

# Guidelines for Paps, HPV Tests and Managing Abnormal Pap Tests

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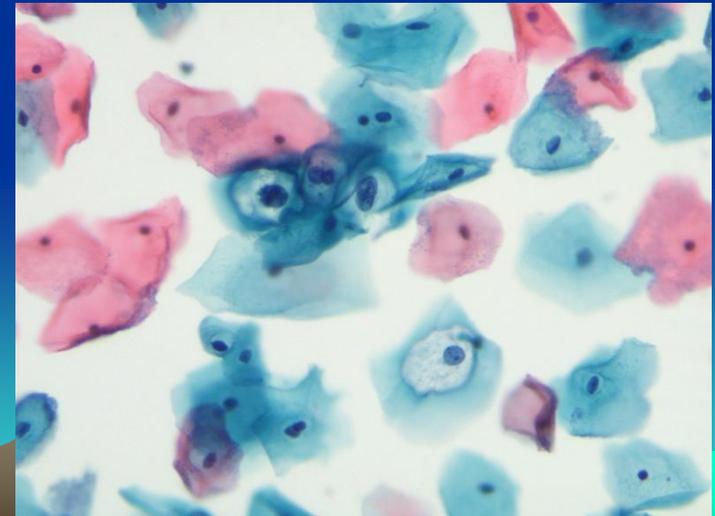
# Objectives

- Describe our current understanding of the natural history of HPV infection and how it relates to the newest recommendations for cervical cancer screening
- Discuss the current role of HPV testing
- Describe recent recommendations from the ASCCP for management of abnormal Pap tests



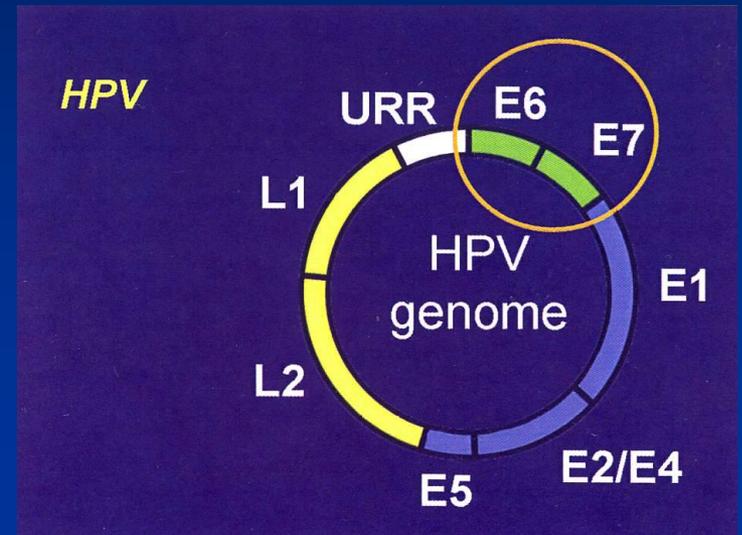
# Natural History of HPV Infection

- Sexual transmission (skin-to-skin)
- Enters cell through microtrauma
- Moves to nucleus of infected cell
- Infected cell exhibits koilocytosis (HPV effect, LSIL)
  - perinuclear halo
  - enlarged nucleus with clumped chromatin

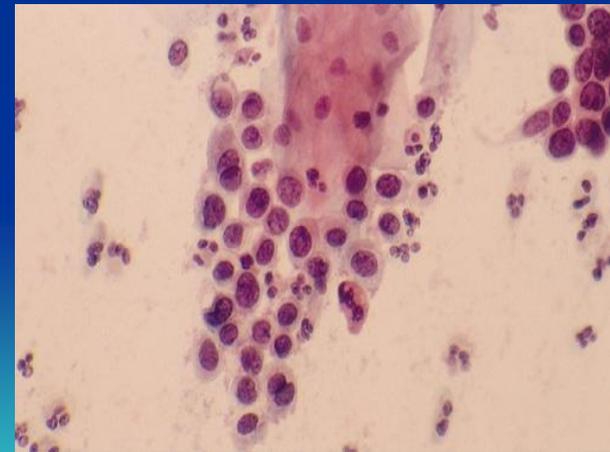
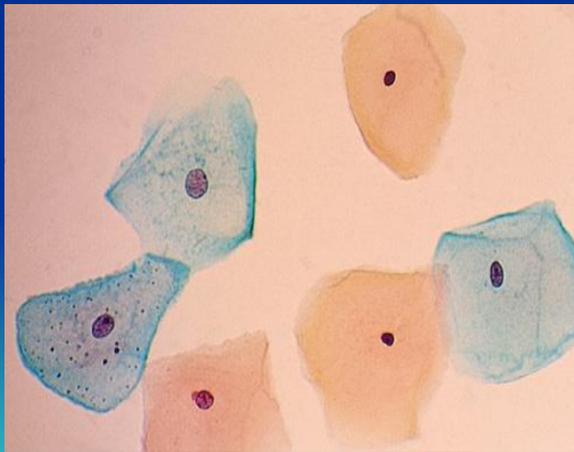
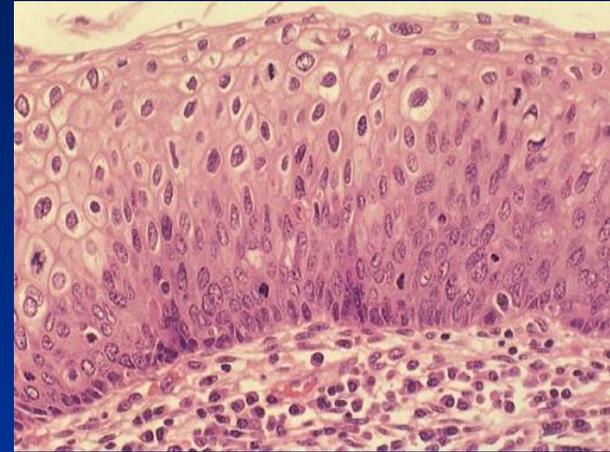
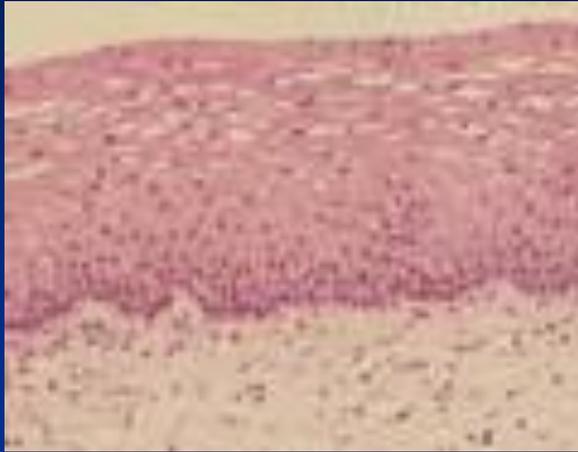


# Activation of Oncogenes

- E6 and E7 are oncogenes
- E7 can activate synthesis of the intracellular protein p16, normally manufactured only in miniscule amounts
- Excess p16 deregulates and stimulates the cell cycle
- Cervical neoplasia (CIN 2/3) results



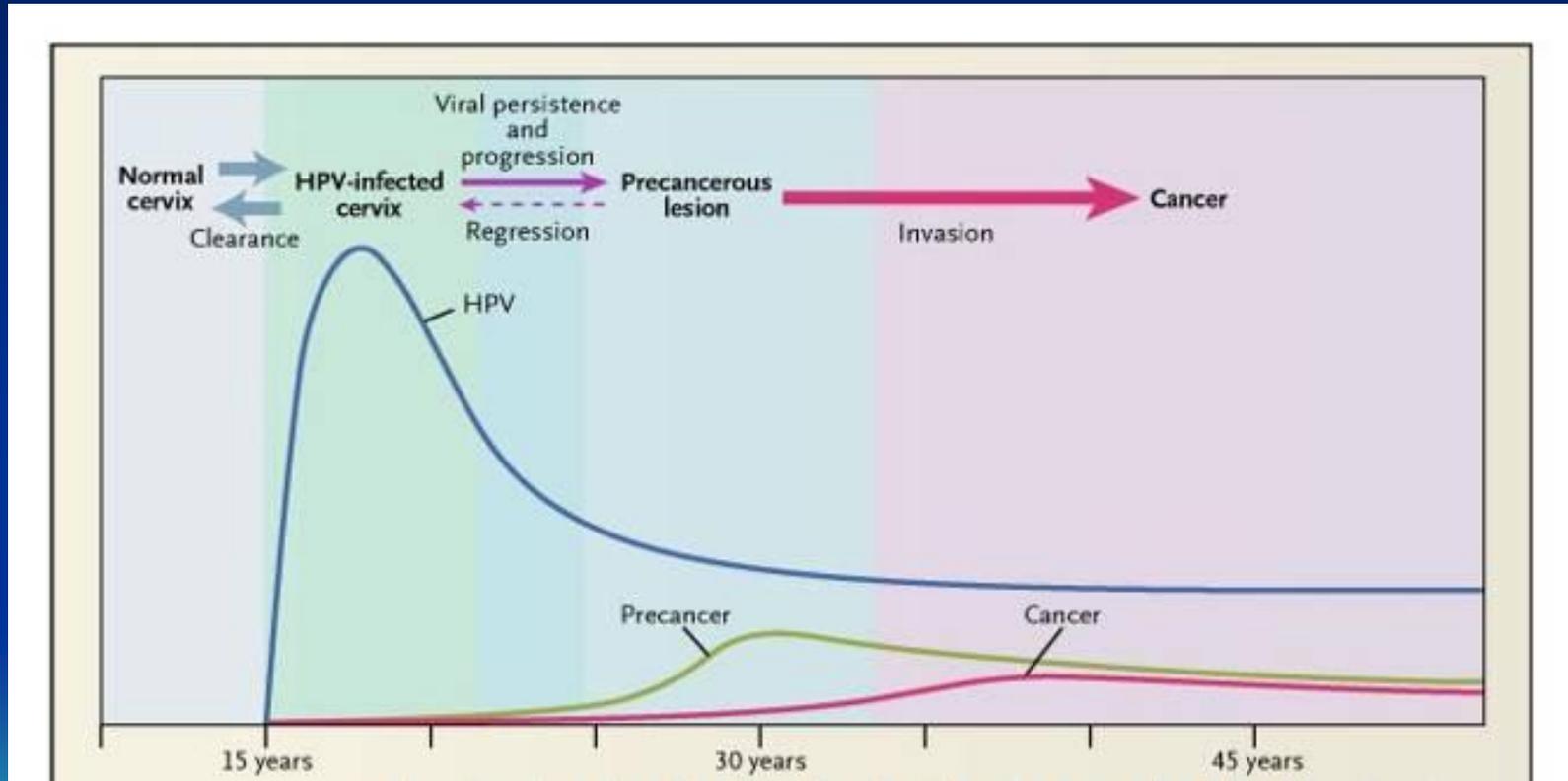
# Progression of Cervical Neoplasia



# HPV – Usually a Transient Infection

- In 608 college-aged women
  - 70% no longer infected at one year
  - 91% no longer infected at 2 years
  - Average duration of infection - 8 months
- Manifestation of disease determined by
  - HPV subtype, viral load
  - Host cofactors

# The Natural History of HPV Infection and Cervical Cancer



# Current Pap Test Recommendations (ASCCP, ACS, ASCP, USPSTF, ACOG)

- First Pap test age 21
- Test every three years until age 30
- Age  $\geq$  30, HPV test with Pap test every 5 years
  - If HPV testing unavailable, Pap every 3 years
- No more testing after hysterectomy (if cervix has been removed) or age 65
  - With negative Pap history

Important: Pap  $\neq$  Well Woman Exam (Still covered by WWC)

# Evidence for New Guidelines

- Yearly Pap interval was chosen arbitrarily when the test was first introduced
- Now we know that
  - Cervical cancer is an STI caused by HPV
  - Most HPV infections are cleared by the body's own immune system
- Likelihood of progression to cancer
  - **Duration/persistence of infection**



# Evidence for HPV Co-Testing

- Before age 30, high prevalence of HPV →  
Do not co-test
- In women  $\geq 30$ , co-testing detects 17-31% more CIN 3 (pre-cancer) AND
- HPV testing is superior to cytology for detecting cervical adenocarcinoma
  - Poorer prognosis, on the rise

# Exceptions to the New Guidelines

- Continue annual Pap testing for
  - Immunocompromised women, especially HIV+
  - Women exposed to DES *in utero*
- Women who have had CIN 2 or CIN 3
  - 5-10% increased risk of cervical cancer for 20 years
  - More intense screening first 5 years
  - Continue routine testing for at least 20 years
- Women treated for cervical cancer
  - Continue regular testing indefinitely



# NOT Exceptions to New Guidelines

- Early onset of sexual activity
- Sexual activity with multiple partners or new sex partner
- Tobacco use



# Advantages of New Guidelines

- Balances benefits and harms
  - Avoids unnecessary emotional and physical trauma, especially for young women
  - LEEP may increase risk of preterm birth
- Frees up time
  - To discuss other important issues
  - To make clinic more efficient
- May increase clinic visits
- Cost savings



# Who should get a Pap this year?

- A 19-year-old who has been sexually active for four years?
- A sexually active 16-year-old who is HIV positive?
- A 31-year-old who had a hysterectomy 3 years ago for endometriosis, previous Paps negative?
- A 41-year-old with a negative Pap in your clinic last year and in 2009 and 2007?
- A 67-year-old s/p LEEP for CIN III five years ago?
- A 71-year-old just returned from a cruise, where she had three sex partners?



# 2012 Consensus Guidelines for Management of Abnormal Pap Tests

Available (with algorithms) at  
[www.ASCCP.org/Consensus2012](http://www.ASCCP.org/Consensus2012)



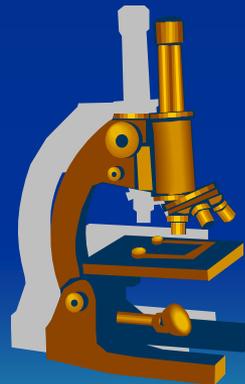
# Guidance on HPV Testing



# Pap Tests vs. HPV Testing

- Pap Test

- 30-87% sensitivity
- High specificity
- Poor reproducibility among observers
  - ASC-US - 43%
  - LSIL - 68%
  - HSIL - 47%(ALTS study)



- HPV Test

- High sensitivity
- Low specificity
  - (only 15% of pts with + HPV and - Pap will develop + cytology within 5 years)
- 97% reproducibility

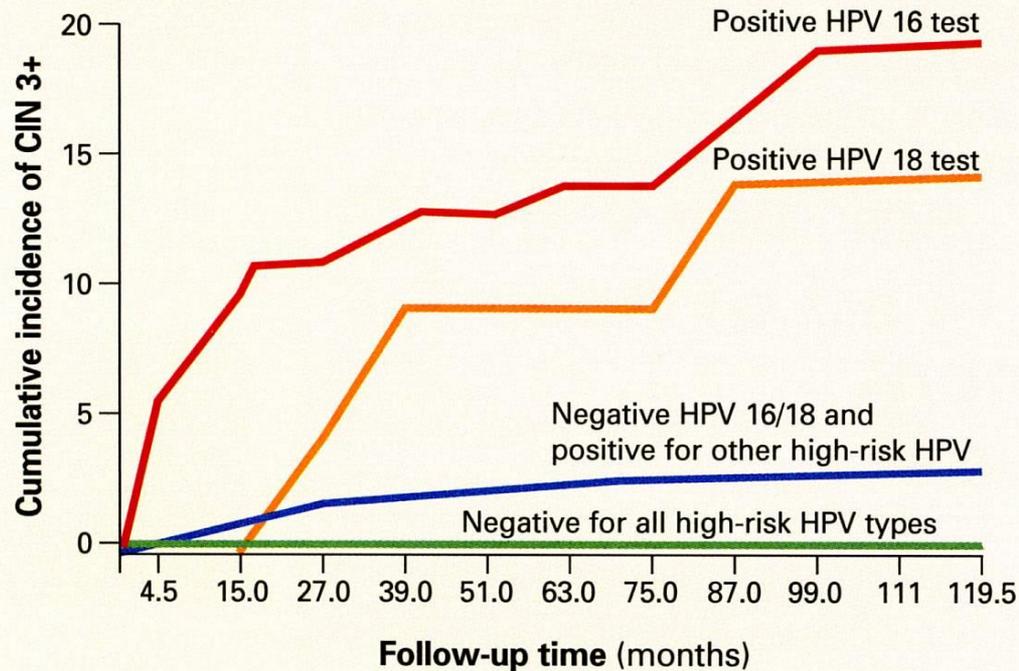
# The Role of High-Risk HPV Testing

- Low-risk HPV testing not meaningful, obsolete
- The only screening indication is for women age  $\geq 30$  in addition to Pap\*
  - Co-testing recommended in this group
  - If both tests negative, do not repeat for 5 years
- Primarily used for triage
  - ASCUS Paps (reflex testing)
- Minimize HPV testing in woman  $<$  age 30

\*Now covered by WWC

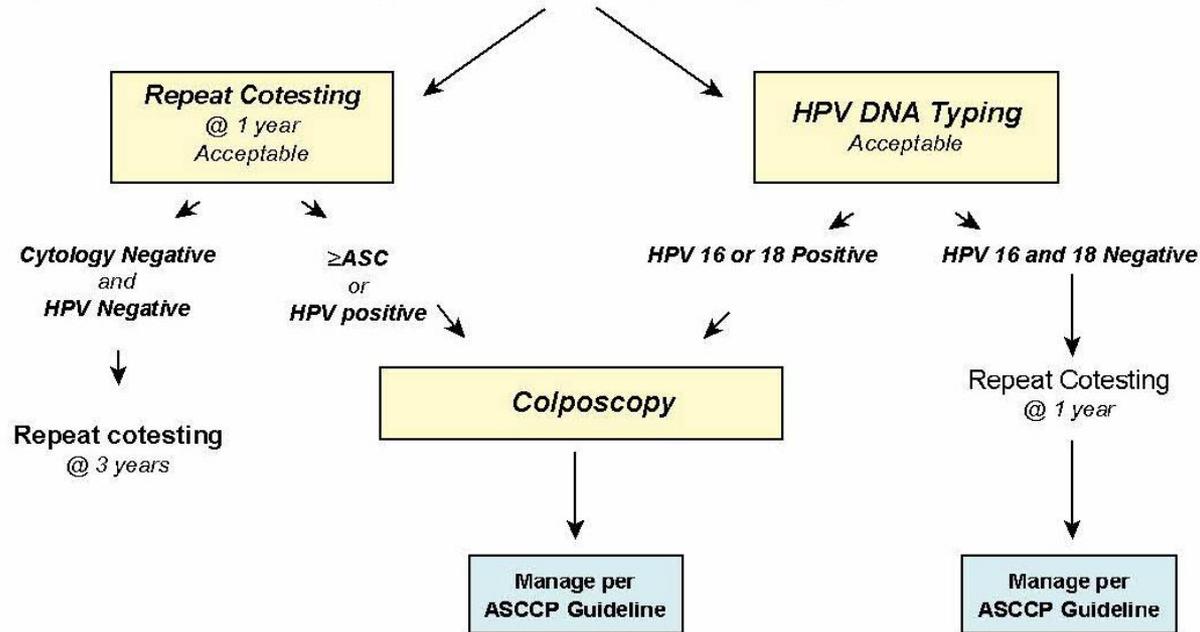
# Role of HPV 16/18 Genotyping

**Positive HPV 16 or 18  
linked to 14% to 17% incidence of CIN3+**



The cumulative incidence of CIN 3+ over a 10-year period, as a function of a single HPV test result at enrollment. Women positive for HPV 16 or 18 had a much greater incidence of CIN 3+, compared to women negative for HPV 16 and 18 but positive for other high-risk HPV types by Hybrid Capture 2, or negative for all high-risk HPV types. Adapted from Khan et al.

### Management of Women $\geq$ Age 30, who are Cytology Negative, but HPV Positive



\*WWC does not cover HPV genotyping

# Who should get an HPV test?

- A 16-year-old who is HIV positive?
- A 23-year-old with an LSIL Pap?
- A 24-year-old considering HPV vaccine?
- A 41-year-old presenting for annual exam?
- A 41-year-old with neg Pap/HPV last year?
- A 50-year-old with an ASCUS Pap?
- A 65-year-old s/p LEEP for CIN III last year?



**BUT** this may all be  
changing again soon!

We may start doing HPV testing  
alone on women  $\geq$  age 25

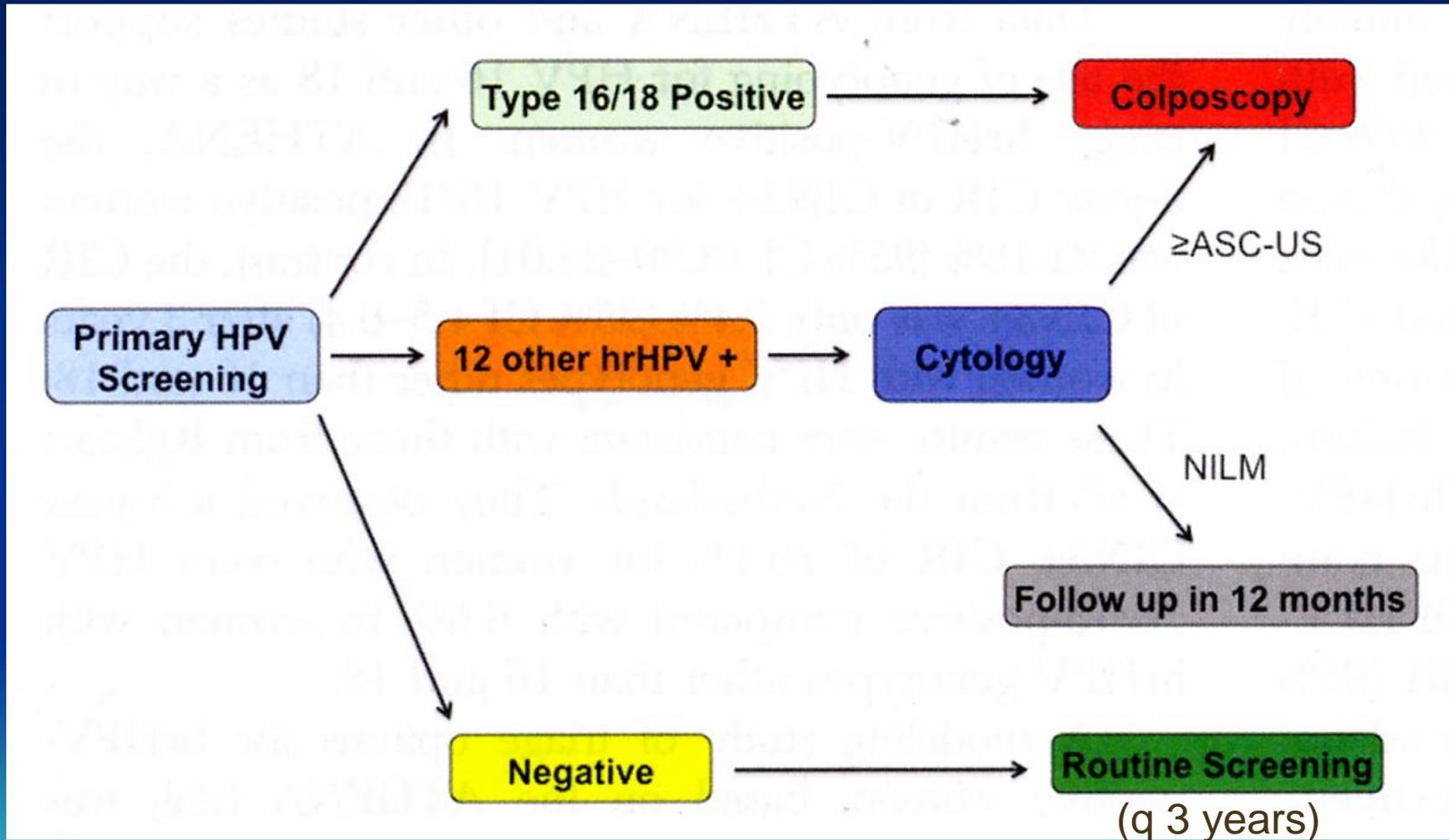


# Supporting Data

- European studies
- Kaiser of Northern California
  - 3 year risk of CIN 3 after a negative HPV test
    - HPV alone q 3 years – 0.069%
    - HPV/Pap cotesting q 5 years – 0.11%
    - Pap alone q 3 years - 0.19%
- ATHENA
  - HPV detected 50% more CIN 3 than Pap
  - BUT doubled the number of colposcopies



# How might this work?



# Caveats

- Only one brand of HPV test (Cobas<sup>®</sup>) is approved for this indication
- Should NOT be used on women < age 25
- Not yet recommended by major organizations (including ACOG, CDC)



# Guidance on Abnormal Pap Tests

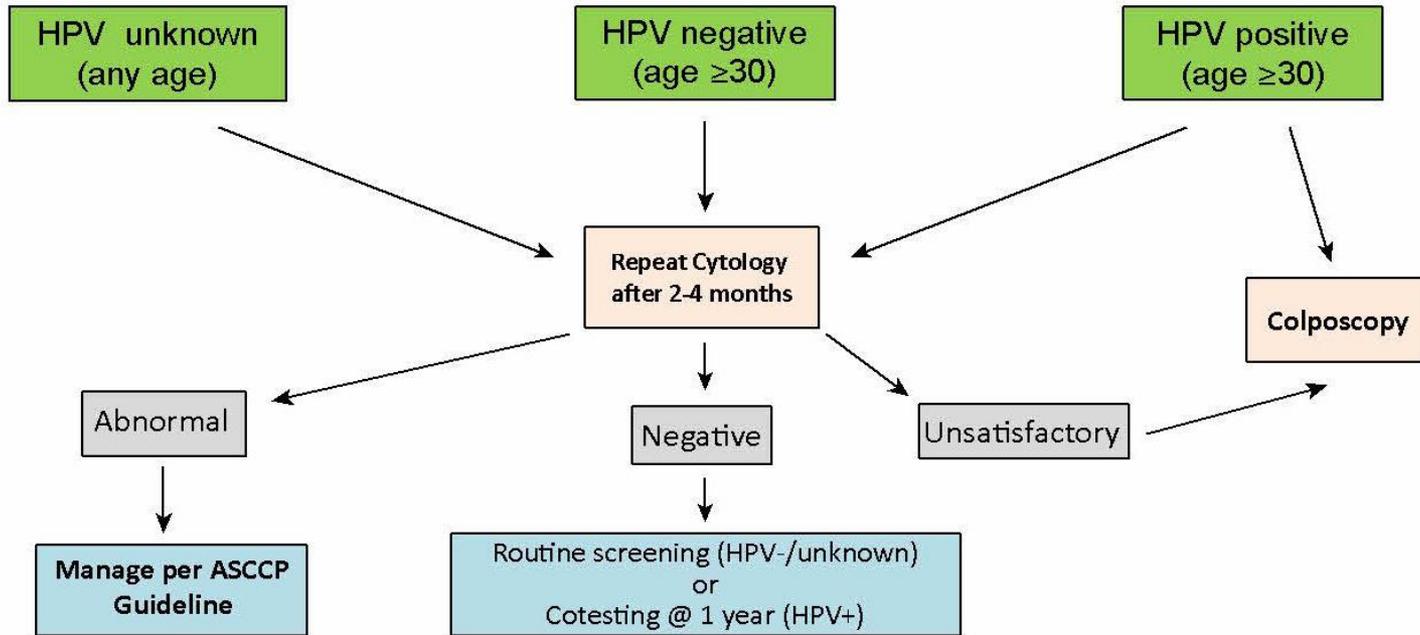


# Unsatisfactory Pap Tests

- With liquid-based testing, usually means not enough cells to evaluate
- Satisfactory reading implies that enough cells were seen for accurate result
  - If inflammation, etc., noted → Pap still negative



### Unsatisfactory Cytology



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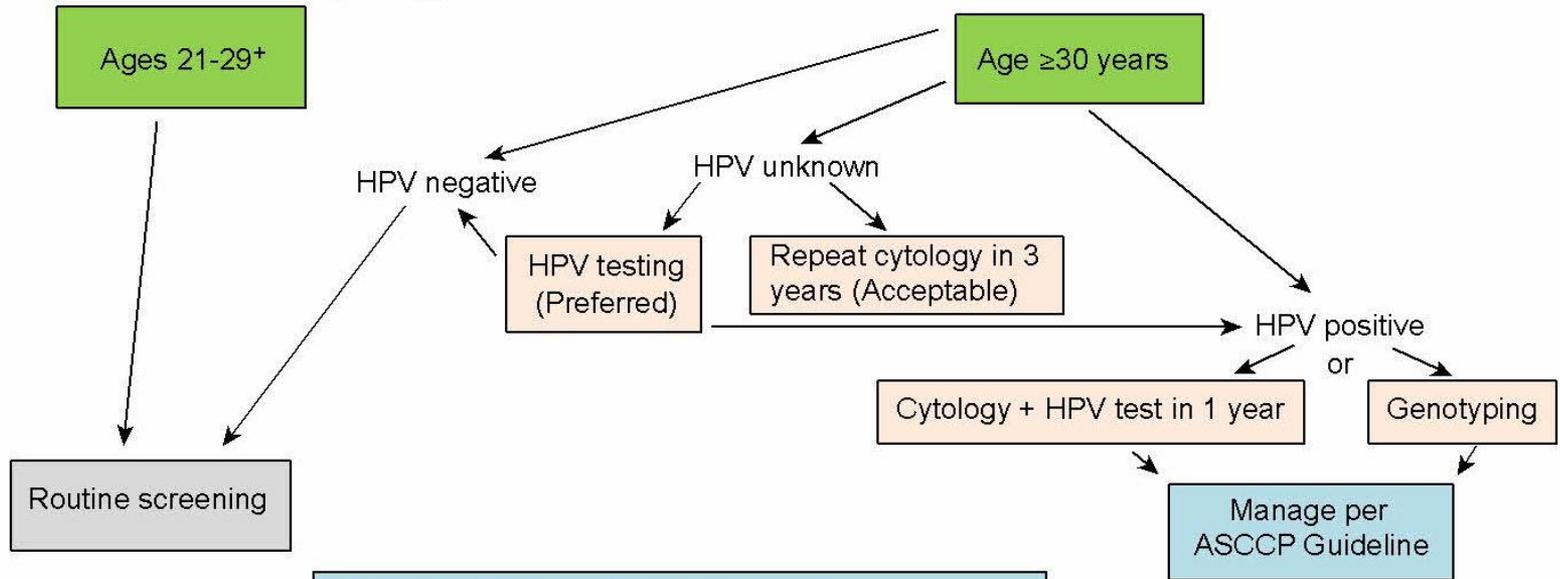
Note: "Manage per ASCCP Guideline" = Go to algorithm for the specific condition

# Negative but No/Insufficient Endocervical Cells

- Now shown not to be associated with missed disease
- In women  $\geq$  age 30, HPV test gives added margin of safety



### Cytology NILM\* but EC/TZ Absent/Insufficient



\*Negative for intraepithelial lesion or malignancy  
\*HPV testing is unacceptable for screening women ages 21-29 years

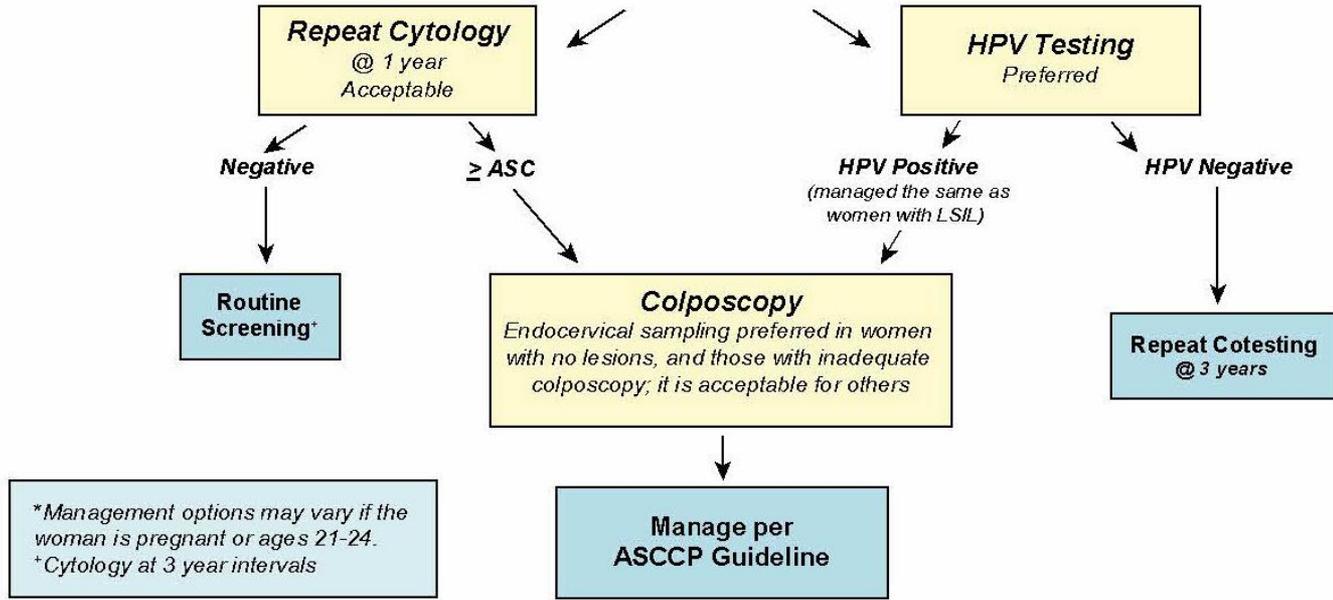
# ASCUS

(Atypical Cells of Undetermined Significance)

- Two choices for management
  - HPV Test
    - Best option
    - Reflex if possible
    - ASCUS + HPV = managed same as LSIL
    - ASCUS - HPV = greater risk than negative Pap
      - repeat co-testing in 3 years, even if > age 65
  - Repeat Pap in 1 year → colpo if any abnormality



# Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology\*



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ASC-US

# LSIL

(Low Grade Squamous Intraepithelial Lesion)

- Usually implies presence of HPV infection, HPV testing not needed
- But Pap is just a screening test:  
Up to 28% actually have CIN 2 or CIN 3



Colposcopy

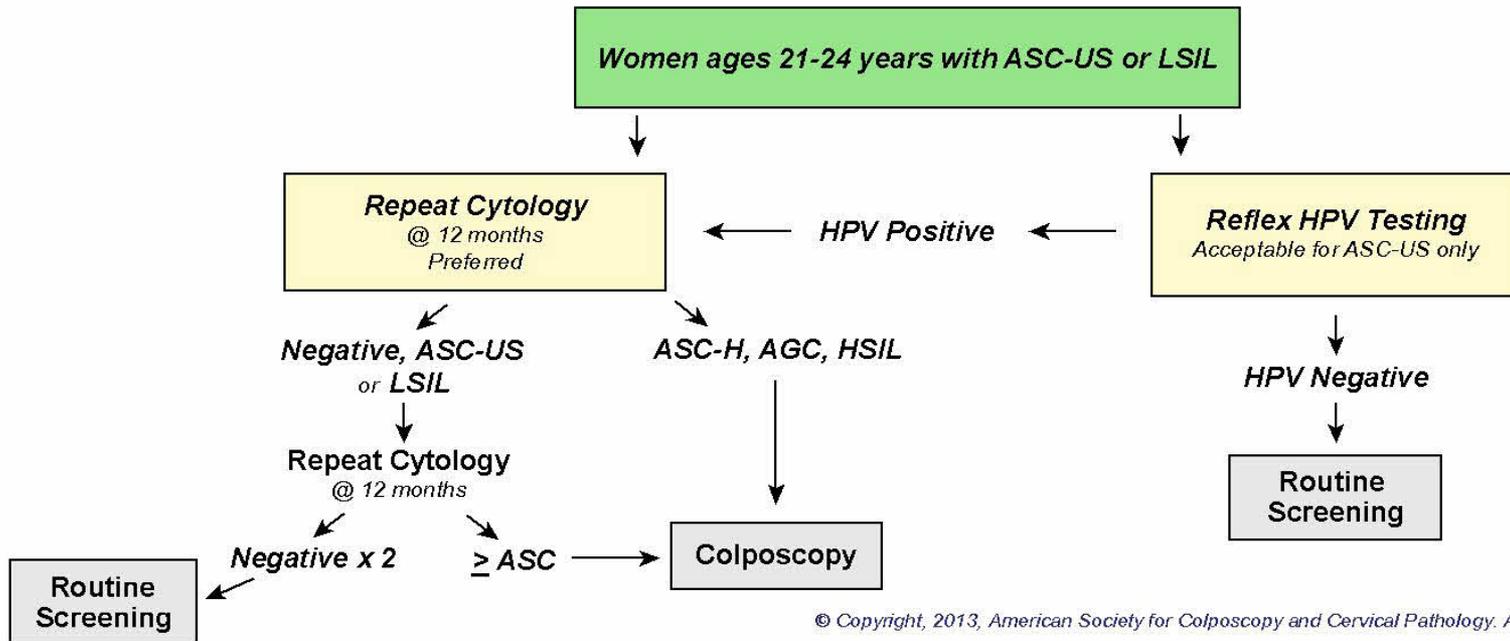
# Exception - Women Ages 21-24

- Risk of cancer 2/1,000,000 at this age
- High incidence of HPV infection
- Cervical injury has potential for harm to future pregnancies

→ Manage more conservatively



**Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)**



# Guidelines for Colposcopy

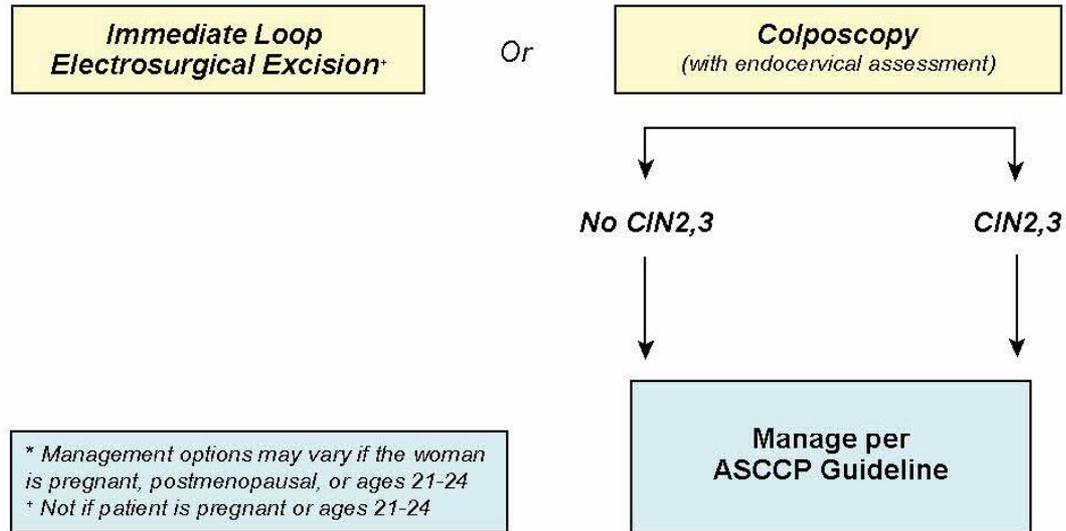
- Always recommended for
  - HSIL (High Grade Squamous Intraepithelial Lesion)
  - ASC-H (Atypical Squamous Cells, Can't Exclude HSIL)
  - AGC (Atypical Glandular Cells)
  - Cervical lesion or abnormal appearing cervix
    - Remove endocervical polyps\*
    - Otherwise, ALWAYS SEND TO COLPOSCOPY
      - regardless of Pap results
    - Even when invasive cervical cancer present, Pap can be negative!

\*WWC will cover

# Further Guidelines for Colposcopy

- Colposcopy is notoriously inaccurate
  - Even “the experts” miss 18-36%<sup>1</sup>
- Biopsies should be done with all colposcopies
  - Random biopsies +/- ECC if no lesions seen
  - 20.9% of random biopsies find CIN 2 or 3<sup>2</sup>
- All visible lesions should be biopsied
- The more cervical biopsies the better!

## Management of Women with High-grade Squamous Intraepithelial Lesions (HSIL)\*

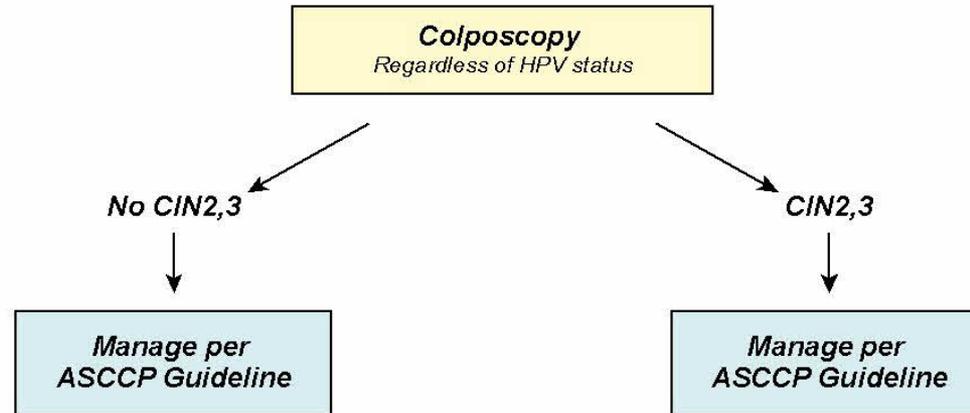


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HSIL

\*WWC will cover immediate LEEP

**Management of Women with Atypical Squamous Cells:  
Cannot Exclude High-grade SIL (ASC-H)\***

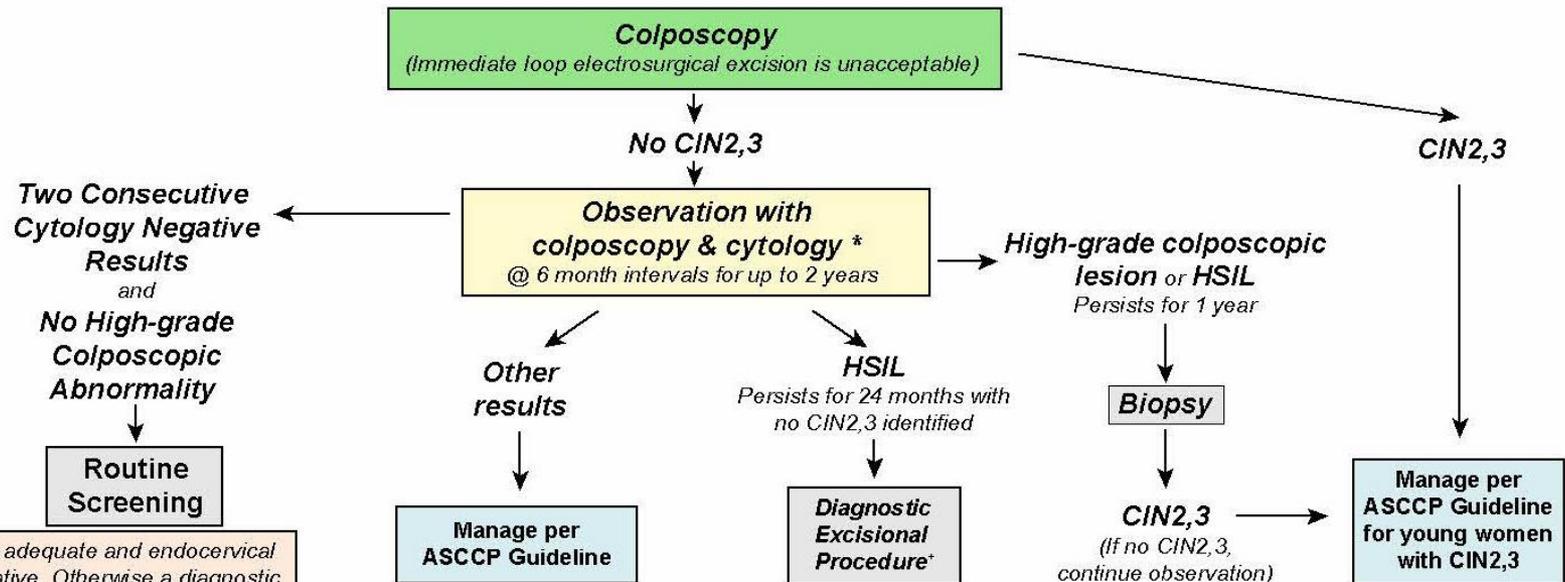


\* Management options may vary if the woman is ages 21-24.

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ASC-H

## Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

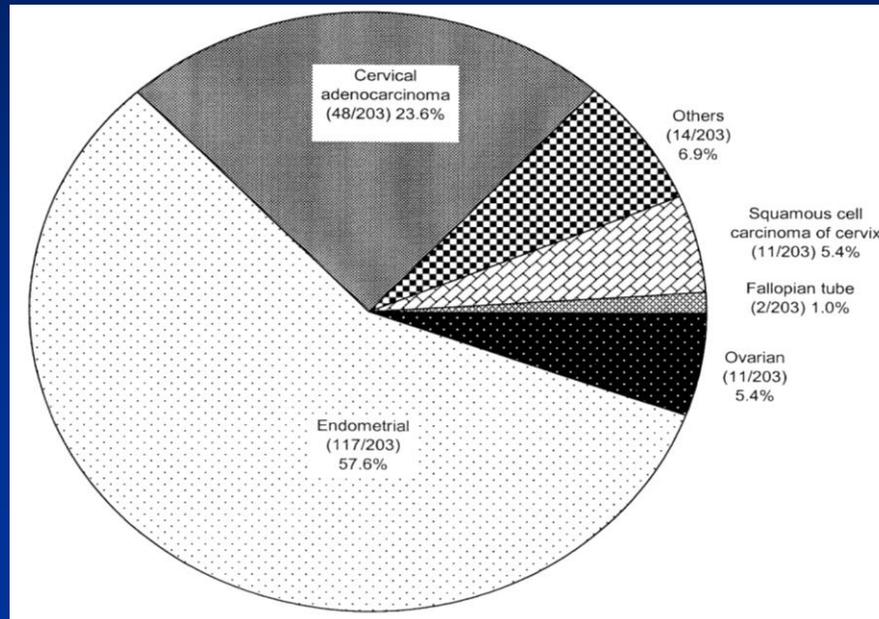


\*If colposcopy is adequate and endocervical sampling is negative. Otherwise a diagnostic excisional procedure is indicated.  
\*Not if patient is pregnant

# The Ominous AGC Pap

## Review of 3,890 AGC (AGCUS) Paps\*

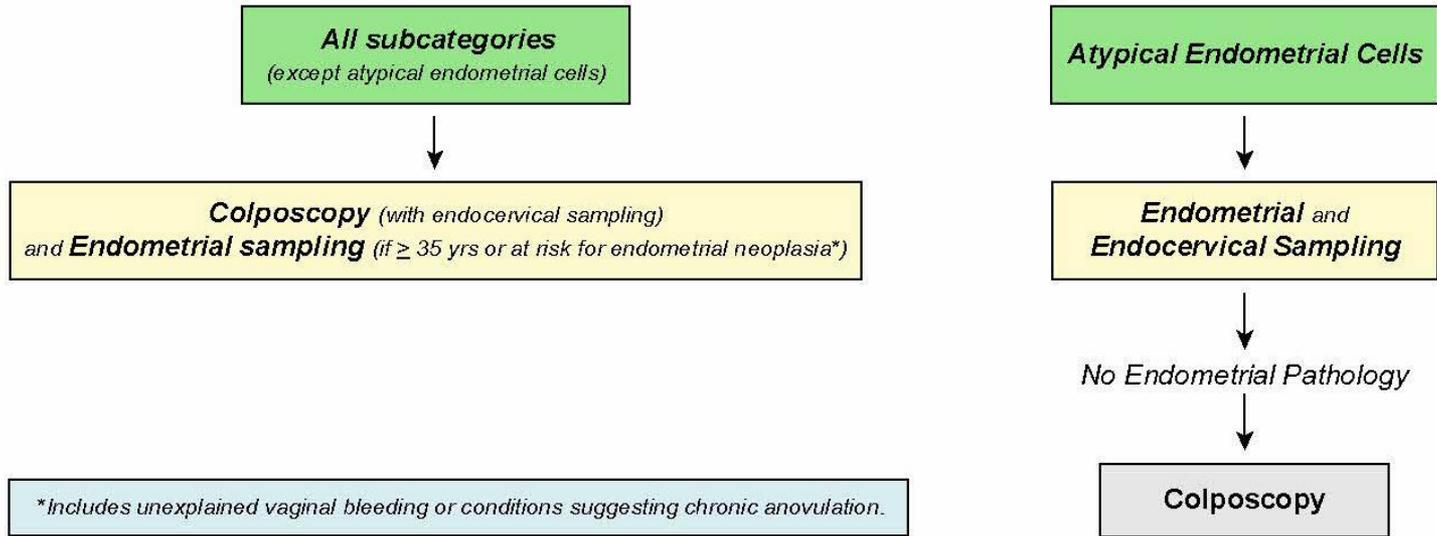
- 5.2% had a malignancy



- Another 23% had a significant finding
  - 8.5% LSIL
  - 11.1% HSIL
  - 2.9% AIS
  - 1.4% endometrial hyperplasia

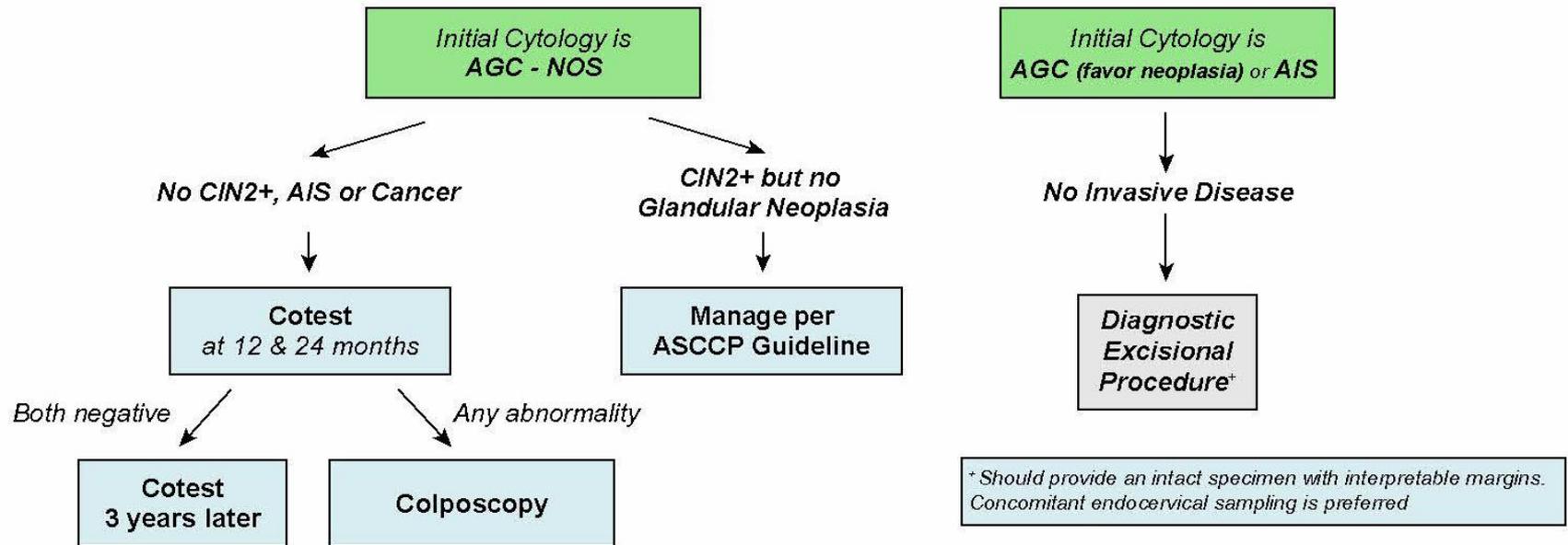
\* Obstet Gynecol 2006;107:701-8.

## Initial Workup of Women with Atypical Glandular Cells (AGC)



\*The only time WWC will cover EMB

## Subsequent Management of Women with Atypical Glandular Cells (AGC)



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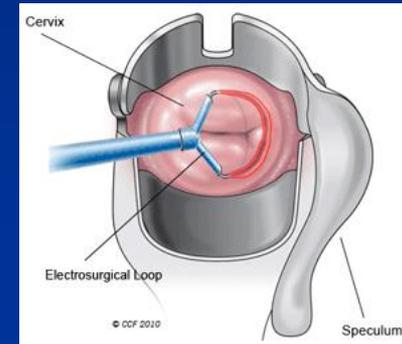
# Who needs Colposcopy?

- A 23-year-old with LSIL Pap?
- A 23-year-old with AGC Pap?
- A 27-year-old with LSIL Pap?
- A 40-year-old with ASCUS, HPV positive?
- A 50-year-old with ASC-H, HPV negative?
- A 60-year-old with LSIL, HPV negative?
- A 63-year-old with AGC, HPV negative?



# Treatments for CIN 2/3

- Ablative
  - Cryotherapy
  - Laser vaporization
- Excisional
  - Loop electrosurgical excision procedure (LEEP)
  - Laser excision/conization
  - Cold knife cone
- All ~90% effective<sup>1,2</sup>
- Follow-up important
  - Cotesting q 12 mos x 2, then in 3 years
    - If negative, cotesting every 5 years for  $\geq 20$  years<sup>3</sup>
    - If positive, re-colposcope



1. Obstet Gynecol 1998;92:737-744. 2. Cancer Treatment Rev 2006;32:515-23.

3. BMJ 2007;335:1077.

# Risks of Treatment

- LEEP and conization may be associated with
  - Preterm delivery
  - Premature ruptured membranes
  - Low birth weight
- Ablation appears to have fewer pregnancy risks
- In a comparative study with cryo and laser, LEEP had highest risk of complications\*
  - 8% bleeding > 24 hrs post treatment
- But LEEP and cone provide histologic specimens

→ Individualize therapy

# Individualized Therapy

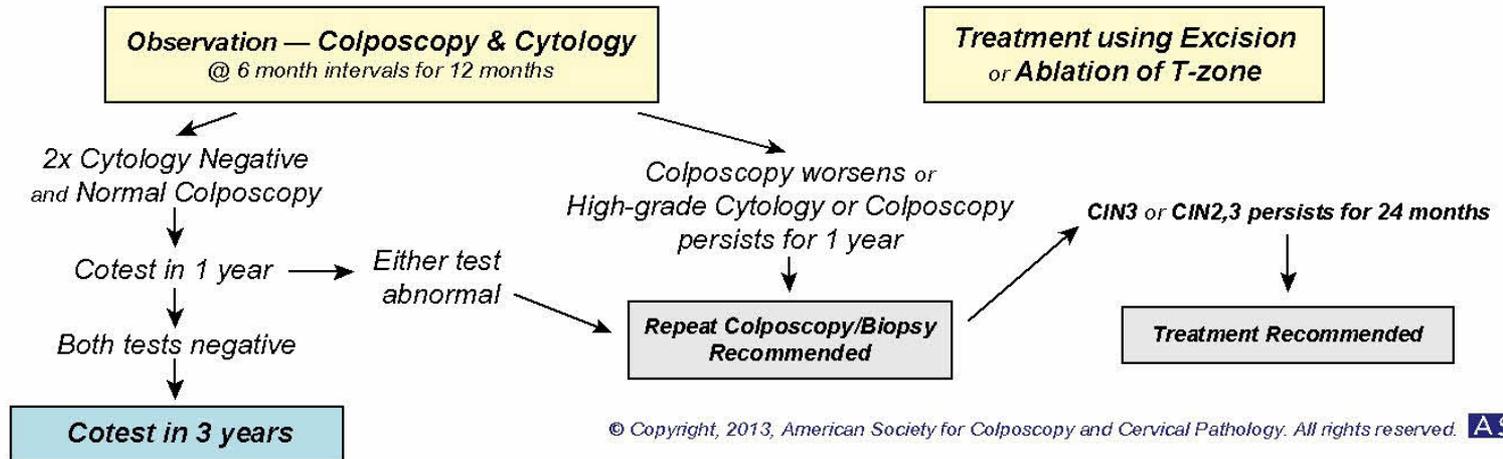
- Avoid treating young women and nullips whenever possible, and minimize treatment for CIN I in all age groups
- Treat CIN 2,3 in women  $\geq 30$  and those who have completed childbearing
- Can closely follow CIN 2,3 in young women (age 21-24 or who plan future pregnancy)



## Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2,3 (CIN2,3) in Special Circumstances

### Young Women with CIN2,3

*Either treatment or observation is acceptable, provided colposcopy is adequate. When CIN2 is specified, observation is preferred. When CIN3 is specified, or colposcopy is inadequate, treatment is preferred.*



# Individualized Therapy

- Ablative therapy preferred in women with plans for future childbearing
- Always need excisional therapy if unsatisfactory colposcopy, lesion in endocervical canal, positive ECC, or previous failed therapy



# What testing is needed?

- 49 year-old with history of hysterectomy at age 39 due to CIN II/III
- 53 year-old with history of hysterectomy with ovaries removed for endometriosis. Exposed to DES in utero
- 60 year-old with negative Pap and HPV two years ago, white lesion noted on cervix at annual this year



# More Questions

- 61 year-old had hysterectomy for fibroids, cervix still present. Pap neg (no ECC) but +HPV. Last Pap neg 2-3 years ago. What testing does she need? What will WWC cover?
- 52 year-old with negative Pap two years ago. Pap done again this year showed HSIL. What will WWC cover?



# Importance of Meticulous Follow-up

- Abnormal Pap tests
  - WWC: time from Pap to diagnosis < 60 days
- Abnormal colposcopies
  - WWC: time from colposcopy to treatment < 60 days
- Continued follow-up after treatment ( $\geq 20$  years)

\*\*\*Tracking system more important than ever now that we are treating less and following more\*\*\*

WWC: Track until patient completes treatment and F/U, informed refusal in chart, or 3 documented attempts to contact patient (one must be by certified letter)



# Cervical Cancer Prevention

- Safer sexual practices
  - Condoms 70% effective in preventing transmission\*
- Avoid smoking
- Healthier lifestyle

\* N Engl J Med 2006;354:2645-2654.

# VACCINES

- Gardasil<sup>®</sup>
  - Prevents infection with HPV 16 & 18 (70% of CIN/CA) and 6 & 11 (90% of genital warts)
  - Also approved for prevention of vulvar, vaginal and anal intraepithelial lesions and CA
  - 3-dose regimen recommended for all females **and males** ages 11-12
    - Approved for ages 9-26
- Does not accelerate clearance of the virus\*

**Coming soon:** Gardasil 9<sup>®</sup> – includes HPV 31, 33, 45, 52, 58 to prevent ~ 85% of cervical cancers

\*JAMA 2007;298:743-53.

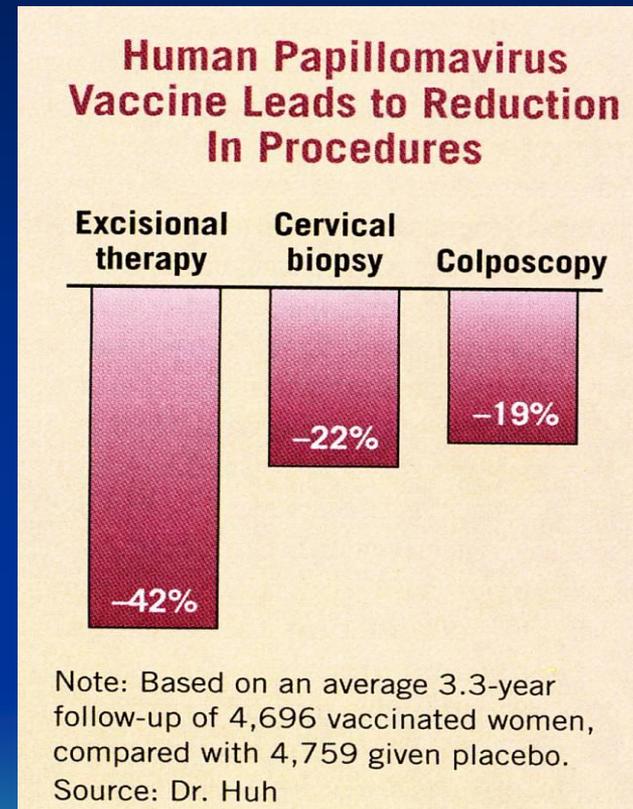
# VACCINES

- Cervarix<sup>®</sup>
  - Prevents infection with HPV 16 & 18
  - 3-dose regimen recommended for all females ages 11-12
    - Approved for ages 10-25
  - New adjuvant → higher antibody response
    - Likely confers longer-lasting immunity
    - Likely offers ↑ cross-protection against related viruses



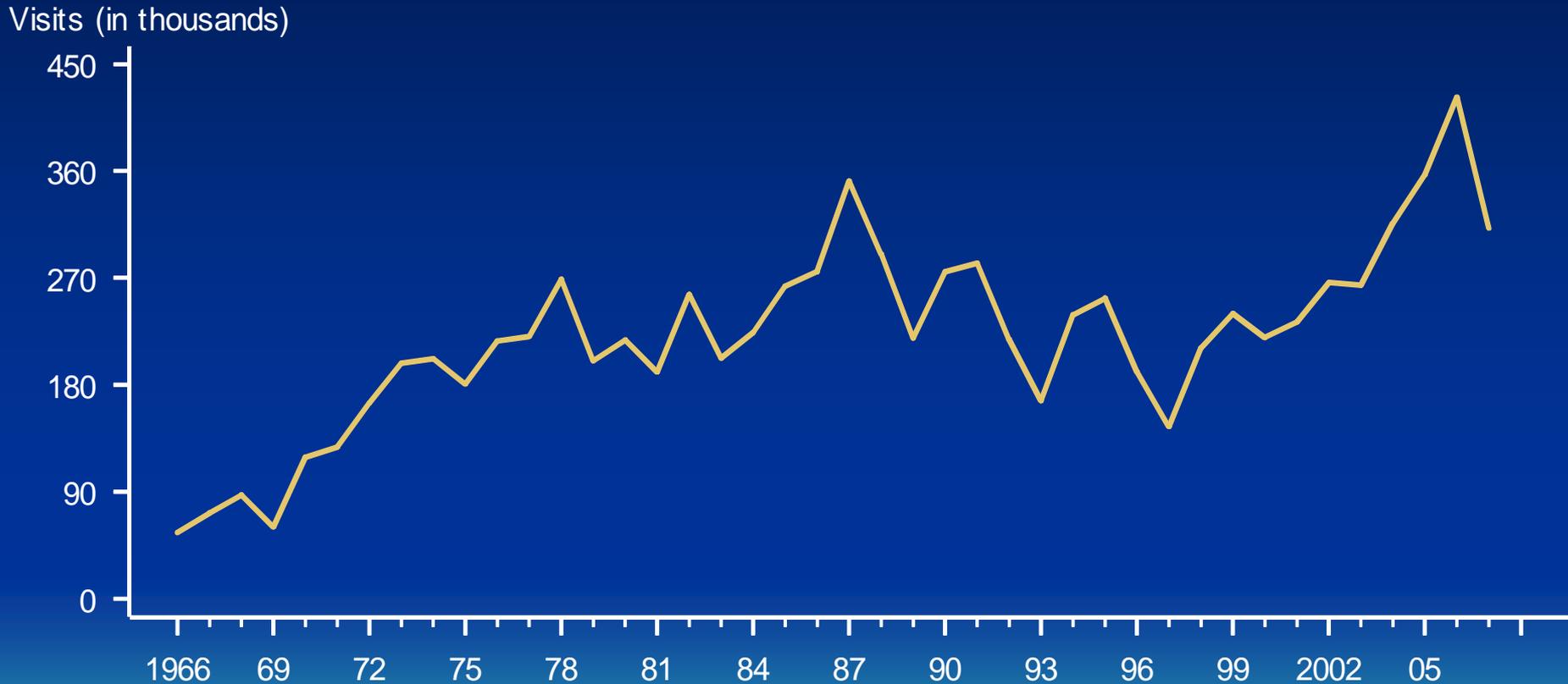
# Results So Far

- 16% ↓ ASCUS
  - 23% ↓ ASCUS + HPV
  - 35% ↓ ASCUS r/o HSIL
  - 14% ↓ LSIL
  - 43% ↓ HSIL<sup>1</sup>
- 
- 50% less HPV in women ages 14-19<sup>2</sup>



# Genital warts

## Initial visits to physicians' offices: United States, 1966–2007



Note: The relative standard error for genital warts estimates range from 17% to 29.3%.

SOURCE: National Disease and Therapeutic Index (IMS Health)

# The Promise of Global Cervical Cancer Prevention