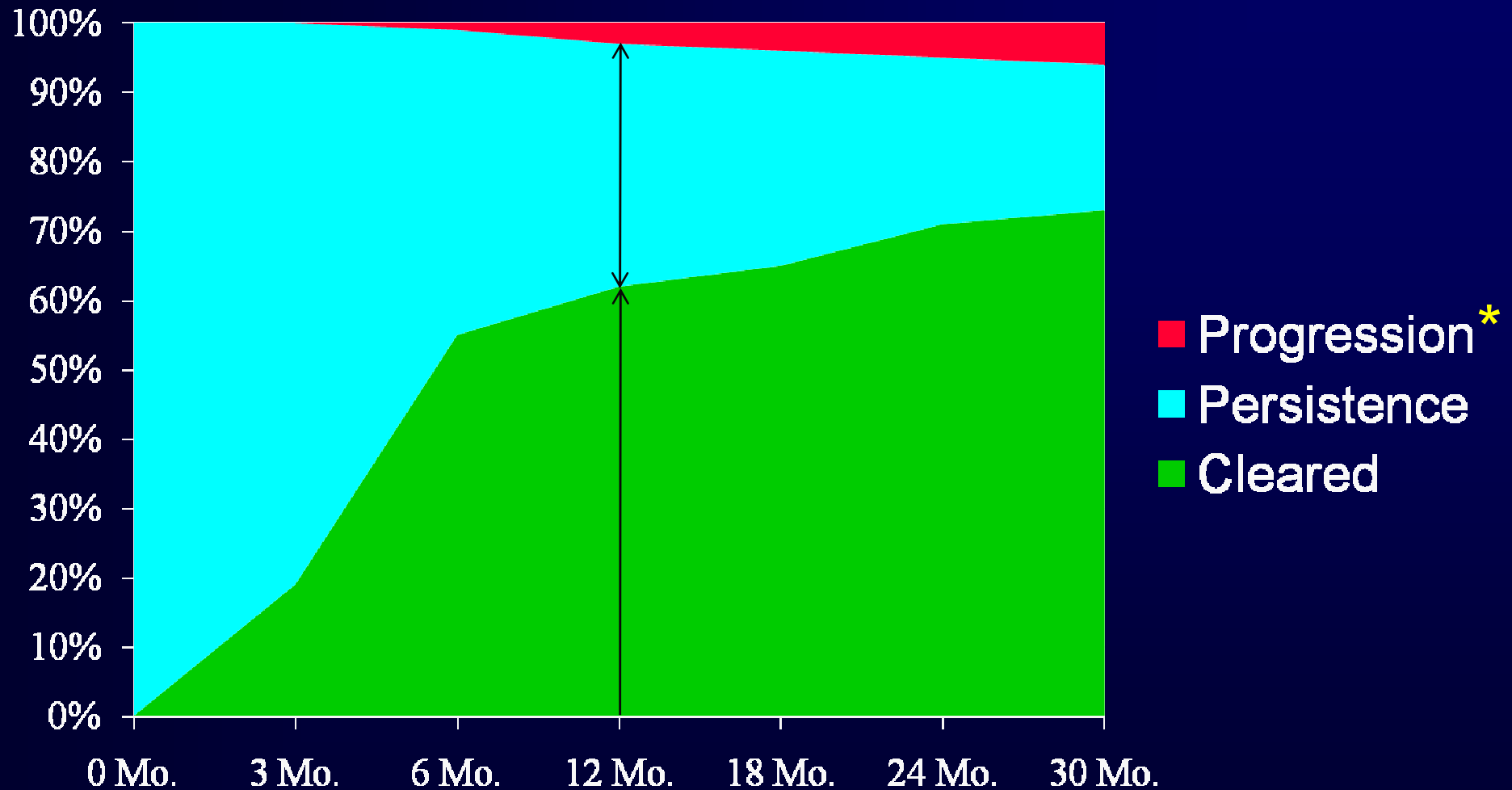
# Why Not Cotesting for All Women 30-64?

- Some sites may lack access to HPV testing
  - Financial
  - Logistical
- Cytology remains effective
  - Requires more frequent visits
  - Requires more colposcopy for equivocal results

## Why Not Annual Cotesting?

- High NPV of one cotest means most abnormal screens at 1-3y intervals are transient HPV infection, not precancer
- Potential harms are amplified without benefit

# Rapid clearance of HPV in Women $\geq 30$



\* Histological progression

Rodriguez AC et al. J Natl Cancer Inst. 2008;100:513-17.

# Managing ASC-US/HPV negative tests

- *“ Women with ASC-US cytology and negative HPV test results should continue screening per age-specific guidelines.”*
- CIN3 risk of ASC-US/ HPV neg <2%, below threshold for colposcopy.

## Managing HPV+/Cytology- Cotests

*“Women cotesting HPV positive and cytology negative should be followed with either (1) repeat cotesting in 12 months, or (2) immediate HPV genotype-specific testing for HPV16 alone or HPV 16/18. Direct referral to colposcopy is not indicated”*



## (1) Repeat cotest in 12 months

- If either repeat test is positive, refer to colposcopy
- If both tests are negative, return to routine screening.

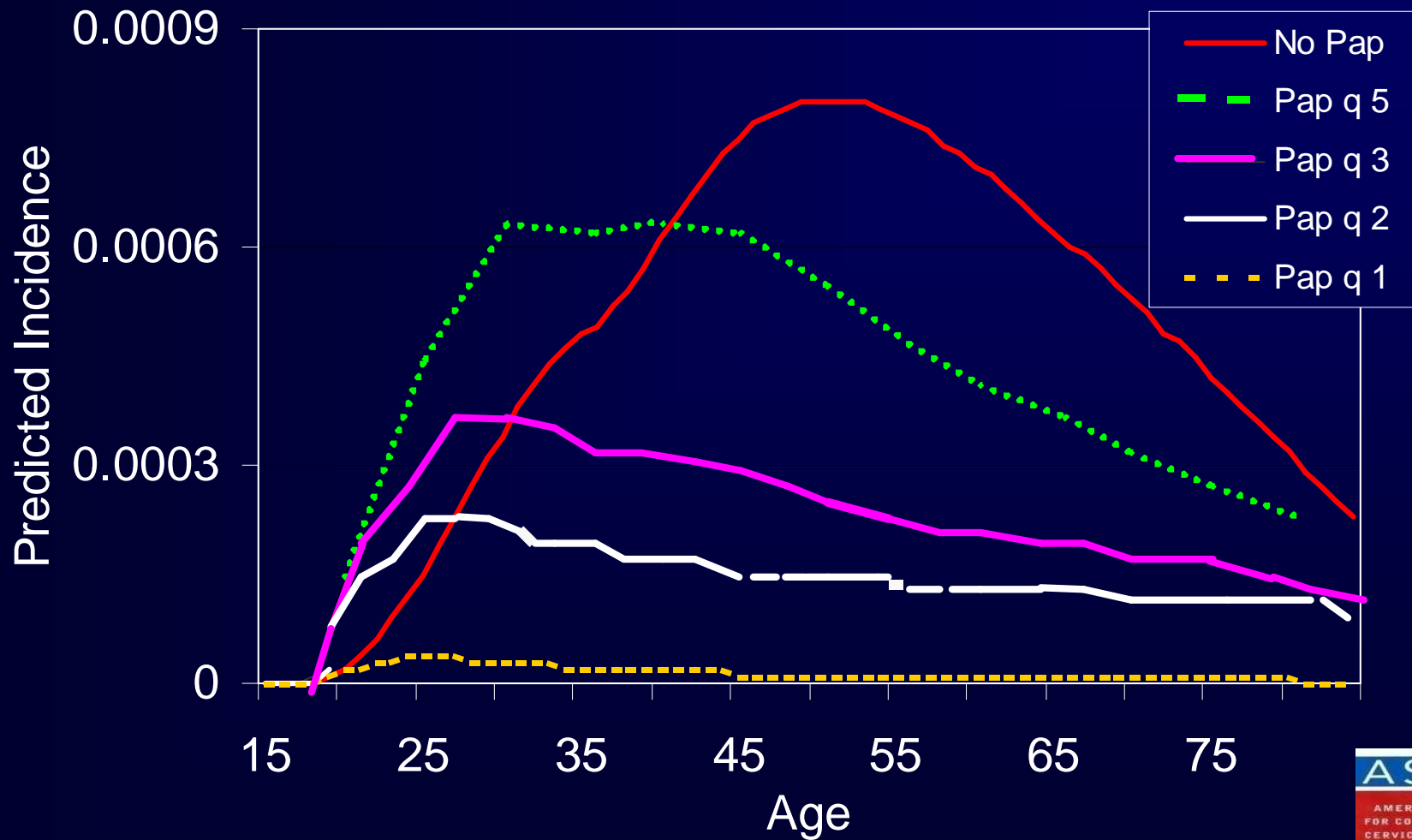
## (2) Immediate HPV genotyping

- If HPV 16 or HPV16/18 positive, refer directly to colposcopy.
- If HPV 16 or HPV 16/18 negative, repeat cotest in 12 months and then...
  - If either repeat test is positive, refer to colposcopy
  - If both tests are negative, return to routine screening.

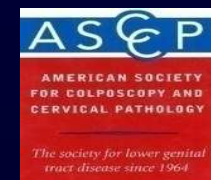
# Managing HPV+/Cytology- Cotests Rationale

- Consistent observational data indicate short term risk of CIN3 far below risk threshold of HPV+/ASC-US and LSIL used for colposcopy referral
- Evidence from cohort studies shows majority of transient infections clear by 12 months allowing most to return to routine screening without excessive risk.

# Predicted Impact of Pap Screening on Cancer Incidence



Myers E 2006 ASCCP Biennial Meeting Las Vegas, NV



# When to Stop Screening

- Stop at age 65 for women with adequate negative prior screening, no CIN2+ within the last 20y.

## ***Definition of adequate negative screening:***

- 3 consecutive negative Paps or
- 2 consecutive negative HPV tests  
(Tests within 10 years of stopping; most recent within 5 years.)

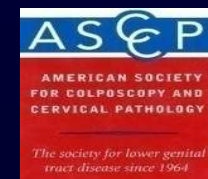
## Stop screening at age 65

- *Screening “should not resume for any reason, even if a woman reports having a new sexual partner.”*

# Rationale for stopping at 65 years

- *CIN2+ is rare after age 65*
  - Most abnormal screens, even HPV+, are false + and do not reflect precancer
- HPV risk remains 5-10%
- Colposcopy/biopsy/treatment more difficult
  - Harms are magnified
- *Incident HPV infection unlikely to lead to cancer within remaining lifetime*

Chen HC et al. JNCI 2011;103:1387-96;  
Rodrigues AC et al. JNCI 2009;101:721-8



## When to stop screening - 2

- Stop after hysterectomy with removal of cervix and no history of CIN2+
- *“Evidence of adequate negative prior screening is not required”*

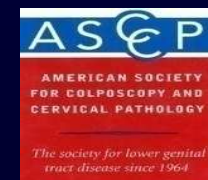


# Rationale for stopping after Hysterectomy

- Vag cancer rate is 7/million/year
- 663 vag cuff Paps needed to find one VAIN
- 2,066 women followed after hyst. for average 89 months
  - 3% had VAIN, 0 had cancer
- Risk of Pap abnormality after hyst = 1%.
- Compare risk of breast cancer in men for which screening is not recommended.

Pearce KF et al. NEJM 1996;335:1559-62;

Piscitelli JT et al. AJOG 1995;173:424-30



## When NOT to stop at age 65 years

If history of CIN2, CIN3, or AIS

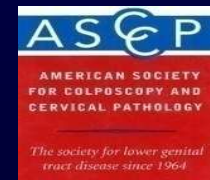
- Continue “routine screening” for at least 20 years, “even if this extends screening past age 65.”

# Screening a Vaccinated Cohort

- *“Recommended screening practices should not change on the basis of HPV vaccination.”*
- Vaccination against HPV 16/18
  - Reduces CIN3+ by 17-33%
  - Reduces colposcopy by 10%
  - Reduces treatment by 25%
- But who is vaccinated?
  - Recall? Completed series? HPV naïve?

# HPV as a Primary Screening Test

- Strong NPV of HPV test suggests it might replace cotesting, but test specificity lacking
  - Follow-up to HPV+ test remains unclear
    - Pap? Repeat HPV in 1y? Genotyping? Colpo?
  - Knowing HPV status biases cytology reports to abnormal
  - Harms undefined
  - No US prospective trials
- *“In most clinical settings, women ages 30-65 should not be screened with HPV testing alone.”*



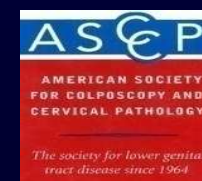
# 2012 Standards

	USPSTF	ACS/ASCCP/ASCP
When to start?	21yo	21yo
How often?	Q3y Paps Cotesting $\geq 30$ years q 5 yrs to lengthen the screening interval	Q3y Paps ages 21-29 Q5y cotesting ages 30-65 Q3y Paps remain an option
When to stop?	65 if adequate prior screens	Age 65 if 3 neg Paps or neg HPV After hysterectomy for benign disease

## Conclusion

- “The biggest gain in reducing cervical cancer incidence and mortality would be achieved by increasing screening rates among *women rarely or never screened. . .*”
- Clinicians, hospitals, health plans, and public health officials should seek to identify and screen these women.”

ACS, 20002



# Caveats

- Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view recommendations as dictates. Even strong recommendations based on high-quality evidence will not apply to all circumstances and all patients.
- Users of guidelines may reasonably conclude that following some strong recommendations based on high quality evidence will be a mistake for some patients. No clinical practice guideline or recommendation can take into account all of the often compelling unique features of individual patients and clinical circumstances. Thus, nobody charged with evaluating clinician's actions, should attempt to apply recommendations in rote or blanket fashion.