

# Pap & HPV Testing and Management of Abnormal Tests in Women Ages 21-65

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WWC Medical Director



# Objectives

- Describe our present 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
- Identify ASCCP recommendations for management of abnormal Pap tests



# Estimated Cancer Incidence in Women (US, 2016)

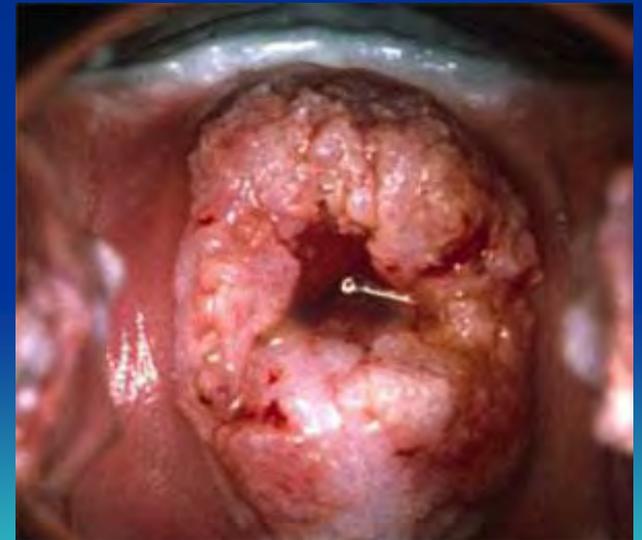
- Breast - 29%
- Lung – 13%
- Colon & rectum – 8%
- Endometrium – 7%
- Thyroid – 6%
- Non-Hodgkin lymphoma – 4%
- Melanoma – 3%
- Leukemia, Pancreas, Kidney - 3%
- Ovary – 2.6%

#13 Cervix – 1.5%

# Cervical Cancer in the US

## Epidemiology

- 1.5% of all cancers in US women
- 4% of all US gynecologic cancer deaths
- Median age 45-55 years



# Cervical Cancer Risk Factors

- Early age at first intercourse
- Multiple sex partners
- Socioeconomic class, race
- Smoking

Same as risk factors as for STIs →  
now known to be caused by HPV



# Virology of Human Papillomavirus (HPV)

- DNA virus in papovavirus family
- Epitheliotropic
- Over 120 subtypes identified
  - at least 40 attracted to mucosa/genital tract
  - low risk - 6, 11, 42, 43, 44
  - high risk - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68



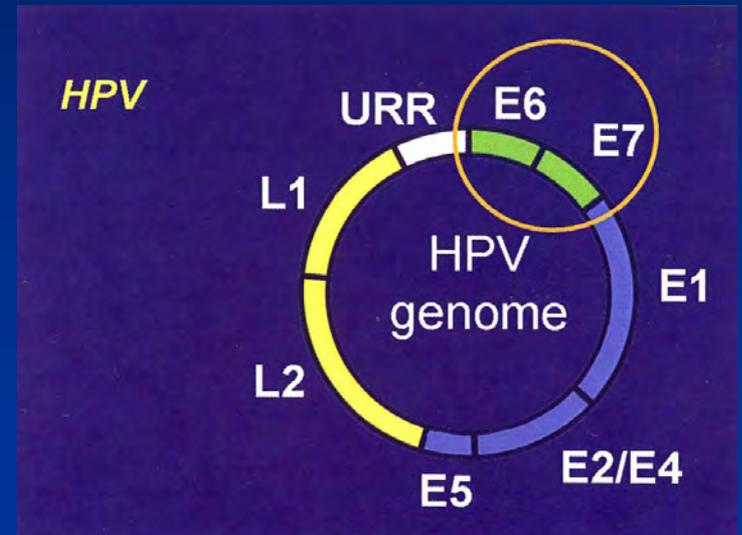
# Natural History of HPV Infection

- 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

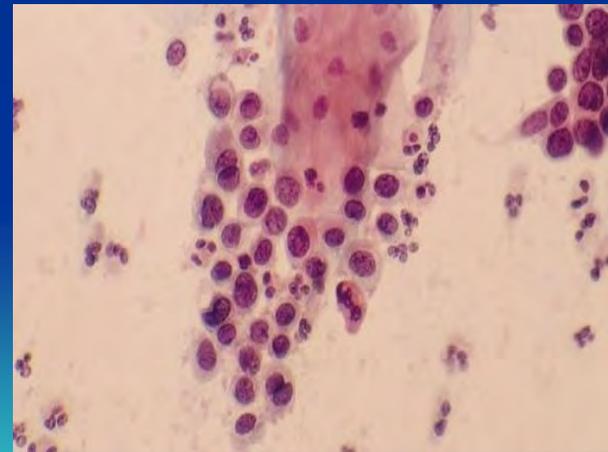
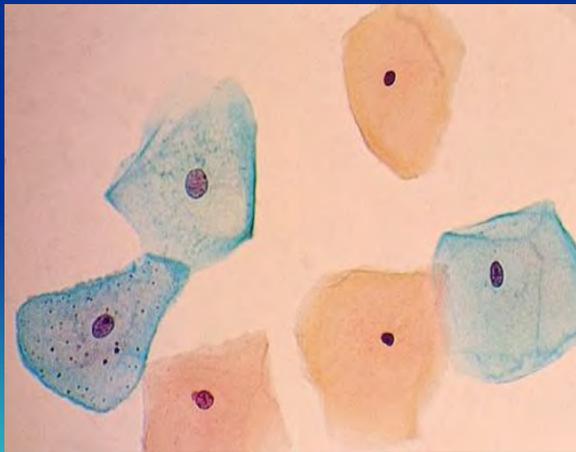
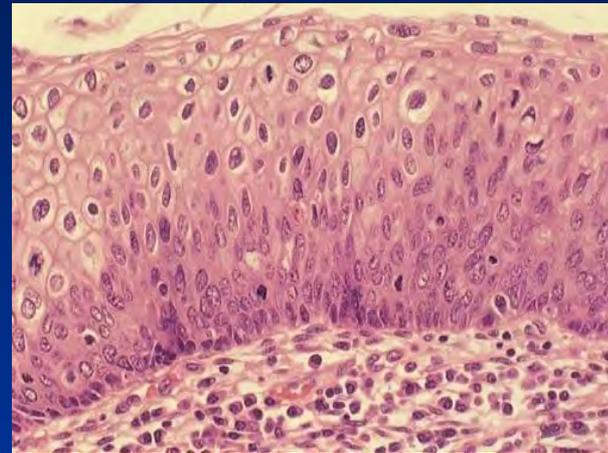
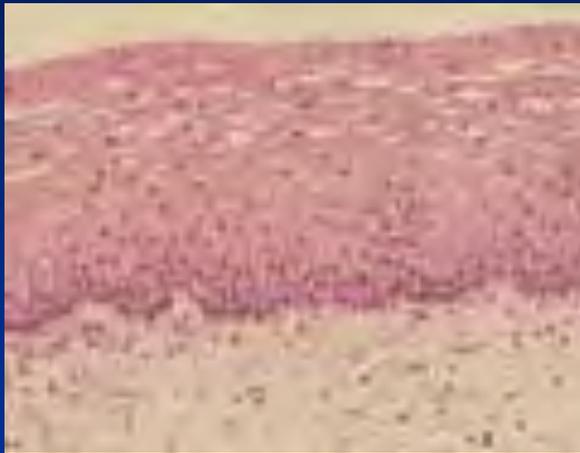


# Activation of Oncogenes

- 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



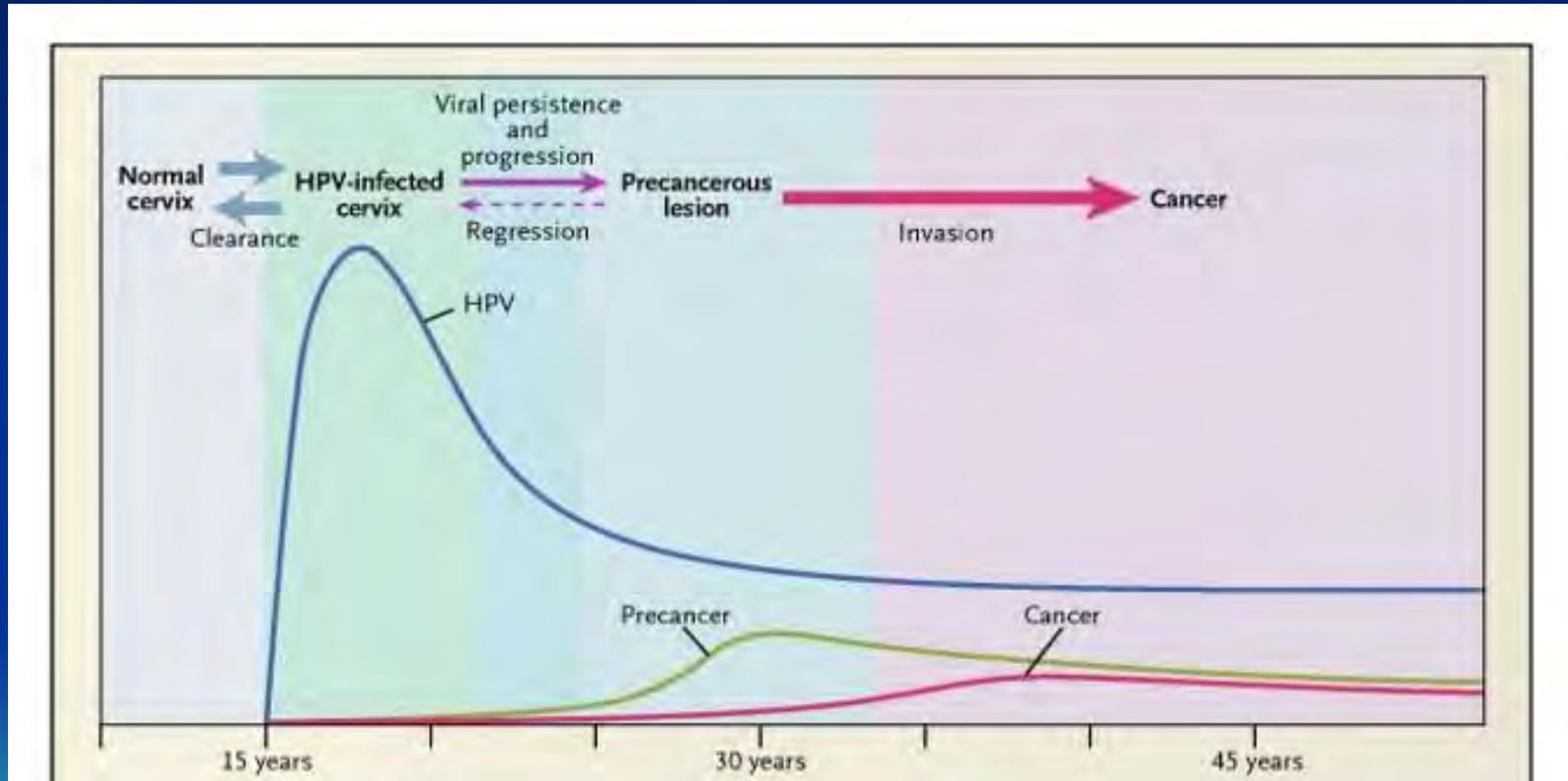
# Progression of Cervical Neoplasia



# 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 Current 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 Cotesting

- Before age 30, high prevalence of HPV →  
Do not cotest
- In women  $\geq 30$ , cotesting 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 Current 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
  - Cotest at 1, 2, and 5 years; colposcope if either test +
  - Continue routine testing for at least 20 years
- Women treated for cervical cancer
  - Continue annual testing indefinitely



# NOT

## Exceptions to Current Guidelines

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



# Advantages of Current 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



# 2012 Consensus Guidelines for Management of Abnormal Pap Tests

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



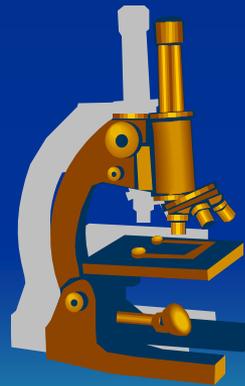
# Guidance on HPV Testing



# 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

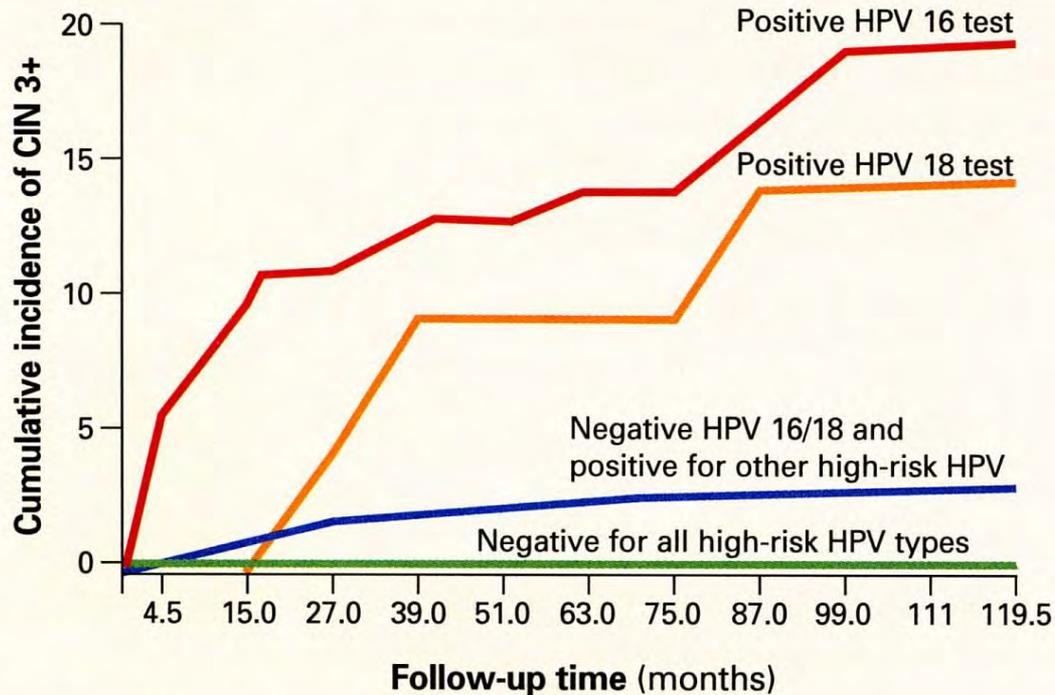
- Minimize HPV testing in woman < age 30
- The only screening indication is for women age  $\geq 30$  in addition to Pap\*
  - Co-testing recommended in this group
    - If both tests negative, do not repeat for 5 yrs
    - If abnormal Pap, follow ASCCP Guidelines
- But what about Pap negative, HPV + ?

\*Covered by WWC

# The Role of HPV 16/18 Genotyping



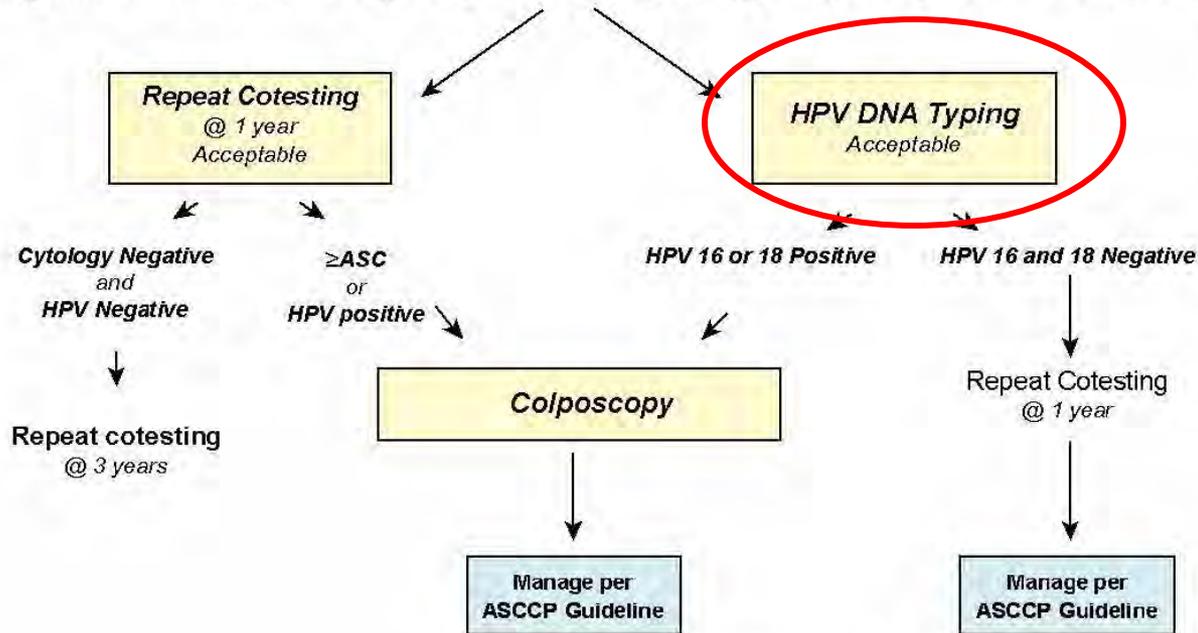
## Positive HPV 16 or 18 linked to 14% to 17% incidence of CIN3+



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.

Normal Cytology/HPV Positive

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



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# WWC now covers HPV genotyping!

# More Roles for HPV Testing

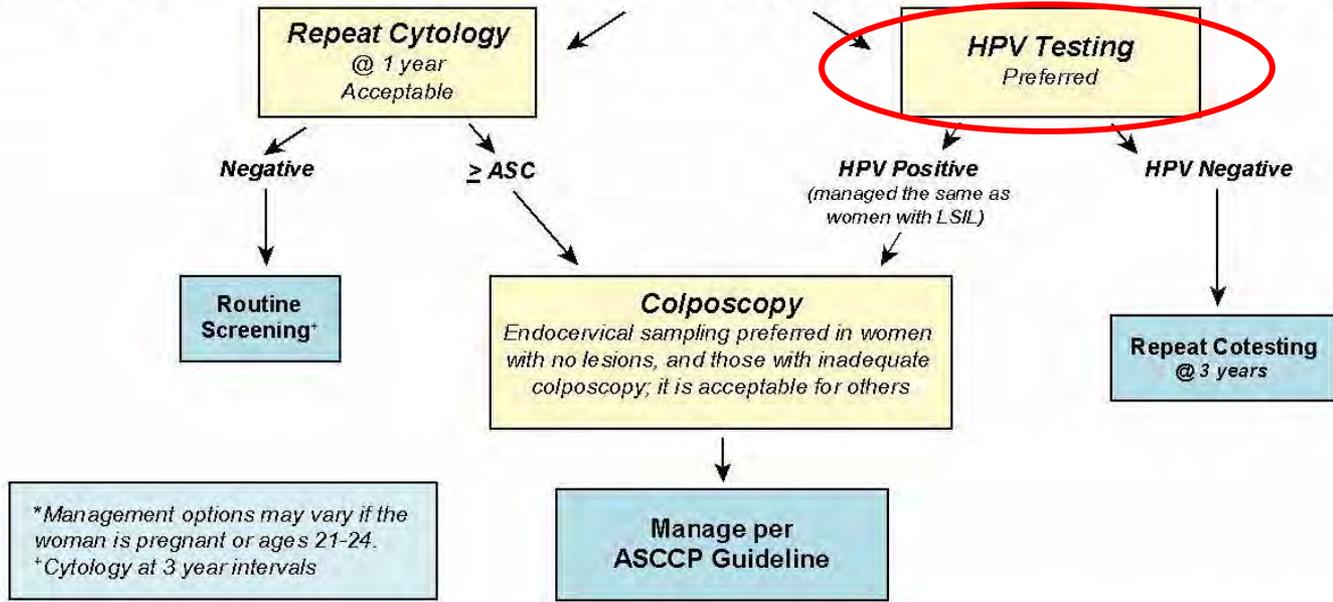
- Co-testing follow up after abnormal or treatment
- Important for triage
  - ASCUS Paps (reflex testing)



# Management of Abnormal Paps



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



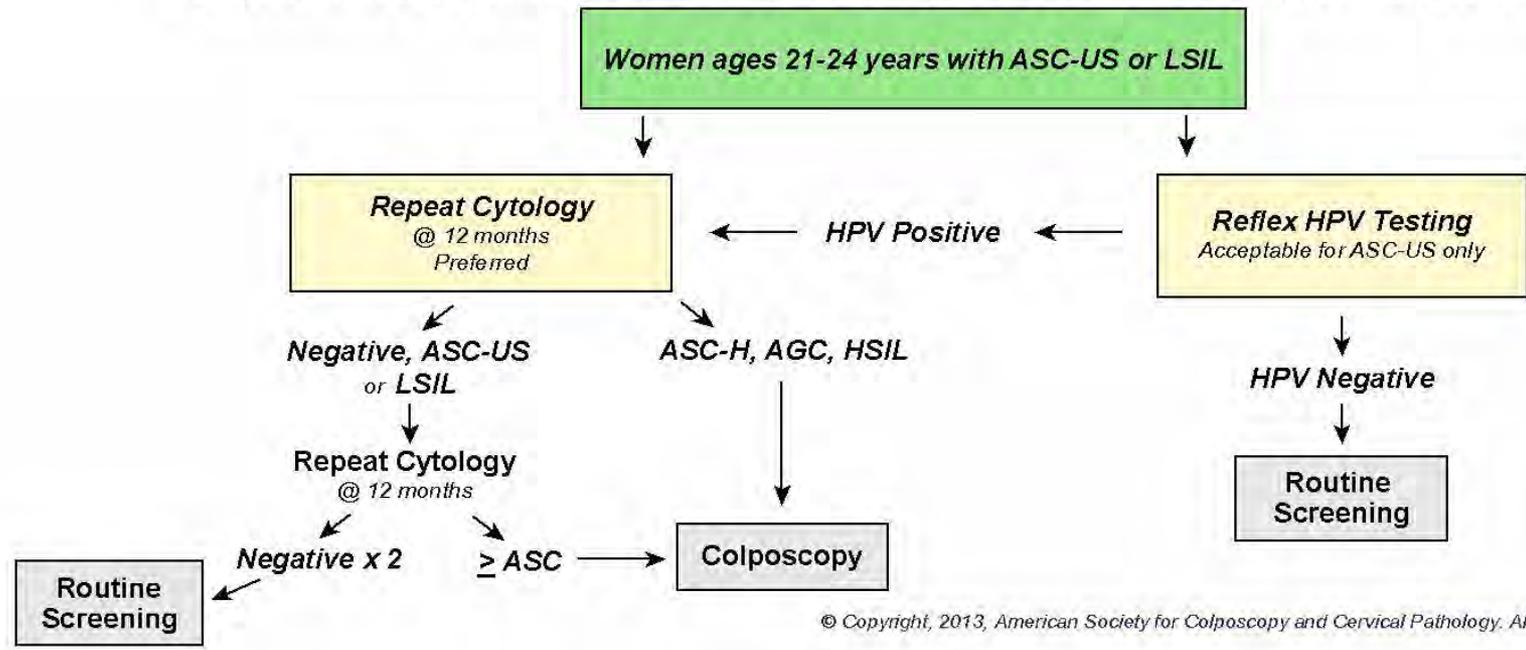
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ASC-US

# Exception - Women Ages 21-24

ASC-US or LSIL: Age 21-24

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



# LSIL

(Low Grade Squamous Intraepithelial Lesion)

- 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

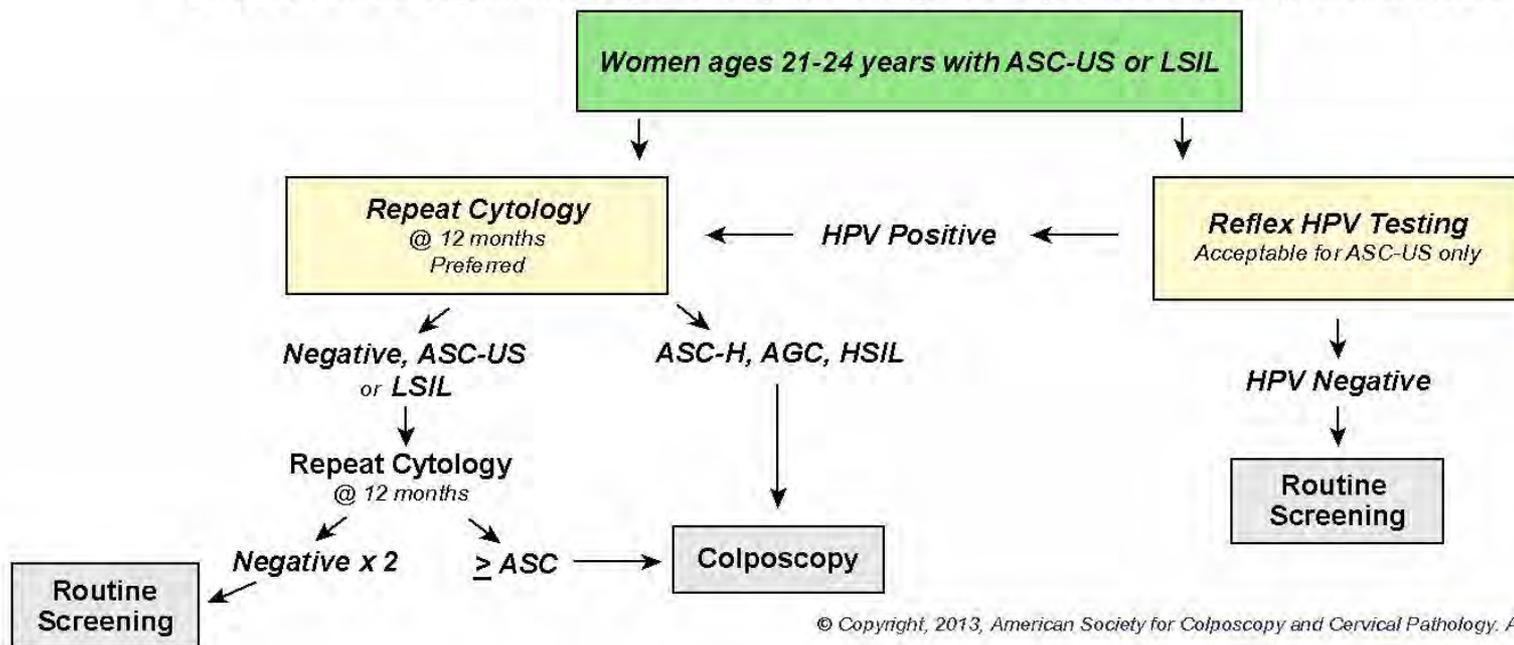
# Exception - Women Ages 21-24

- 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)

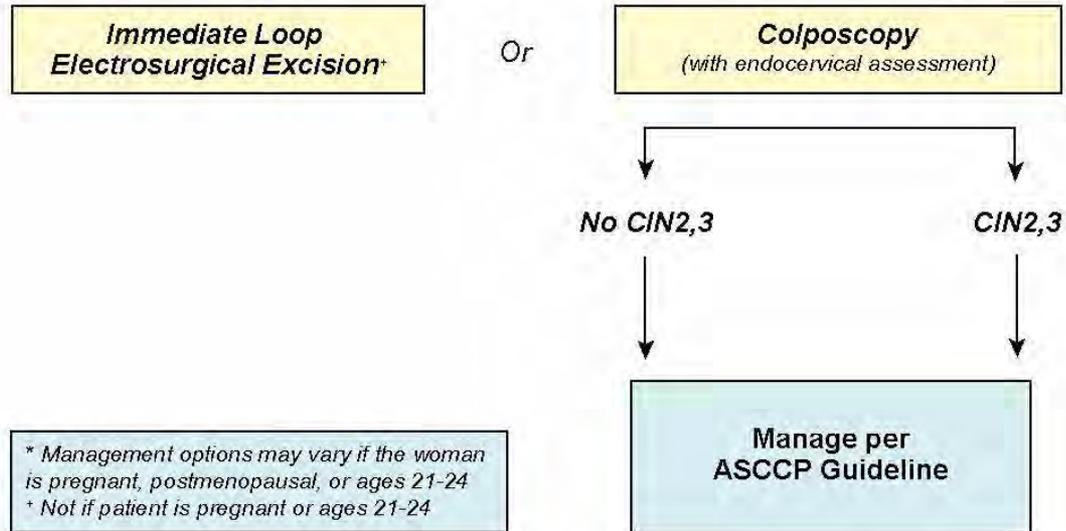


# Guidelines for Colposcopy

- 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

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

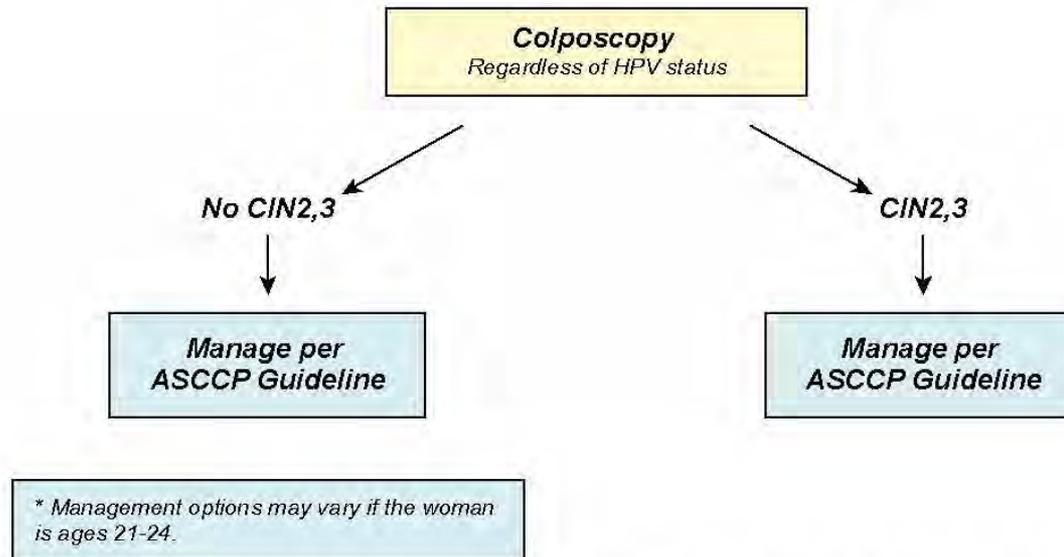


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HSIL

**\*WWC will cover immediate LEEP if indicated**

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



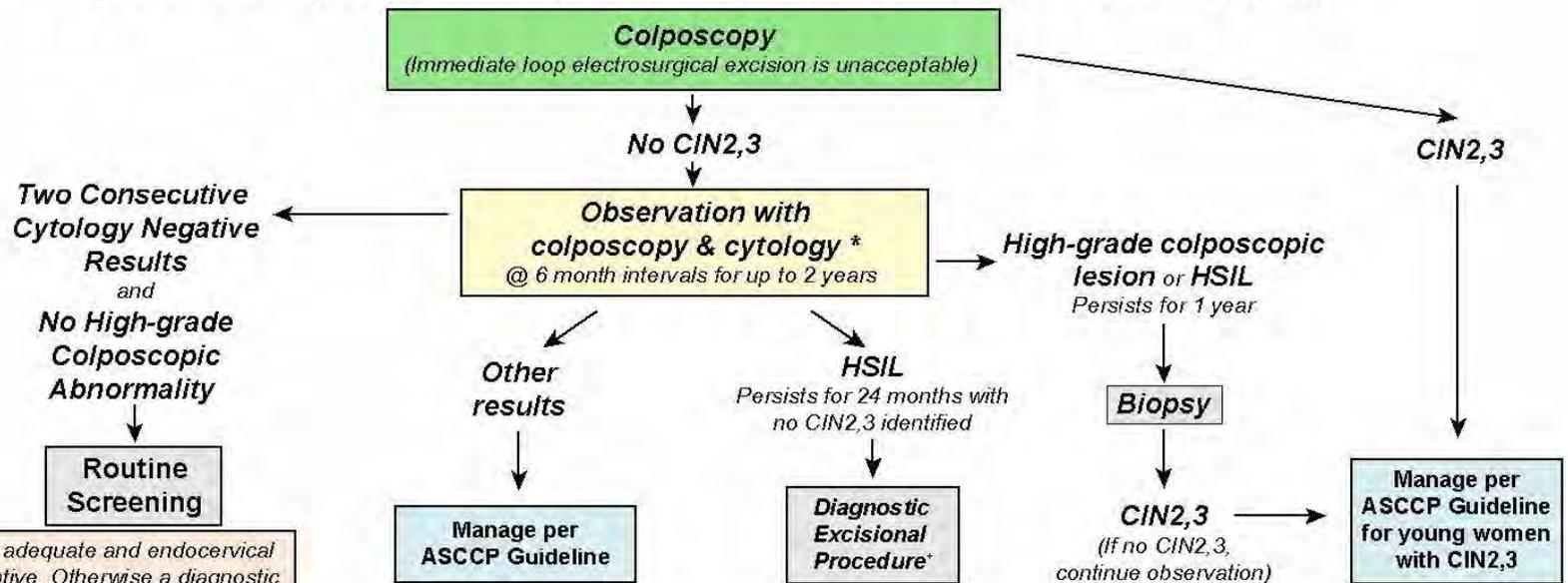
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ASC-H

# Exception - Women Ages 21-24

ASC-H and HSIL: Age 21-24

## 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)



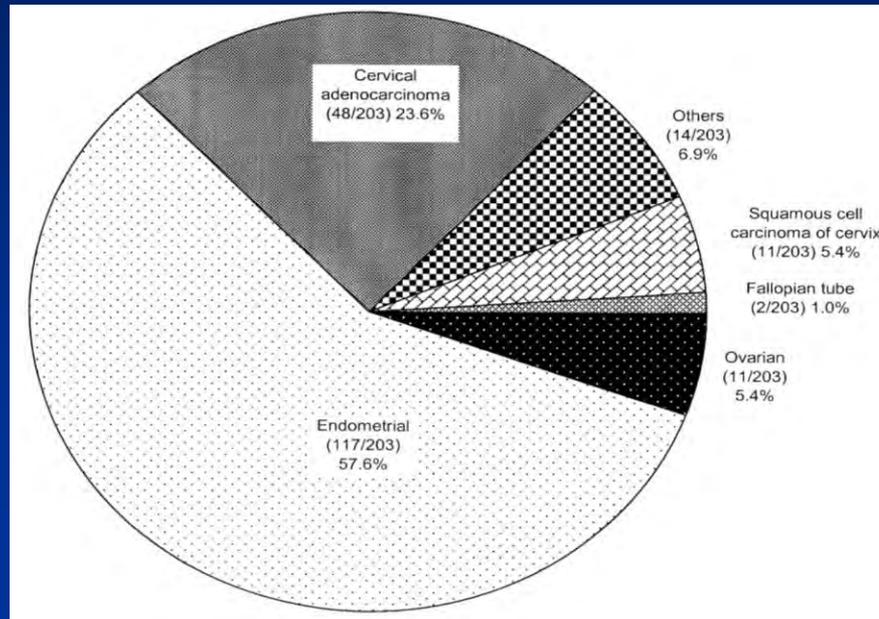
\*If colposcopy is adequate and endocervical sampling is negative. Otherwise a diagnostic excisional procedure is indicated.  
\*Not if patient is pregnant

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# The Ominous AGC Pap

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

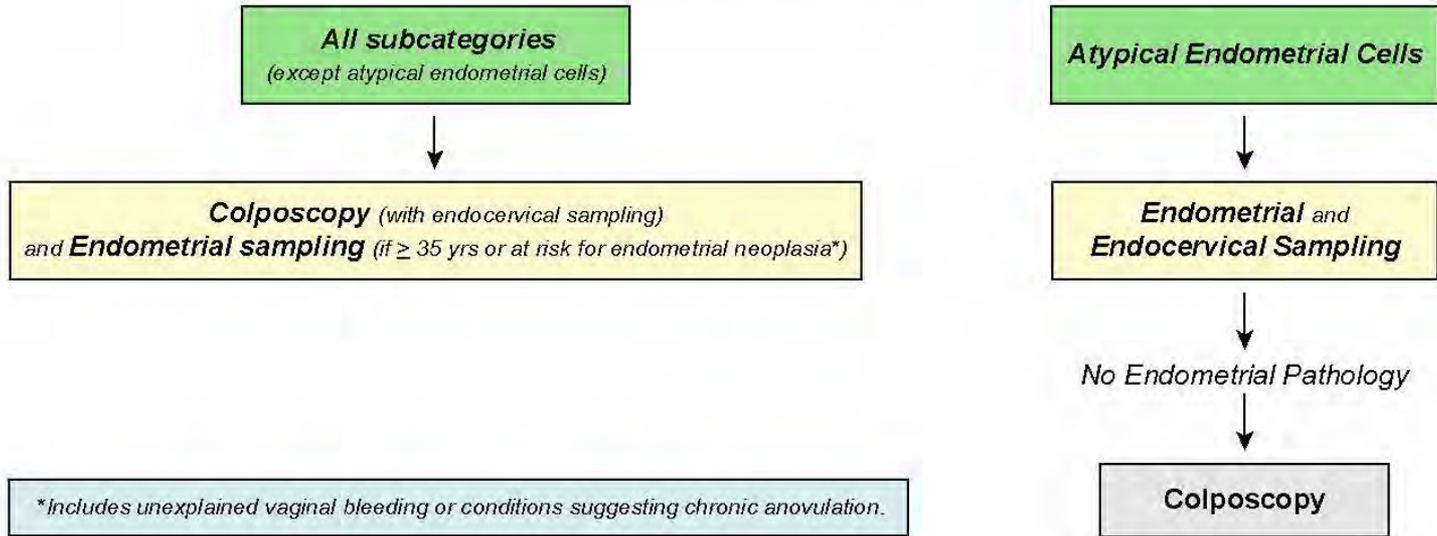
- 5.2% had a malignancy



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

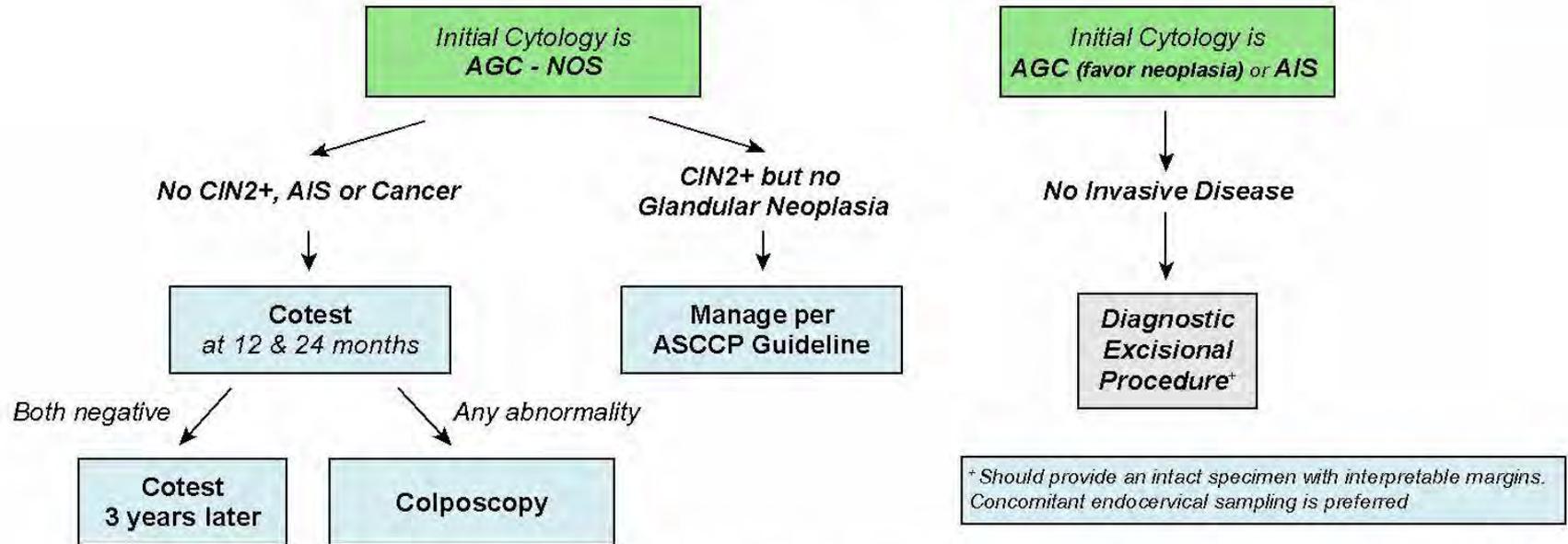
\* Obstet Gynecol 2006;107:701-8.

## 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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AGC Subsequent Management

# 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!

# Case

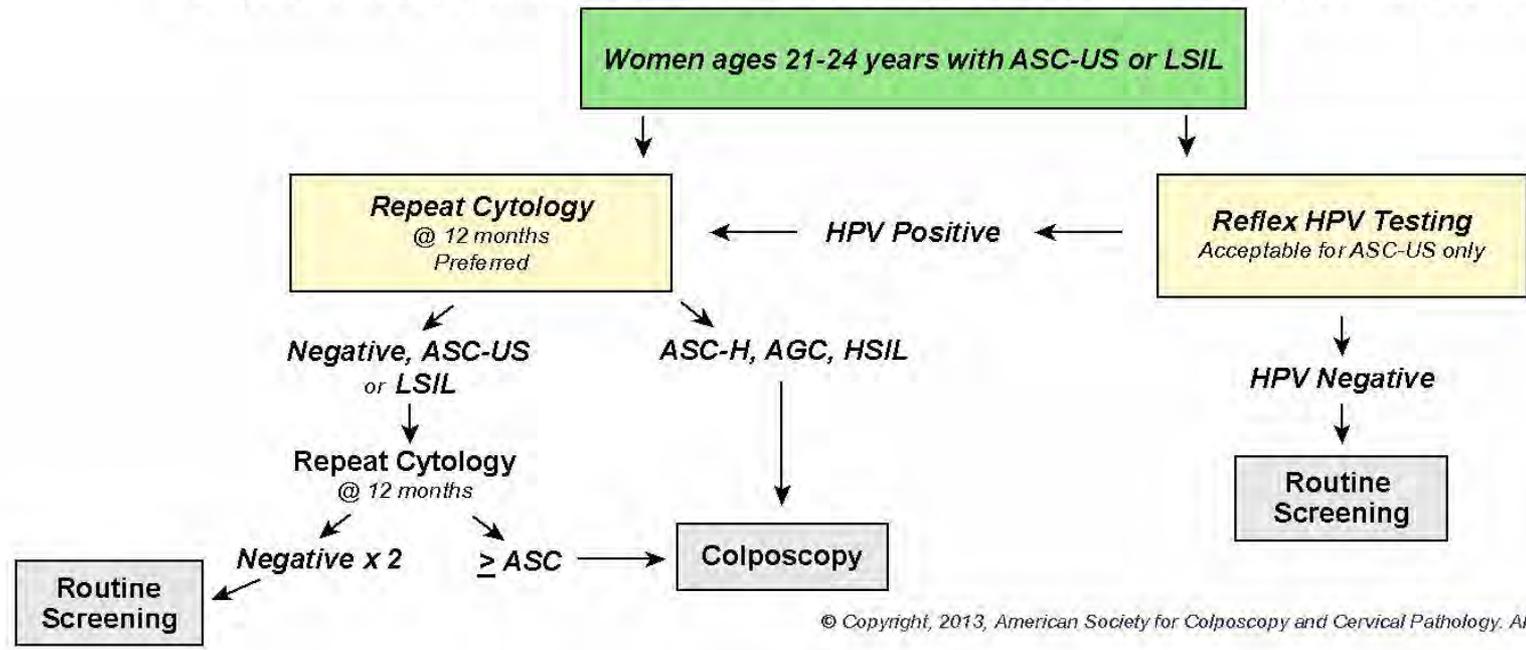
- Naomi is 24 years old and had a Pap test covered by WWC. The result was LSIL.
- Naomi should
  - a) Be referred for colposcopy
  - b) Get an HPV test
  - c) Repeat Pap in one year
- Which would be covered by WWC?



# Exception - Women Ages 21-24

ASC-US or LSIL: Age 21-24

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



# Case

- Mary is a 37 year old G3P3 presenting for an annual exam. She reports having an abnormal Pap 9 years ago with no follow up. She now qualifies for cotesting covered by WWC. Results: Pap -, HPV +.
- What would be her ideal follow up?
  - a) Colposcopy
  - b) HPV Genotyping
  - c) Repeat Pap and HPV in one year

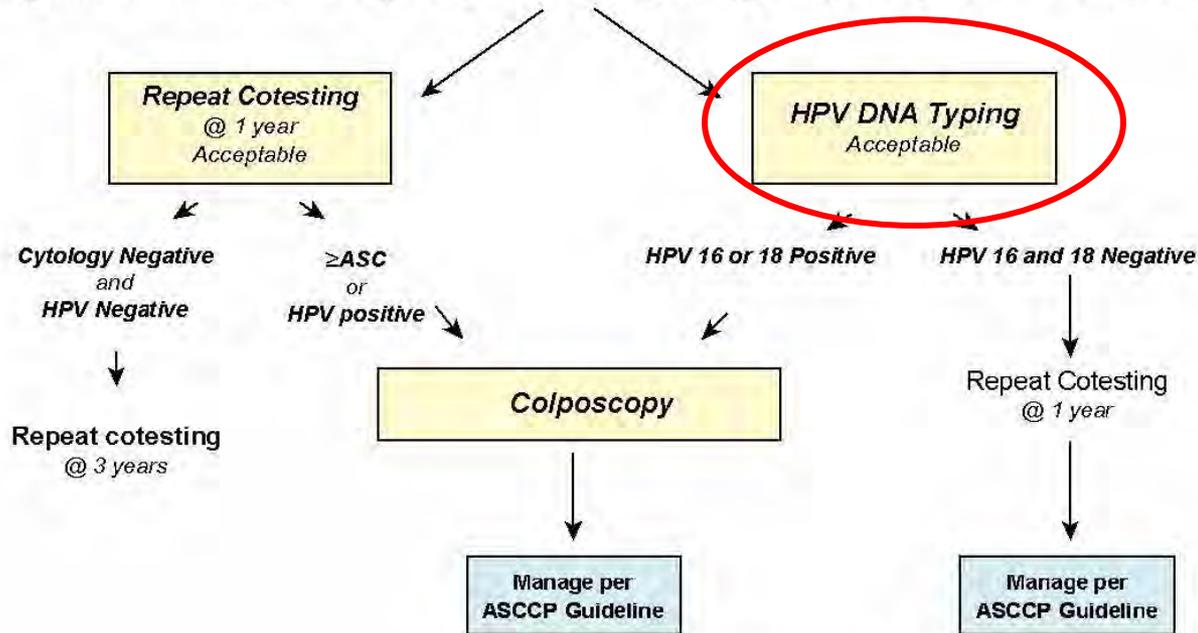
# Case (continued)

- HPV genotyping reveals HPV 16. What is the next step?
  - a) Colposcopy
  - b) LEEP
  - c) Repeat Pap and HPV in one year
- What will WWC cover?



Normal Cytology/HPV Positive

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

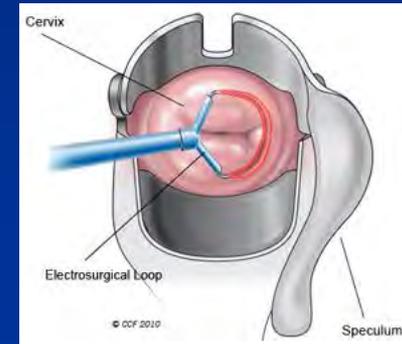


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# WWC now covers HPV genotyping!

# 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)



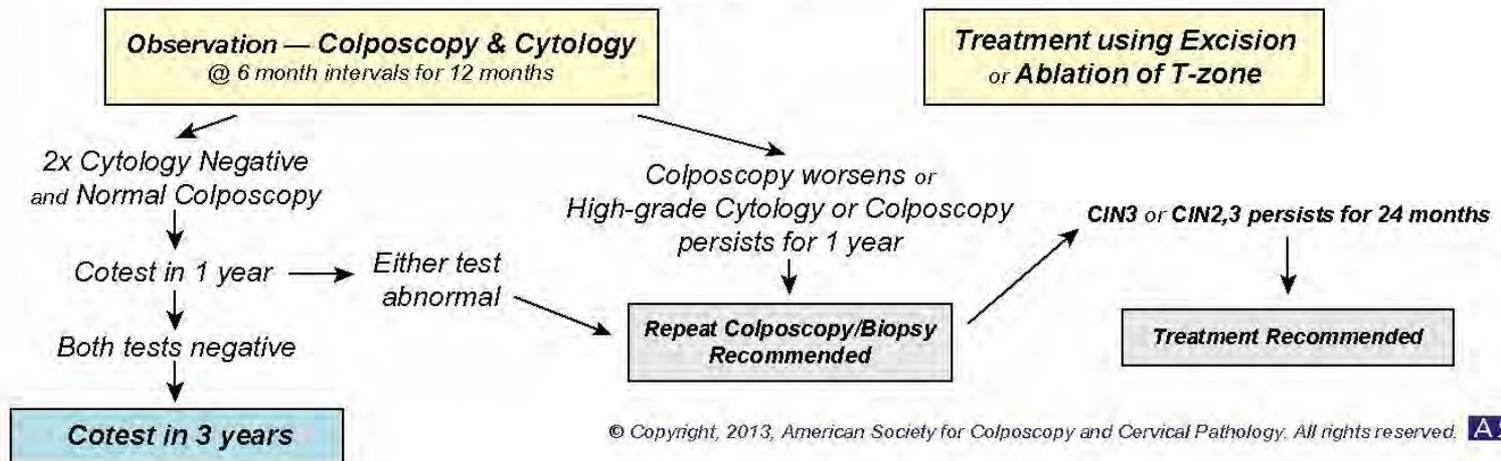
# Exception - Women Ages 21-24

CIN2,3 in Young Women

## 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.*



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# 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



# Case

- Tanya is a 27 year old G0 who receives a Pap covered by WWC. Result: HSIL.
- What should Tanya's management be?
  - a) Colposcopy
  - b) HPV Test
  - c) Repeat Pap in one year



# Case (continued)

- Colposcopy reveals a single area of CIN 2-3 from 1-3 o'clock, ECC negative. What are her treatment options?
  - a) Cryotherapy
  - b) LEEP
  - c) Pap with HPV in one year
  
- How will WWC manage this?



# Prevention of HPV-Related Cancers

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

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

# VACCINES

- Gardasil®
  - 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\*

**Now:** Gardasil 9® – includes HPV 31, 33, 45, 52, 58 to prevent 85-90% of cervical cancers

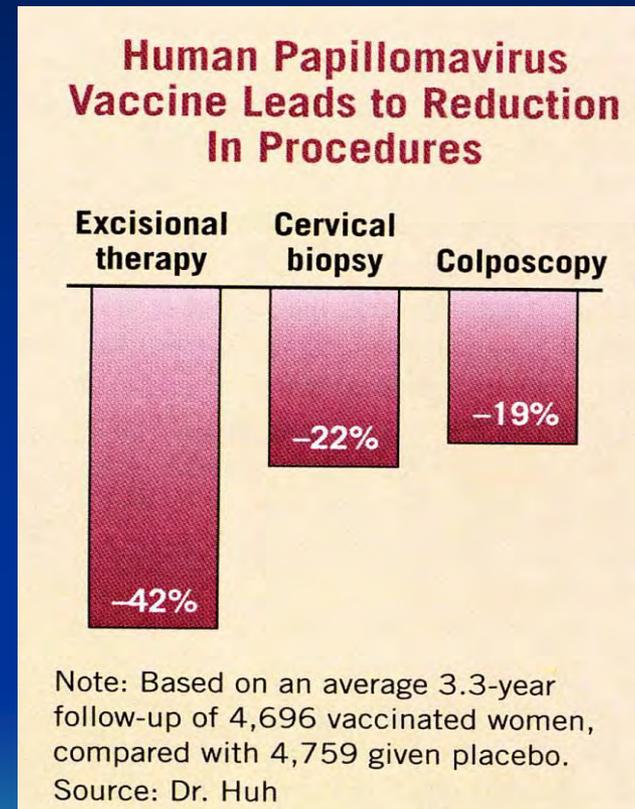
\* JAMA 2007;298:743-53.

# Case

- Sue is 21 years old and presents for her annual exam and OCP refill. When you advise her that she should have her first Pap test this year, she says she doesn't need it because she has had all 3 Gardasil shots.
- What do you tell her?
  - a) She is correct, she doesn't need the Pap
  - b) She should get an HPV test to see if she is immune to all the high-risk types
  - c) She should get the Pap test

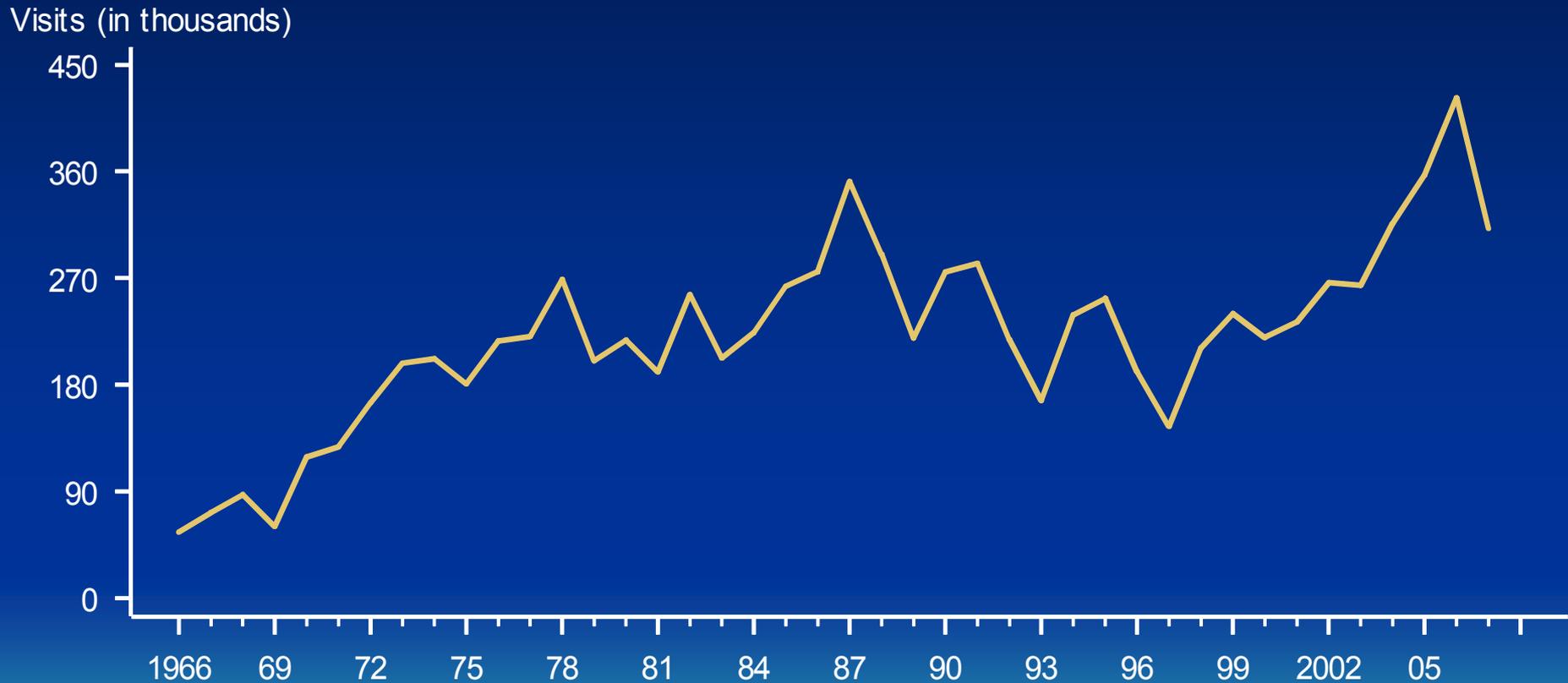
# Since Gardasil Became Available

- 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