

Updated Guidelines for Cervical Cancer Screening and Prevention

Management of Abnormal Results

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Objectives

- Overview of cervical cancer and oncogenic HPV
- Review of cervical cancer prevention and screening recommendations
- Case based review of management of abnormal Pap results utilizing 2012 updated consensus guidelines

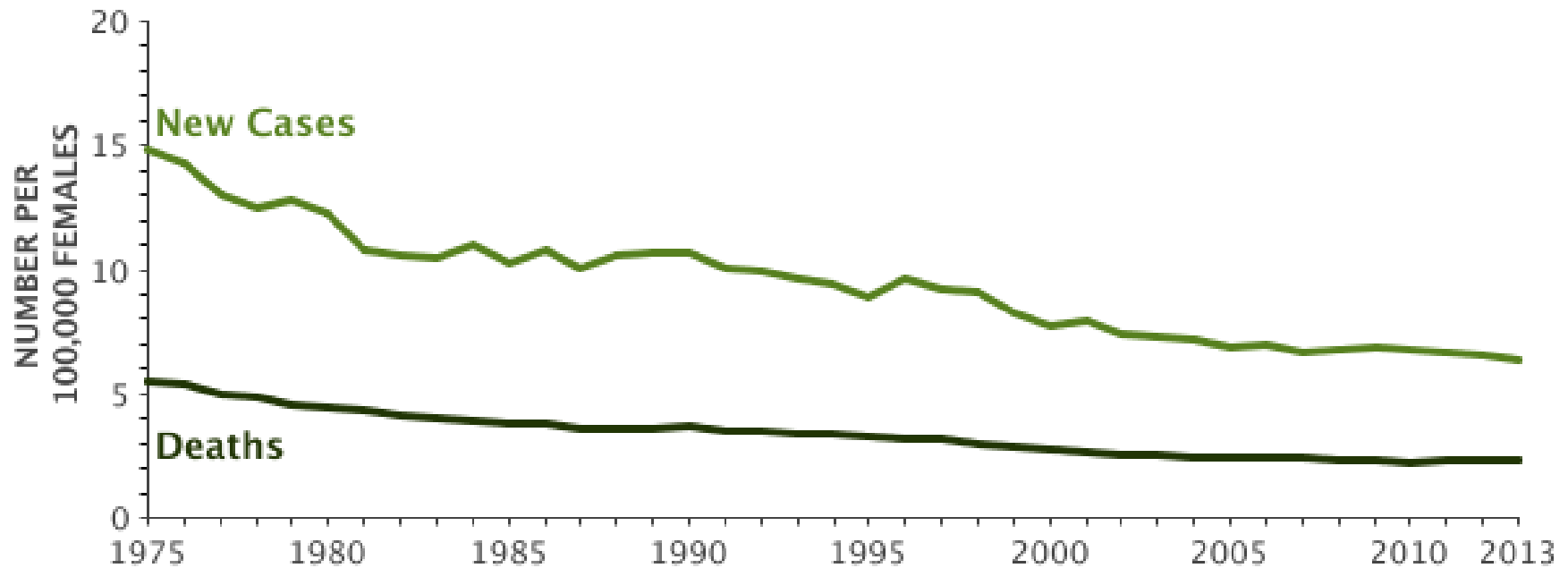
No Disclosures

Cervical Cancer

- In US about 12,000 cases resulting in 4,000 deaths per year
 - 50% never screened
 - 10% not screened in last 5 years
 - Mean age 48 years old
- Who are rarely or never screened?
 - Minorities
 - Low socioeconomic status
 - Foreign born
 - Living in the US < 10 years
 - No usual source of healthcare

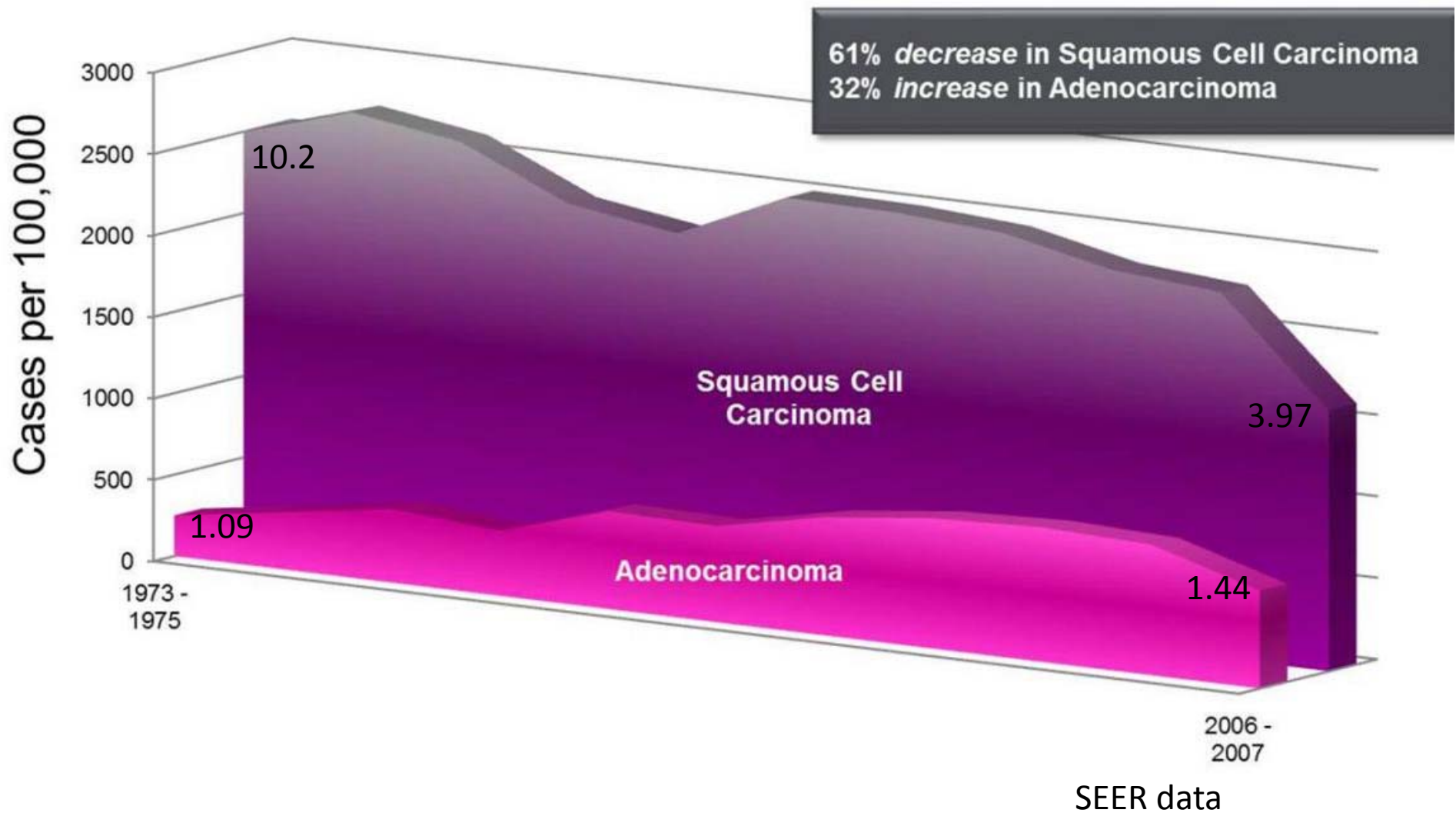
Cervical Cancer in the U.S.

Incidence and mortality has decreased 50% over the past 30 years because of widespread screening.



SEER Data

Rising incidence of cervical adenocarcinoma

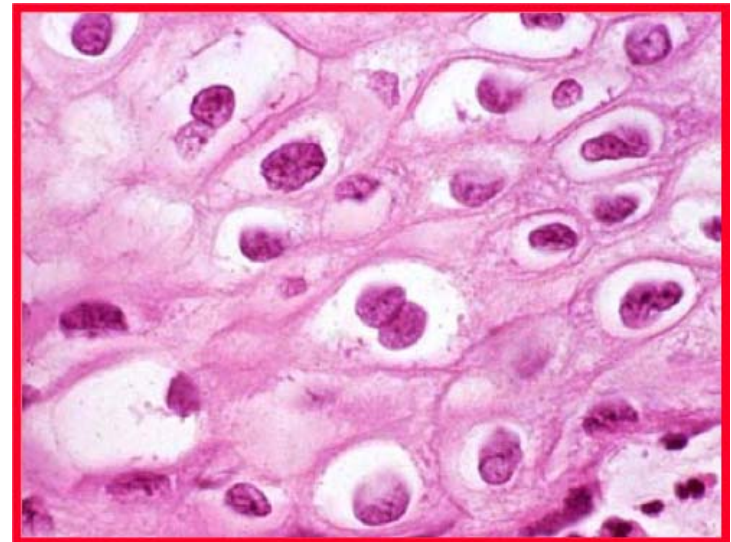


Cervical Cancer and HPV

- Key to getting cancer: **persistent** HPV
- DNA tumor virus with over 150 genotypes
- Oncogenic HPV causes cervical cancer
 - 40 types of genital HPV, 14-15 are oncogenic
- HPV Infection
 - 80% of sexually active adults will acquire HPV
 - Most common in teens and women in early 20's
 - Smoking, immunosuppression, HIV infection increase likelihood of persistent infection

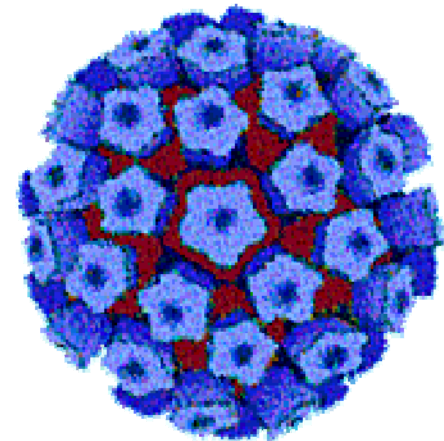
Natural History of HPV Infection

- Skin to skin transmission
- Enters cell via microtrauma
- Moves to nucleus of infected cell
- Infected cell exhibits koilocytosis
 - Perinuclear halo
 - Enlarged nucleus with clumped chromatin

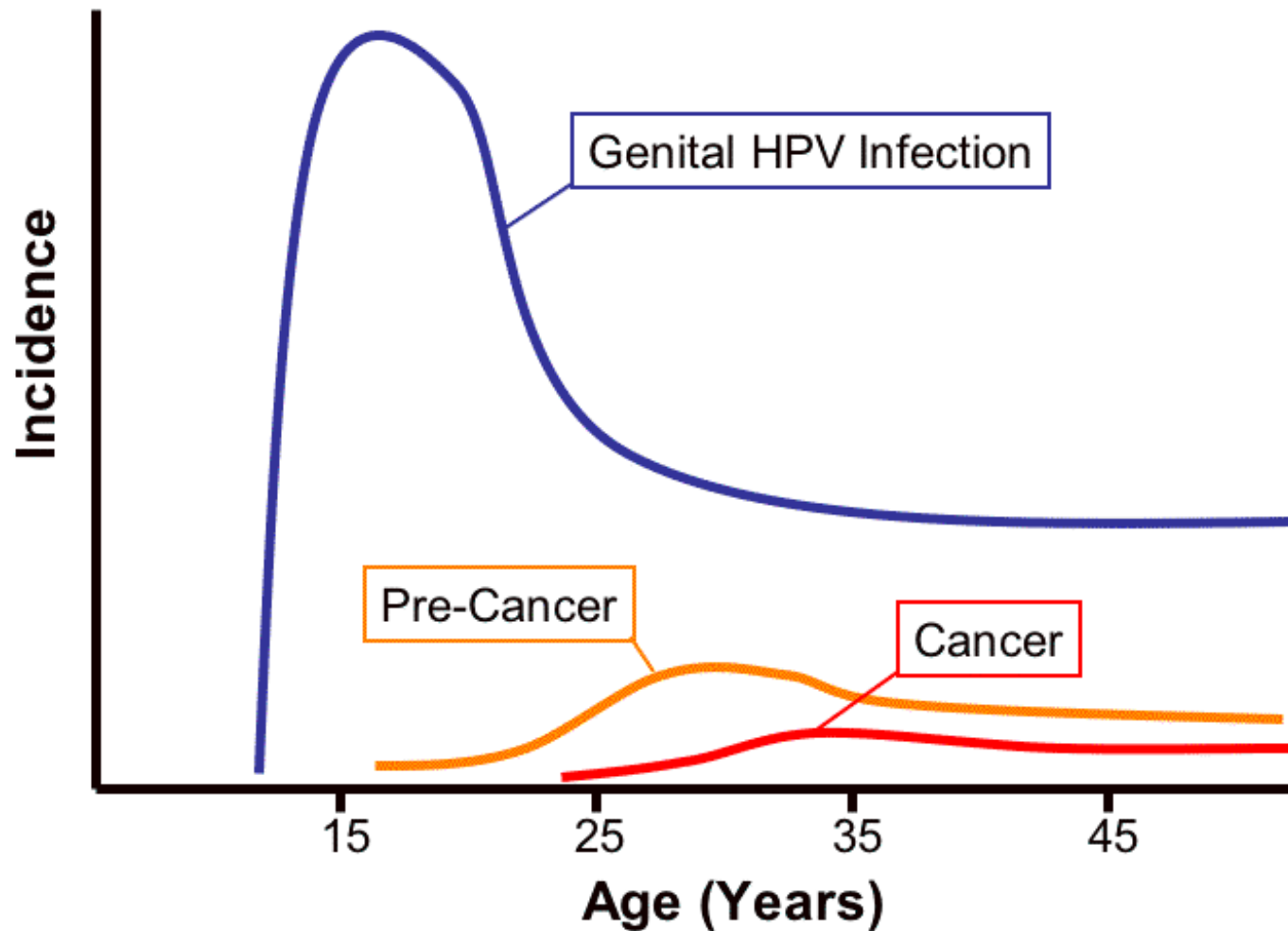


HPV Usually a Transient Infection

- 608 college aged women
 - 70% resolved infection at one year
 - 91% resolved infection at 2 years
 - Average duration of infection 8 months
- Manifestation of disease determined by
 - HPV subtype
 - Viral load
 - Patient factors



Incidence of genital HPV infection

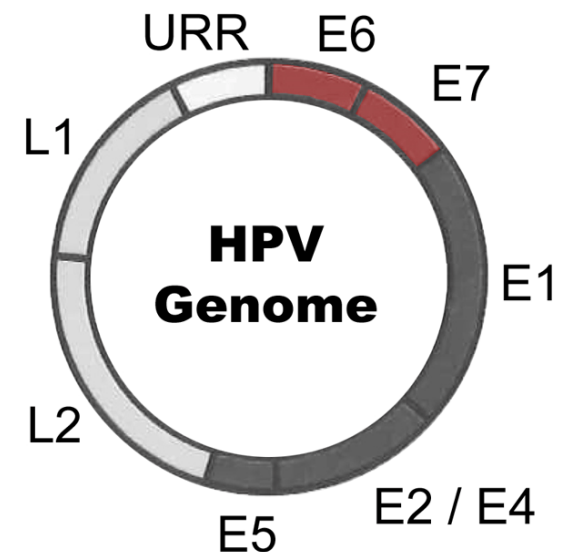


Cervical Cancer and HPV

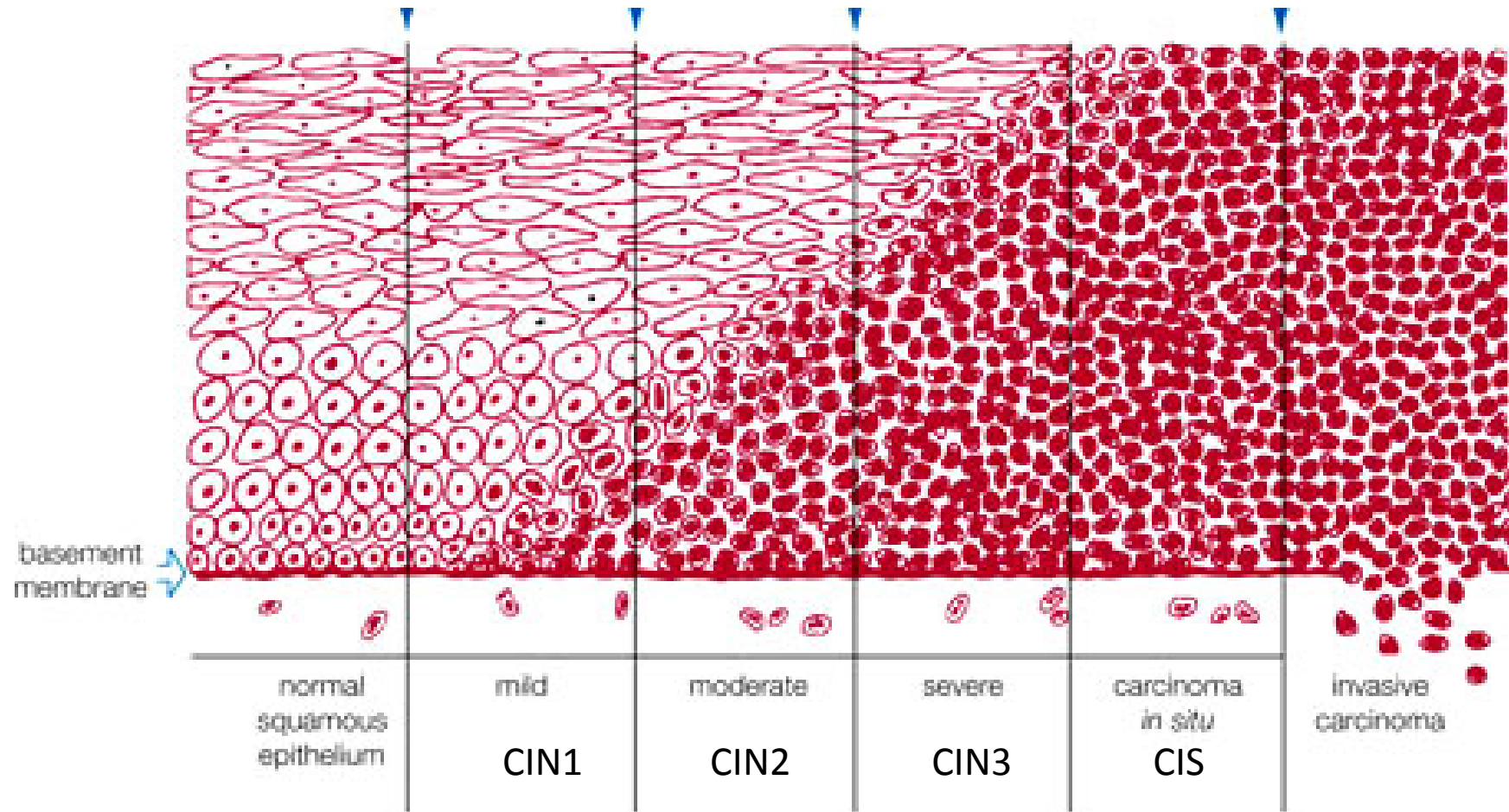
- HPV genotype most important determinant of persistence and progression
- HPV 16 highest carcinogenic potential
 - 55-60% of all cases of cervical cancer
 - OR of cervical cancer if HPV 16+ vs HPV- is 435
- HPV 18 next most carcinogenic
 - Causes 10-15% of cervical CA
 - Associated with adenocarcinoma
- 13 other genotypes cause the remainder
 - 31,33,35,39,45,51,52,56,58,59,68,73
 - Vary greatly in carcinogenic strength

Oncogenic HPV

- E6 and E7 mRNA cause oncogenic transformation by disrupting tumor suppressors
- E6 degrades p53, inhibits DNA repair and regulation of apoptosis
- E7 inactivates Rb cell cycle regulation
- E7 activates synthesis of the intracellular protein p16
- Excess p16 deregulates and stimulates the cell cycle



Progression of Cervical Neoplasia



HPV Related Cancers

- 99% cervical cancers
- 90% anal cancers
- 65% vulvar and vaginal cancers
- 35% penile cancers
- 70% head and neck cancers

Cervical Cancer Prevention



HPV Vaccines

- 2006 Quadrivalent vaccine HPV 6,11,16,18
 - 90% genital warts and **70%** of HPV related cancers
- 2009 Bivalent vaccine HPV 16, 18
 - Different adjuvant conferring higher antibody response
- 12/2014 Nonavalent vaccine HPV 6,11,16, 18,31,33,45,52,58
 - 90% genital warts and **90% of HPV related cancers**

Bivalent Vaccine

Prevents infection with HPV 16 and 18

Approved for **females** age 9-26

3 dose regimen recommended for all females ages 11-12 as 3 dose series at 0,2, and 6 months

Anaphylaxis to latex is a contraindication

Different adjuvant higher antibody response

- Likely confers longer lasting immunity
- Likely offer increased cross protection against other related HPV types

Nonavalent vaccine (9vHPV)

- **Females and males** age 9-26 as a 3 dose series at 0,2, and 6 months
- Recommended as a routine vaccination at age 11-12
- Recommended for immunocompromised persons including those with HIV

Impact of HPV vaccination in the US

- 40% girls and 20% boys completed full series
- 60% girls and 40% boys have received one or more doses
- In US among girls age 14-19 vaccine type HPV prevalence decreased from 11.5% in 2003-2006 to 4.6% in 2009-2012
 - **64% decline despite 3 dose vaccine coverage of only 38% in this age group**
 - 34% decline in women age 20-24

We can do better!
Make America Vaccinate Again!

PROTECT
them from
CANCER

get them the
HPV
VACCINE

A young boy in a green shirt and a young girl in a pink shirt are sitting on the ground between the text. The boy is standing behind the girl, who is sitting cross-legged. They are both smiling. The background is a light green map of the United States.

Goals of Cervical Cancer Screening

- Prevent cervical cancer by detecting and treating true cancer precursors
 - Not find abnormal cytology
 - Not find HPV infection
- Prevent overzealous treatment of precursor lesions that most likely will regress or disappear for which harms of management outweigh the benefits

Cervical Screening Guidelines

- **Fall 2011**
 - USPSTF declined to recommend HPV and Pap co-testing
- **Spring 2012**
 - ACS, ASCCP, ASCP recommend co-testing for screening women age 30-65
- **March 2013**
 - Management guidelines devised for every abnormal co-test and biopsy
- **April 2014**
 - FDA approves one assay for primary HPV testing for women ≥ 25

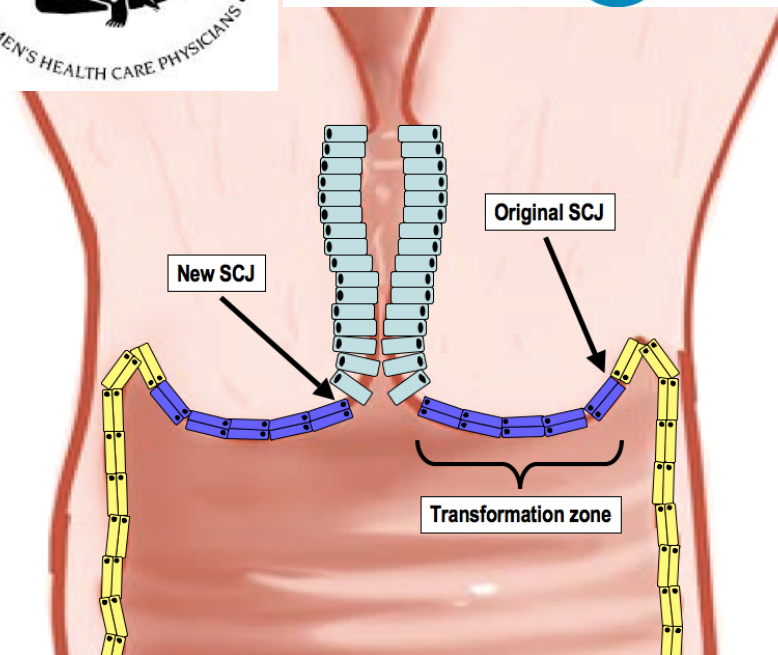


Start screening at age 21

- 0.1% of cervical cancer cases
- 1-2 cases/1 million females age 15-19
- US and UK studies showed that earlier screening did not decrease cervical cancer rates in this population
- If <21 and screened, and abnormality detected, follow guidelines for 21-24 yo

Screening 21-29

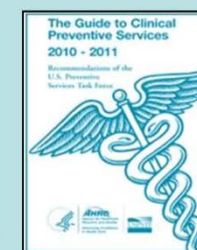
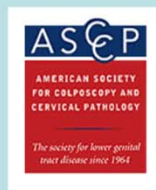
- **Every 3 years with cytology alone**
- High prevalence of HPV
 - **Co-testing with HPV should NOT be performed**
- Annual screening should **NOT** be performed



Screening women age 30-65

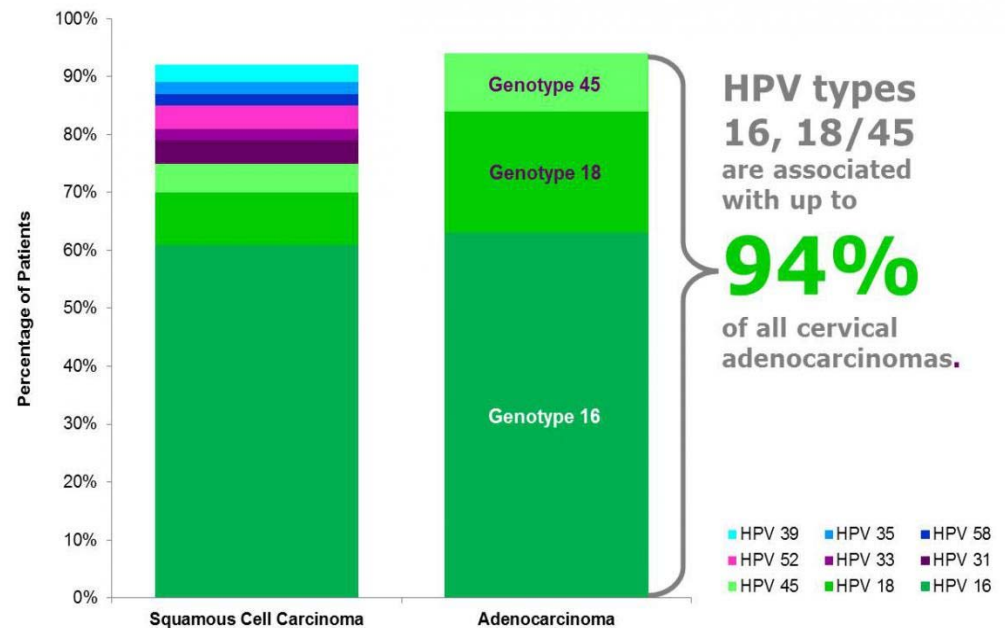
Age 30-65. Testing with cytology alone every 3 years or co-testing with cytology and testing for high-risk HPV types every 5 years.

- Co-testing “preferred” and cytology “acceptable” by all but USPSTF.
 - USPSTF says either acceptable



Screening age 30-65

- In women ≥ 30 yrs co-testing detects 17-31% more CIN3 (precancer) than cytology alone
- HPV testing is superior to cytology for detecting cervical adenocarcinoma
 - Poorer prognosis and incidence is increasing



When to stop screening

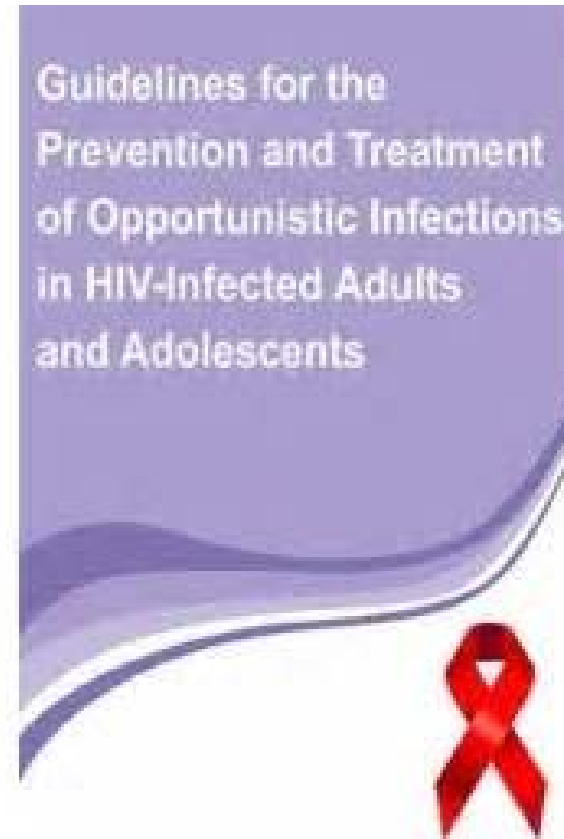
- **Age 65** and not at high risk for cervical cancer
- Discontinuation **assumes adequate prior negative screening**
- Three consecutive negative cytology results or 2 negative co-test results within the previous 10 years, with the most recent within 5 years
- No prior history of cervical cancer, CIN 2/3 in the prior 20 years

When to stop screening

- After total hysterectomy if no CIN2/3 or cervical cancer
- If CIN2+ and cervix removed, after initial post treatment surveillance, continue screening of vaginal cuff with cytology every 3 years for 20 years, even if >65
- Screening should not resume for any reason even if a woman reports having a new sexual partner

Screening young women with HIV

- **Begin screening at age of initiation of sexual activity**, regardless of mode of HIV transmission, but no later than age 21. Annual cytology without HPV testing traditionally advised
- **New per ACOG:** If < age 30, screen with cytology at time of diagnosis and then annually. If 3 consecutive annual cytology screens normal, then cytology screening can be done every 3 years



Women with HIV age 30 and older

- Once has 3 consecutive annual cytology results can be screened with cytology alone every 3 years
- Once has had one negative co-test can be screened with **co-testing every 3 years**
 - ? Utility of this recommendation given high prevalence of HPV in HIV infected women

Screening immunocompromised women

- No studies or major recommendation exists
- Traditionally annual cytology has been done
- Per ACOG it is reasonable to extrapolate recommendations for women with HIV infection to this group with screening beginning at age 21

Screening DES exposed women

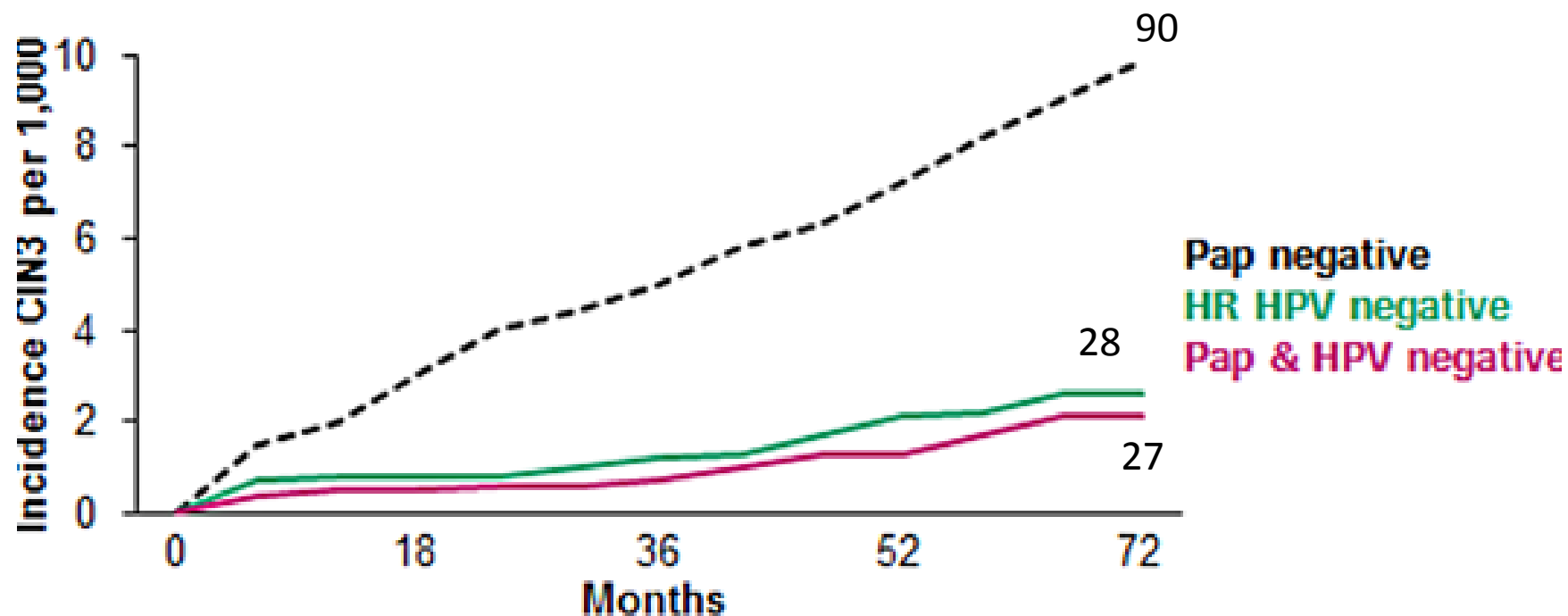
- Used in the US from 1940 to 1971
- Women exposed to DES in utero at increased risk for clear cell adenocarcinoma
- Advise cervical and 4 quadrant vaginal cytology annually and digital exam of vagina annually
- No recommendations from major groups for upper age limit of screening

Primary Screening with HPV Only

FDA Approved April 2014

- US FDA approved a **single** HPV assay for primary screening among women age 25-65 following 3 year 47,000 woman registration trial ATHENA
- Almost all the benefits of co-testing are due to inclusion of the HPV testing
 - Cytology adds very little to the initial screen
- Cytology is not without costs
 - Evaluating the Pap, work up of Pap NIL/HPV+
- Eliminating cytology greatly simplifies screening
 - Cytology adds very little to the initial screen

Risk of CIN3+ After Negative Screening Test



- 24,295 women from 7 primary HPV screening studies in 6 European countries
- At least 1 cytology or histopathology exam during follow-up

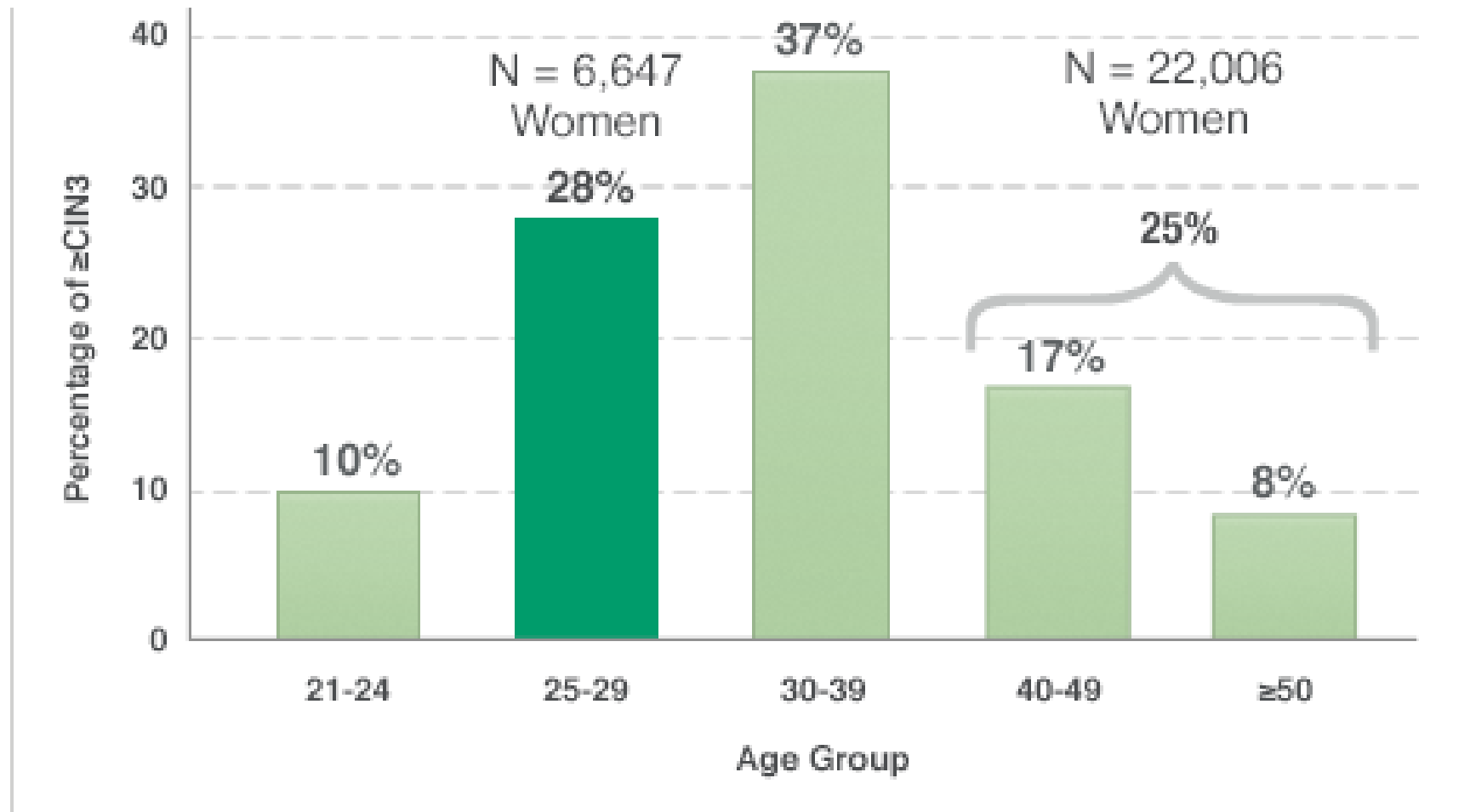
HPV Primary Screening

Why Begin at Age 25?

- More CIN3+ in 6,647 women 25-29 years than in 22,006 women ≥ 40 years
- Cytology was read as negative in over half of women age 25-29 years with CIN3+
- Prevalence of HPV is 21.9%; **prevalence of HPV 16 is 5.3% and HPV 18 is 1.6%**
- Abnormal cytology rate \geq ASC-US was 9.5%

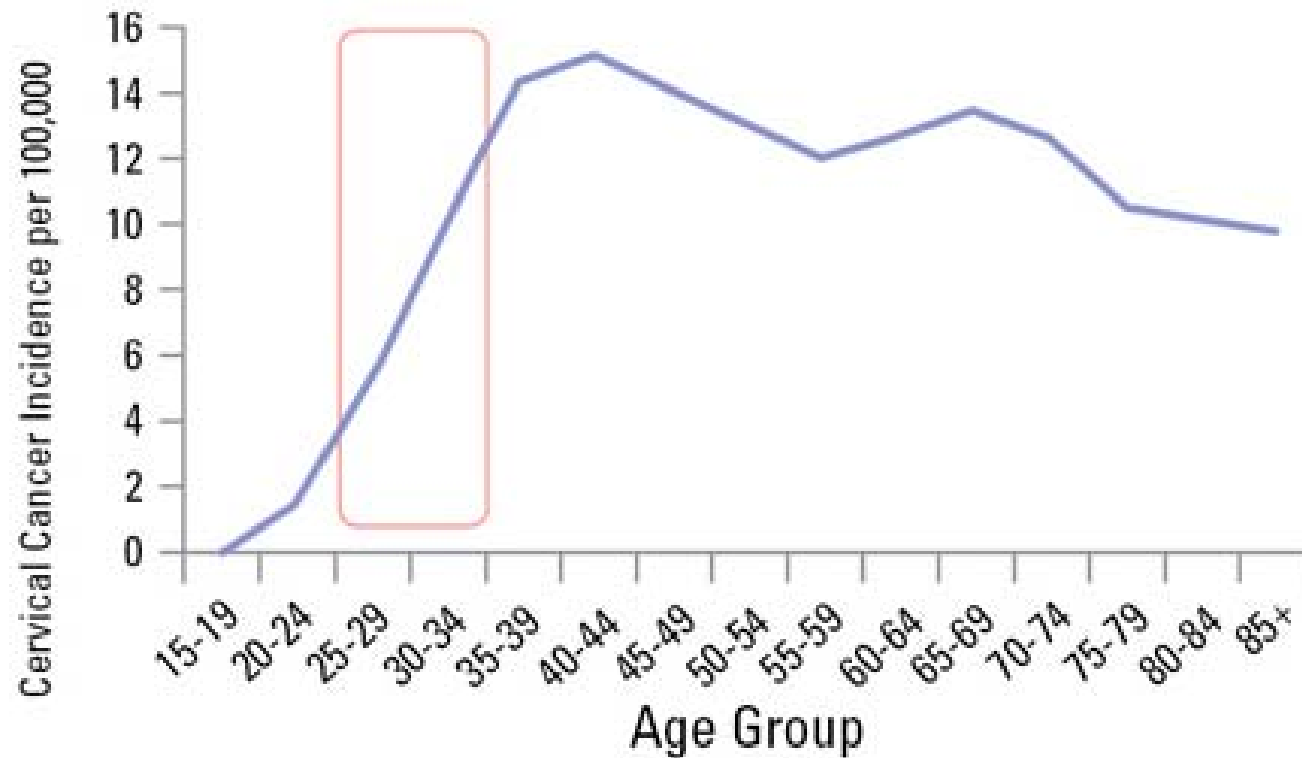
Prevalence of CIN3+ by Age

ATHENA trial



More CIN3+ disease in women aged 25-29 years than in women aged ≥ 40 years

Invasive Cervical Cancer in the US SEER Tumor Registry (1975-2010)



Comparison of Strategies in Women 25-29 Years ASCP

*Trade-offs between CIN3+ detected & colposcopy**

Strategy	Screening Tests	CIN3+ detected	CIN3+ Missed	Colpos	Colpos to detect 1x CIN3+
Cytology with reflex HPV for ASCUS	7,854	51	68	640	12.6
HPV Primary	10,226	102	17	1,247	12.2

Wright et al. Presented at Int. Papillomavirus Meeting 2014, Seattle, WA

* At the Baseline visit

Cervical Cancer Screening Test Performance

Sensitivity =

True Positives ÷
(True positives + False negatives)

Specificity =

True Negatives ÷
(True negatives + False positives)

Maximizing benefits by
minimizing false
negatives

Imperative for 5 year
screening intervals

Minimizing harms by
minimizing false positives

Reduces unnecessary
colposcopies, consults,
biopsies, etc

ACOG Practice Bulletin January 2016

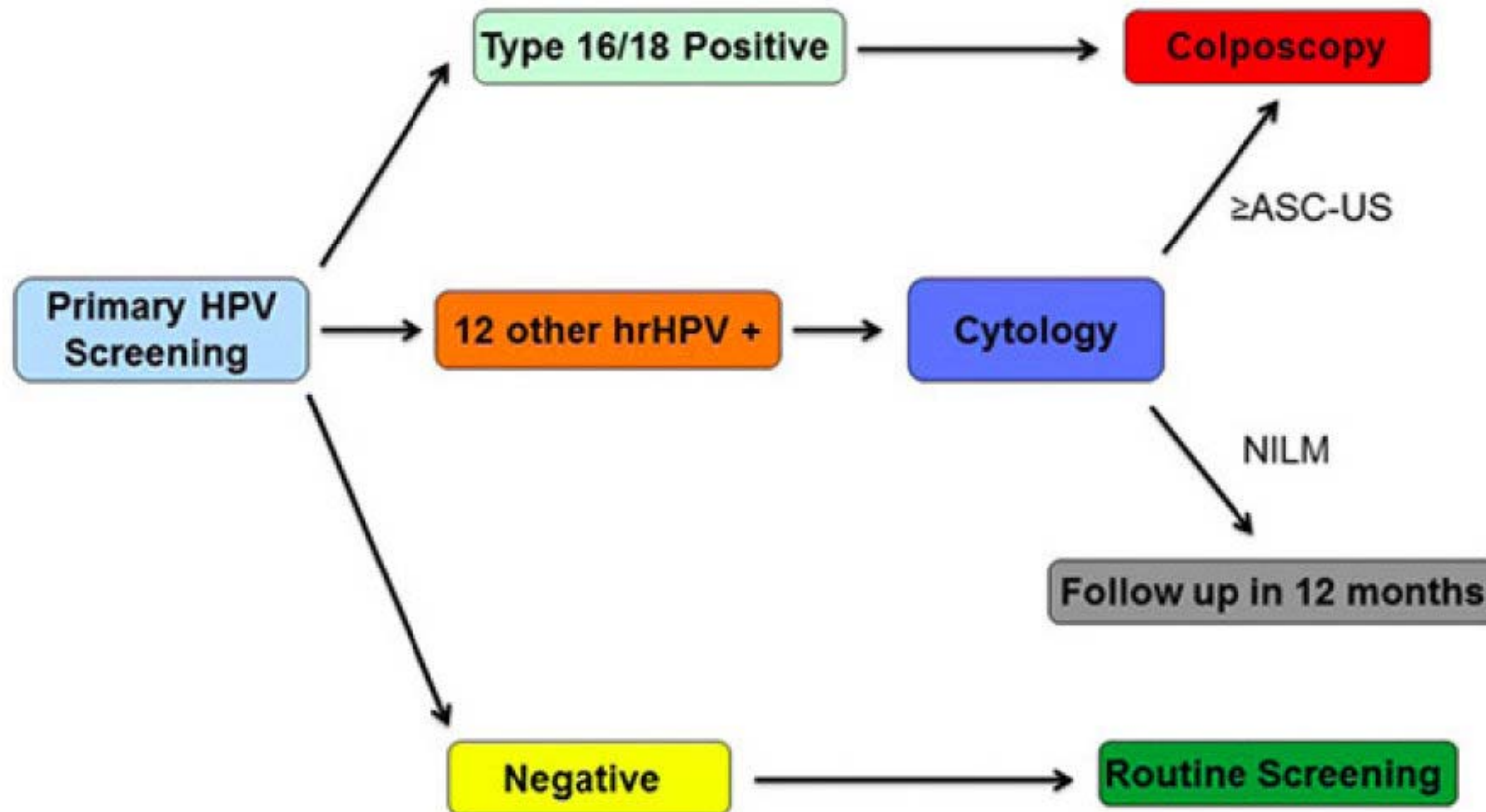
Cervical Cancer Screening and Prevention

- In women ≥ 25 the FDA approved primary HPV screening test can be considered an **alternative** to current cytology based screening. **Cytology alone and co-testing remain the options specifically recommended in current major society guidelines.** If used, should be performed as per ASCCP and SGO interim guidance

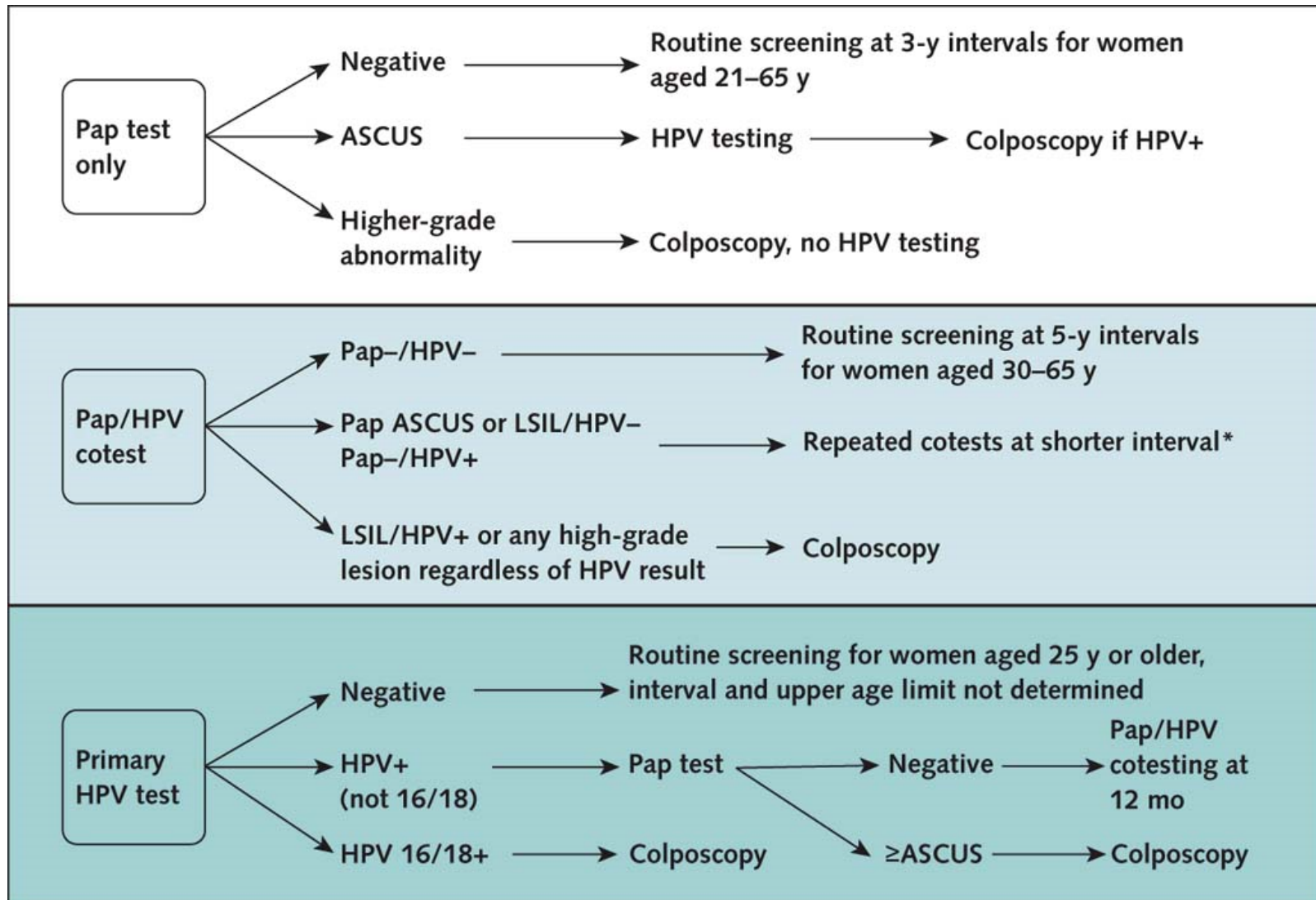
Primary HPV Screening Algorithm

Age ≥ 25 every 3 years

Recommended Primary HPV Screening Algorithm



Summary of Cervical Cancer Screening Guidelines



ACS/ASCCP/ASCP 2012 Updated Consensus Guidelines

- Based on large numbers of clinical observations over 8+ years
- Data from **1.4 million women** from KPNC* provided evidence on risk after abnormal tests
 - More than 1 million women age ≥ 30 with co-testing
 - 440 cancers; 3,231 CIN3+; 7,581 CIN2+
 - Almost 400,000 women < 30 with ASC-US cytology results and HPV triage
 - 26 cancers; 1,231 CIN3+; 4,193 CIN2+

Principles of ASCCP Management Guidelines

- Preventing all cervical cancer is unrealistic
- Attempts to eliminate all risk result in unanticipated harm from excessive evaluation and treatment
- **Management by risk** – similar risk means similar management
- Immediate risk determines immediate management
- Risk over time determines follow-up interval

Benchmarking of risk to accepted management strategy based on KPNC data

5 year risk of CIN 3+	Management
> 5%	Immediate colposcopy
2-5%	6-12 month return
0.1 – 2%	3 year return
0.1%*	5 year return

* Risk comparable to co-testing in women without a history of abnormality

Benchmarking cotest risks to implicit 5-year CIN3+ Pap-only risk thresholds

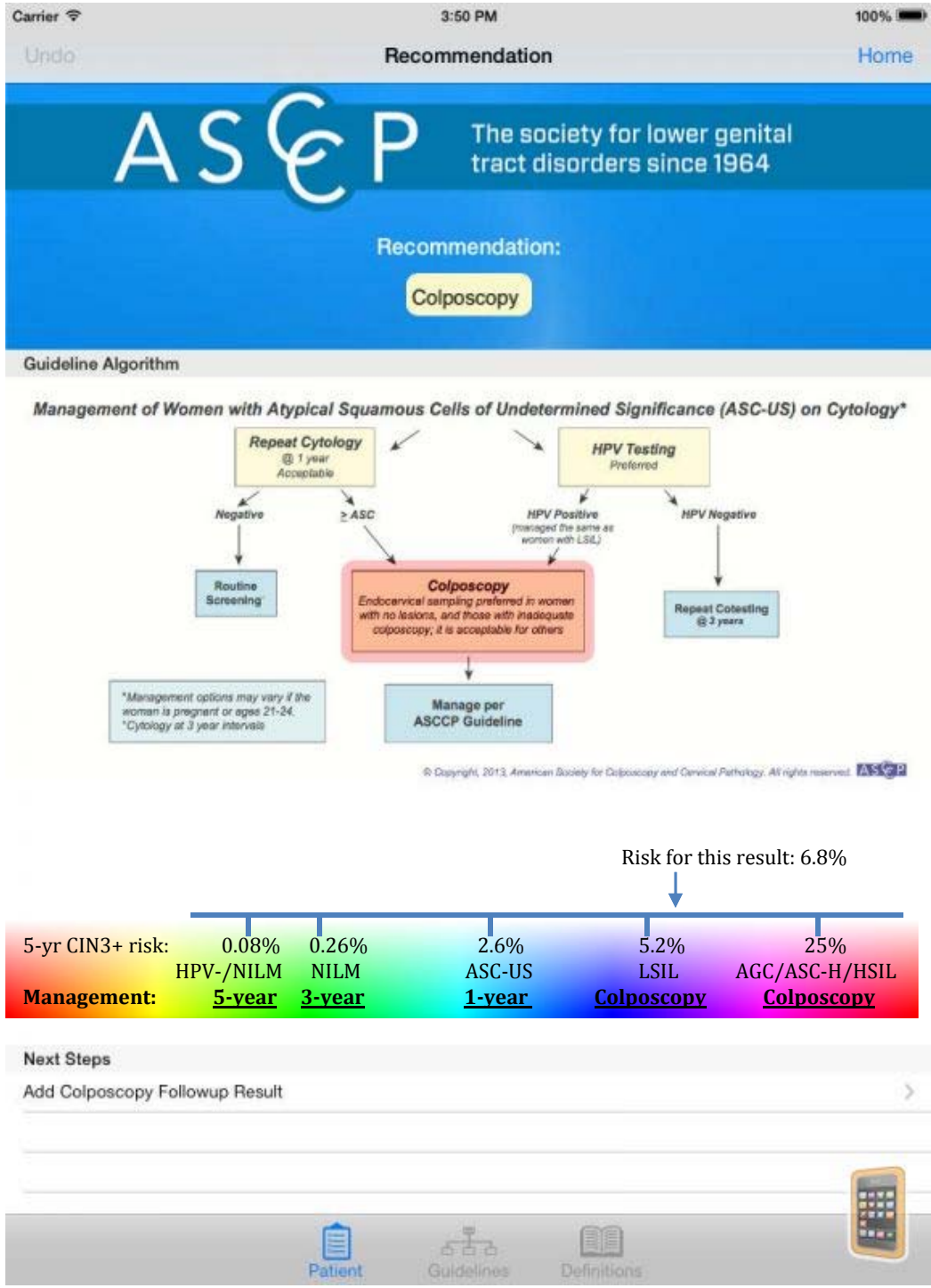
Current return based on Pap only	Pap-only 5-year CIN3+ risks (implicit risk thresholds)			Cotest 5-year CIN3+ risks		
	Pap result	Frequency	CIN3+ risk	HPV/Pap result	Frequency	CIN3+ risk
Immediate colposcopy (high-grade Pap abnormalities)	SCC	<0.01%	83%	HPV+/ HSIL	0.20%	49%
	HSIL	0.21%	47%	HPV+/ AGC	0.05%	33%
				HPV-/ HSIL	0.01%	30%
				HPV+/ ASC-H	0.12%	25%
	ASC-H	0.17%	18%			
	AGC	0.21%	8.5%			
				HPV-/ ASC-H	0.05%	3.5%
Immediate Colposcopy				HPV-/ AGC	0.16%	0.9%
				HPV+/ ASC-US	1.1%	6.8%
6-12 month return				HPV+/ LSIL	0.77%	6.1%
	ASC-US	2.8%	2.6%	HPV+/ Pap-	3.5%	4.5%
3-year return				HPV-/ LSIL	0.18%	2.0%
	Pap-	95.6%	0.26%	HPV-/ ASC-US	1.8%	0.43%
5-year return				HPV-/ Pap-	92.1%	0.08%

2013 ASCCP management guidelines

Does anyone understand them?

- How to manage abnormalities that did not exist before co-testing
- Define what combination of test results after an abnormal permit safe return to routine screening
- Reflect new data on management of specific results

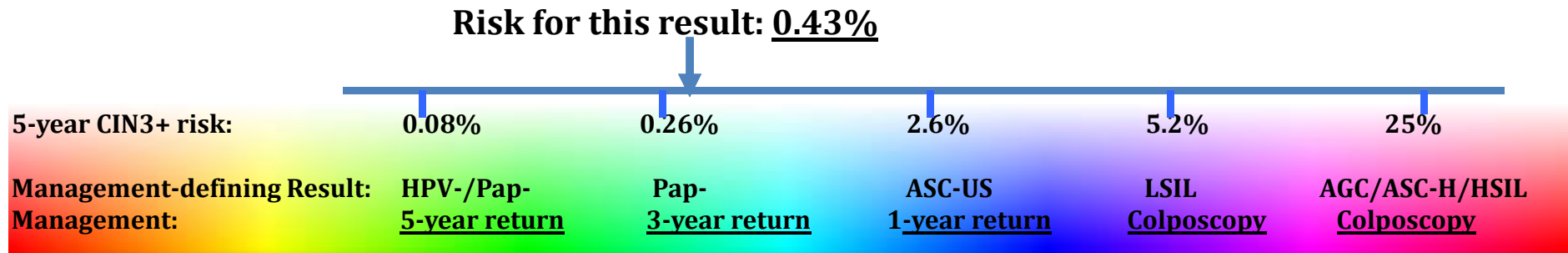




ASCCP Algorithms Mobile App

- The ASCCP App is a big step forward for teaching and communicating guidelines
- Goals of the App:
 - Improve understanding of the evidence underlying a guideline
 - Improve acceptance of guidelines
- Presents the logic of “Similar Management of Similar Risks”

A “Risk Bar” for the App



- “Similar Management of Similar Risks” logic must be obviously and immediately apparent
- The risk calculation underlying the recommendation is displayed on the continuum
- “Why is the recommendation for HPV-negative/ASC-US a 3-year return?”
 - “Oh, the data say it’s just like a negative Pap. I get it.”

Cervical Cancer Screening Targets

- **CIN 3 is a true precancer**, 30-50% progress to cancer over 30 years
 - **Must treat** since it cannot be predicted which CIN3 lesions will progress to invasion
- CIN 2 is a collection of CIN 3 and CIN1
 - 50% regression rate, low risk of invasion
 - **Observation acceptable**, especially in **younger women**
- CIN 1 is a transient or stable HPV infection with minimal cancer risk – **DO NOT TREAT!**

LAST (Lower Anogenital Squamous Terminology)

- Goal to create a dichotomous separation of morphologic designations that reflect transient active HPV replication (LSIL) versus persistent HPV associated precancer (HSIL)
- **Histologic LSIL – CIN 1**
- **Histologic HSIL – CIN 2, CIN 3**

LAST (Lower Anogenital Squamous Terminology)

- Accepts CIN3 as a true precancer
- CIN 2 – highest interobserver variability
- Recommends p16 immunostaining to adjudicate equivocal precancers – CIN2
 - Concern for overtreatment of CIN2 if merged into HSIL. Advised that the 2 tier diagnosis be qualified with the relevant –IN category in parentheses
- Advise against using p16 staining in CIN1 cases with result of upgrading and overtreating lesions that represent infections
 - 30% of CIN 1 lesions p16 positive

2012 Guidelines Essential Changes

- Cytology reported as unsatisfactory requires repeat in 2-4 months even if HPV neg
- CIN1 on ECC should be managed as CIN1, not as positive ECC
- Cytology reported as negative but lacking endocervical cells can be managed without early repeat
- For cytology negative/HPV + - genotyping triages women with HPV 16 or 18 to earlier colposcopy
- Colposcopy is indicated for all women* with HPV and ASC-US, regardless of genotyping result

2012 Guidelines Essential Changes

- For ASC-US cytology, immediate colposcopy is not an option
 - Serial cytology option for ASC-US incorporates cytology at 12 months, not 6 and 12 months, and then if negative, every 3 years
- ASC-US HPV negative should be followed with co-testing at 3 years rather than 5 years
- ASC-US HPV negative results are insufficient to allow exit from screening after age 65
- Management options for CIN2 are more clearly defined

2012 Guidelines Essential Changes

- More strategies use co-testing to reduce follow up visits
 - Pap only strategies are now limited to women younger than 30 years, but
 - Co-testing is expanded even to women younger than 30 years in some circumstances
- Women age 21-24 are treated more conservatively

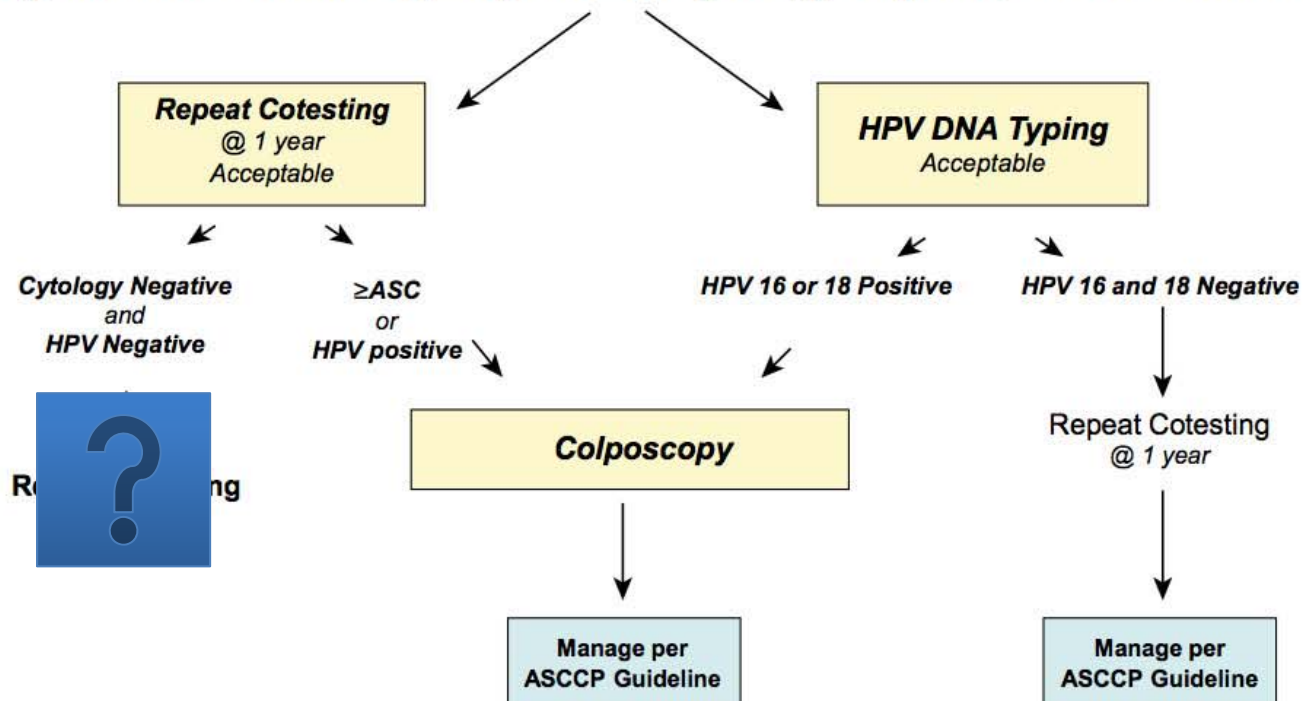
Case Studies

34 yo G2P2 has a **NIL Pap and a positive hrHPV test**. She was previously screened with Pap only but has had no screening in 5 years. What is the next step?

1. Immediate colposcopy
2. Co-testing in 3 years
3. Co-testing in 1 year
4. Order HPV DNA genotyping
5. Download the ASCCP mobile app

Women with this result have a 5 year CIN3+ risk of 4.5%

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

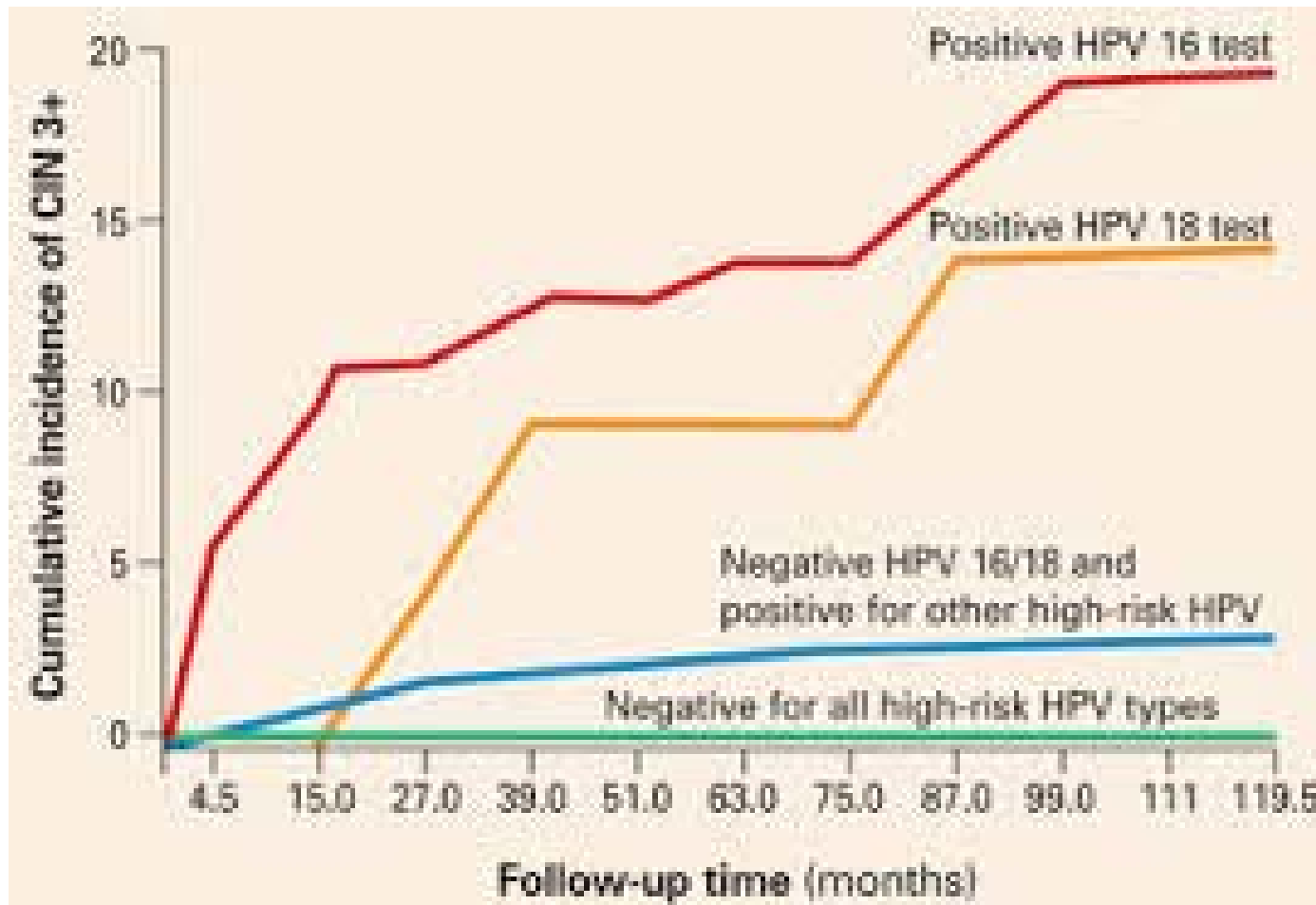


HPV Genotyping

- Both DNA and mRNA tests available
- 5 year risk of CIN2+ if HPV 16+ is 10%
- Risk of CIN2+ is lower if HPV 18, but there is an association with adenocarcinoma

ASCCP guidelines state HPV genotyping is acceptable without recommending for or against.

Role of HPV 16/18 Genotyping

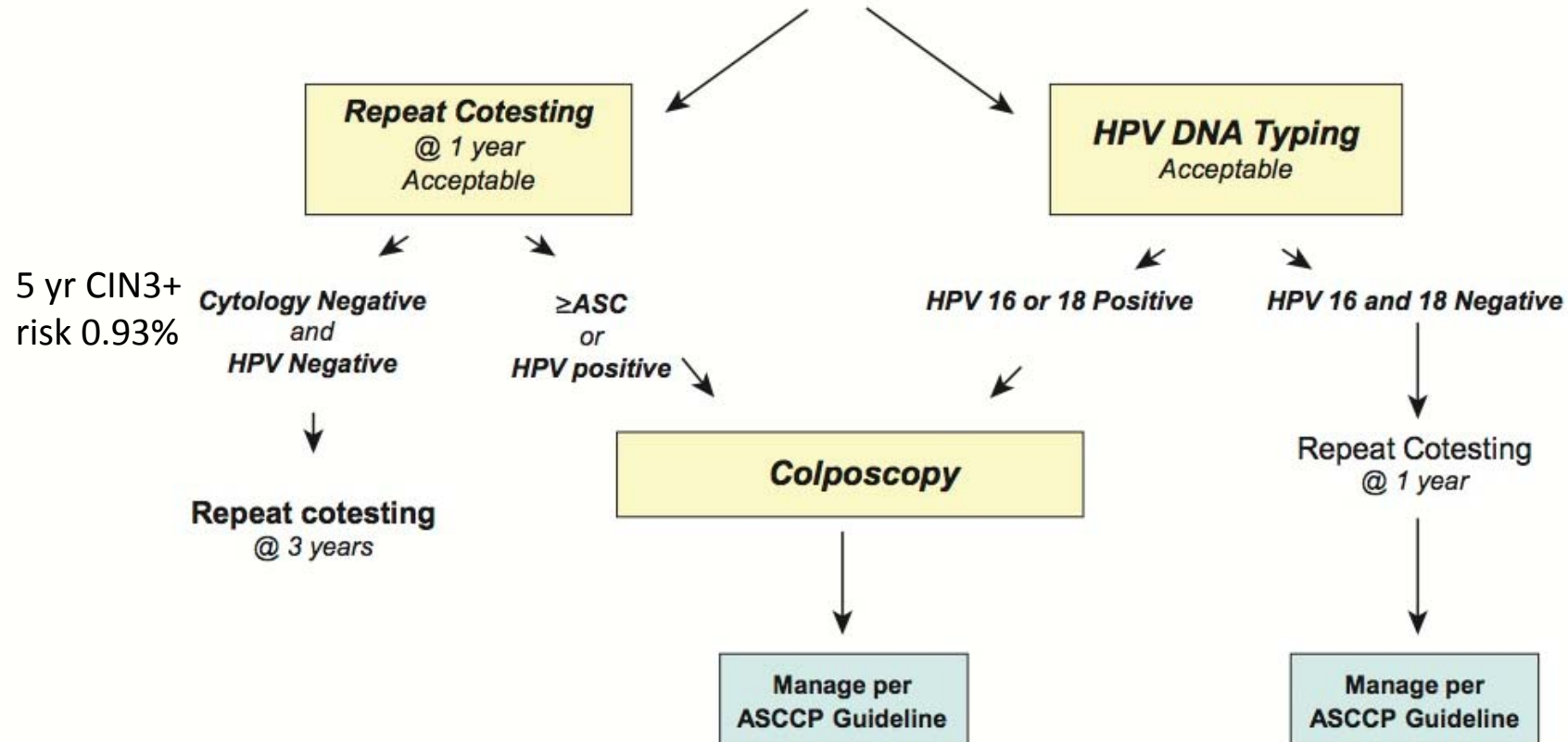


She returns in one year. Co-testing shows Pap NIL and HPV negative. What is the next step?

1. Pap only in 3 years
1. Repeat co-testing in one year
2. Repeat co-testing in 3 years
3. Repeat co-testing in 5 years

Cytology Negative, HPV Positive

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

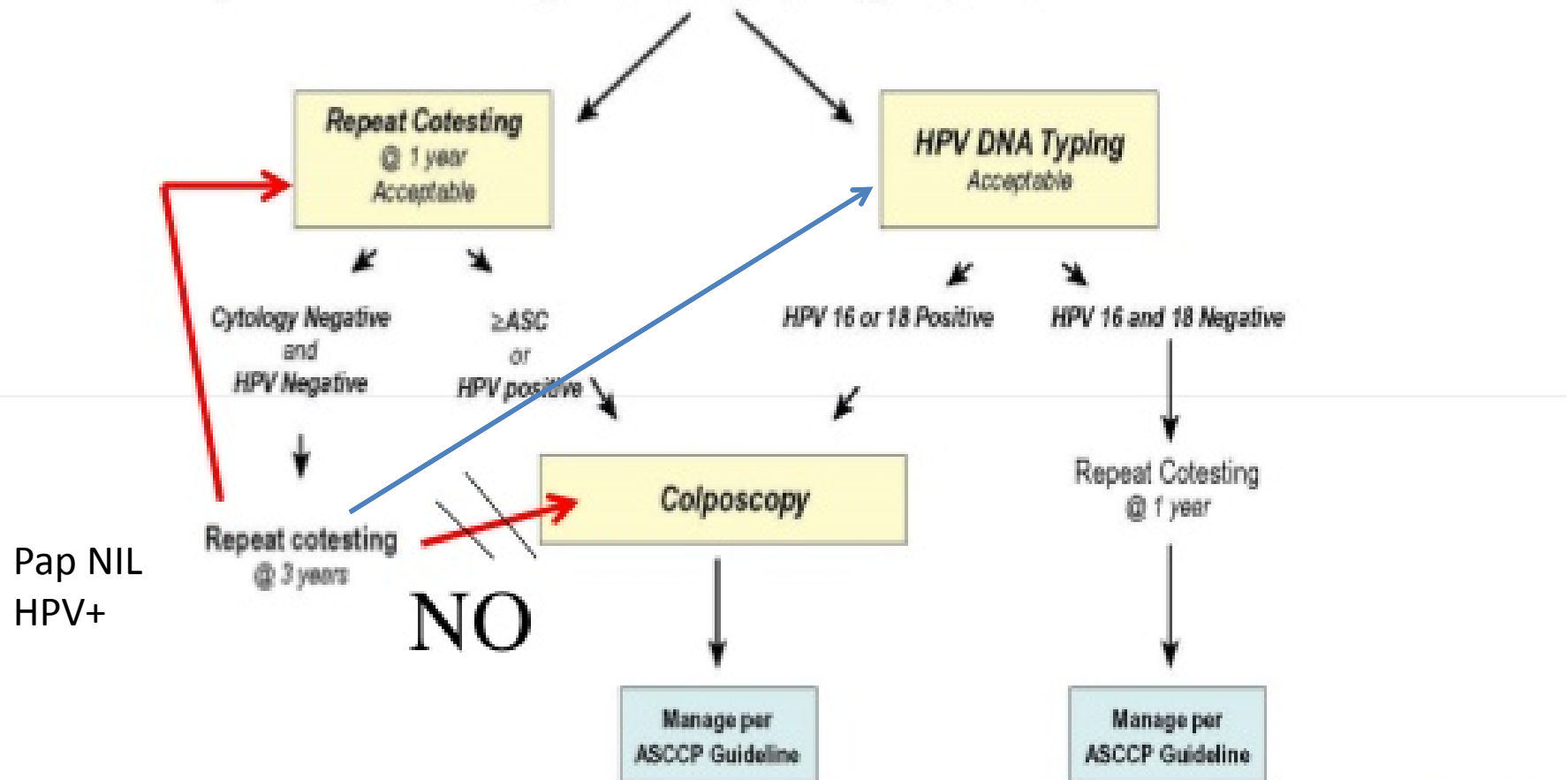


She returns in 3 years and her co-testing Pap is NIL and HPV positive. What do you do now?

1. Co-testing in one year
2. Immediate colposcopy
3. HPV genotyping
4. Look up algorithm in your ASCCP app

2013 ASCCP **mgt** guidelines Women \geq age 30, Pap - HPV +

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



Dilemma: 65 yo with Pap NIL and HPV other positive X 3 years. All colposcopies with random biopsies negative for dysplasia. Follow up management?

- Continue yearly co-testing and colposcopy as long as same results
- Change to co-testing every 2-3 years
- Change to cytology alone every 3 years
- Assume this is a false positive HPV test and stop testing

21 year old has first Pap which shows ASC-US.

You get reflex HPV testing and she is HPV +.

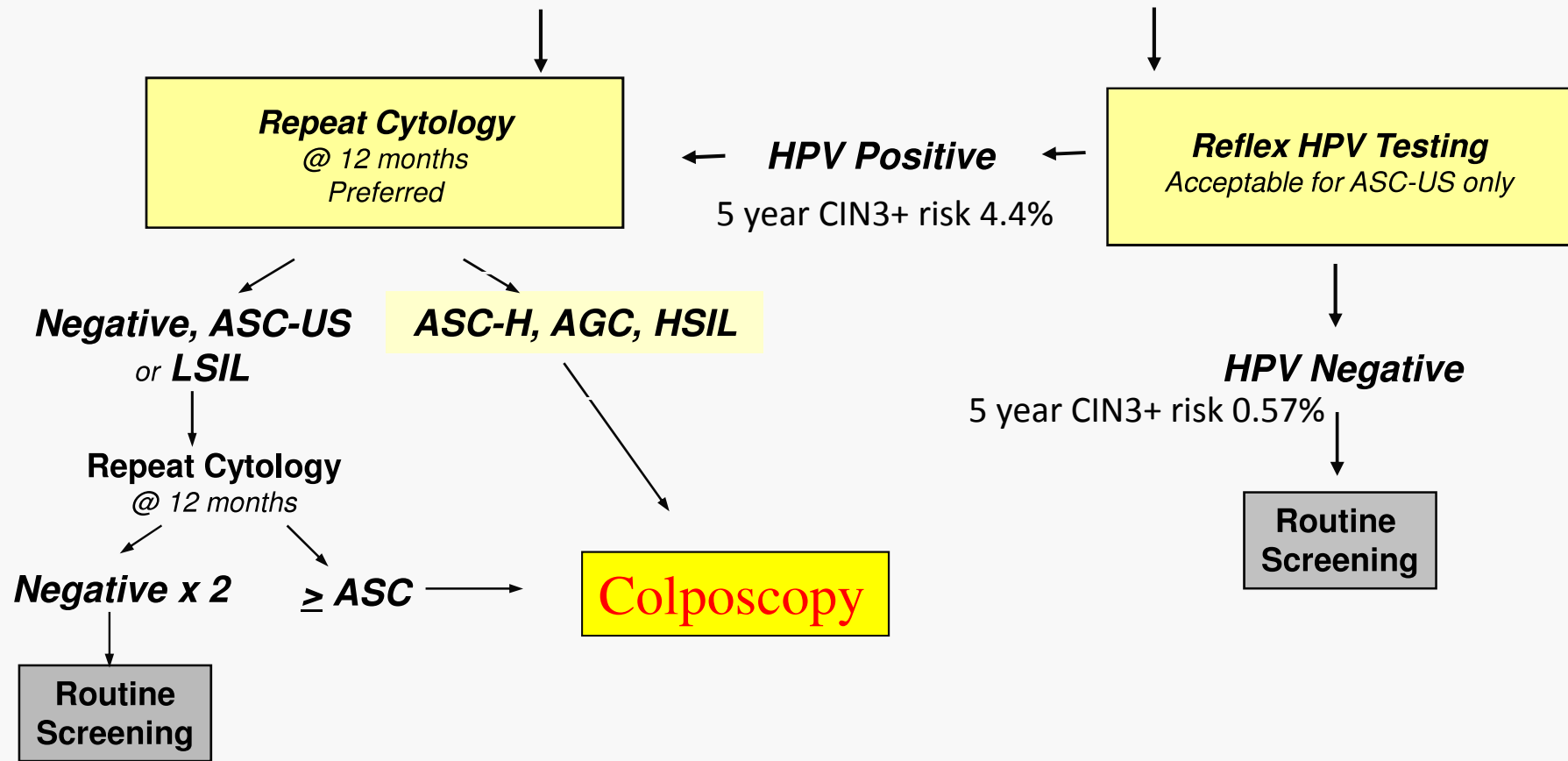
What is next step?

1. Refer for colposcopy
2. Repeat Pap in one year
3. Repeat Pap and HPV test in one year
4. Repeat HPV test alone in one year

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

5 year CIN3+ risk 3.0%

Women ages 21-24 years with ASC-US or LSIL



Managing Women Ages 21-24

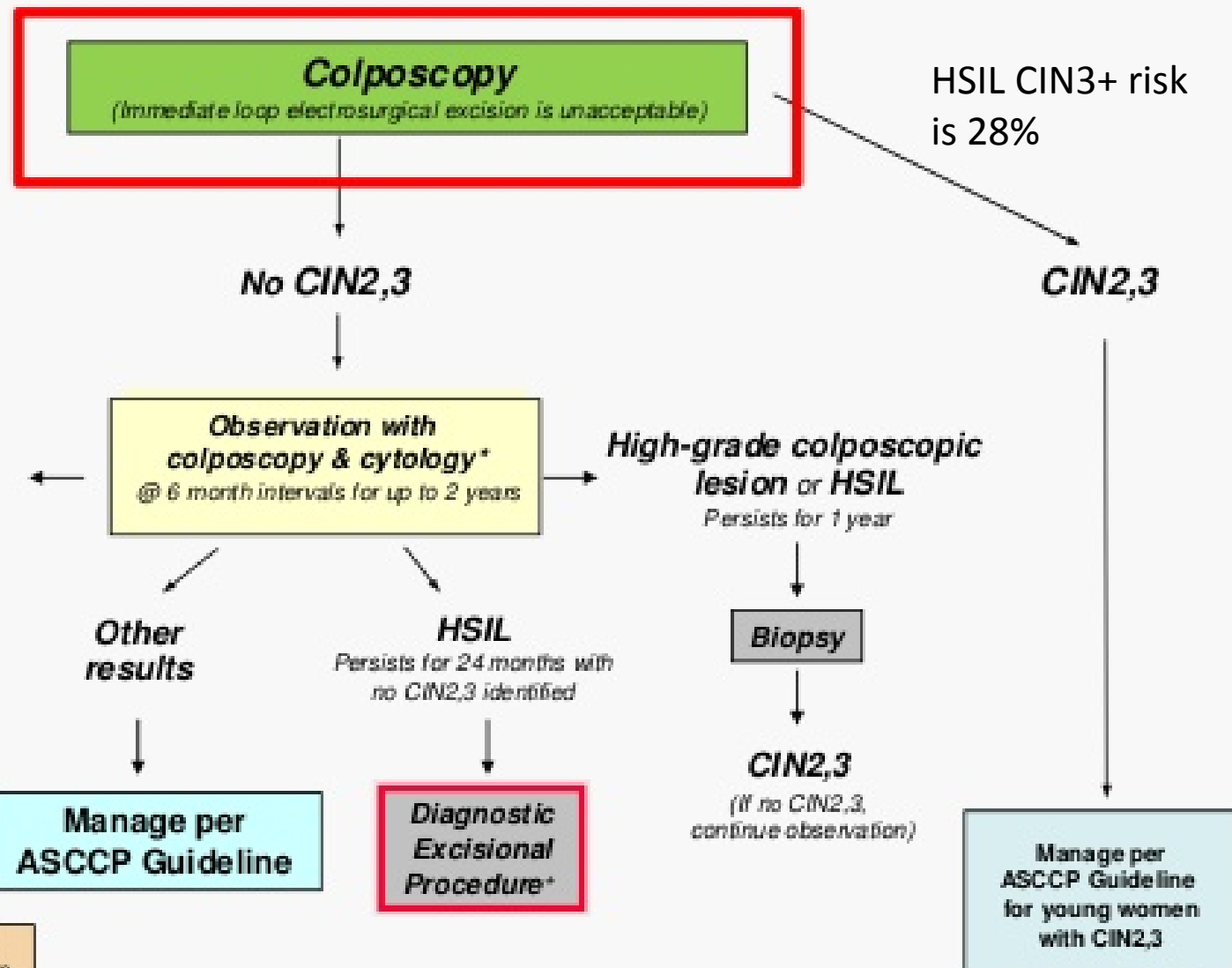
- HPV infection incidence peaks in this age group
- 5 year risk of CIN3+ after ASC-US or LSIL is 3%
- Treatment can have adverse consequences on future pregnancy
- Be conservative in your management

22 year old has a Pap showing HSIL. Her previous Pap last year was ASC-H. She did not follow up until now. What is the next step?

- 1. Repeat Pap in one year
- 2. See and treat with LEEP
- 3. Ask for HPV testing
- 4. Colposcopy

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)

ASC-H 5 year CIN3+ risk is 16%



HSIL CIN3+ risk is 28%

Figure 9

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



Her colposcopic directed biopsies show HSIL (favor CIN 2). What is the next step?

- 1. Repeat Pap in one year
- 2. Treat with excisional LEEP
- 3. Treat with cryotherapy ablation
- 4. Repeat Pap and colposcopy in 6 months

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.

Observation - Colposcopy & Cytology
@ 6 month intervals for 12 months

Treatment using Excision or Ablation of T-zone

2x Cytology Negative
and Normal Colposcopy

Colposcopy worsens or
High-grade Cytology or Colposcopy
persists for 1 year

Cotest in 1 year

Either test
abnormal

Both tests negative

**Repeat
Colposcopy/Biopsy
Recommended**

CIN3 or CIN2,3 persists for 24 months

Treatment Recommended

Cotest in 3 years

ASCCP Definition of “young women”

- Those who after counseling by their clinicians consider risk to future pregnancies from treating cervical abnormalities to outweigh the risk for cancer during observation of those abnormalities.
- **Age is not specified**
 - 32 year old infertility patient
 - 24 year old G3P3 status post tubal ligation

ASC-H and HSIL in Women Ages 21-24

- Precancer risk higher than after ASC-US/LSIL
- 5 year risk of CIN3+
 - 16% after ASC-H
 - 28% after HSIL
- Most CIN2 in this group will regress – up to 49%
 - Risk of progression but usually takes time
 - Treat if CIN 2 persists for 2 years – ablation preferred
- Treatment recommended for CIN3
- Cancer unlikely during extended observation

Cryotherapy ablation

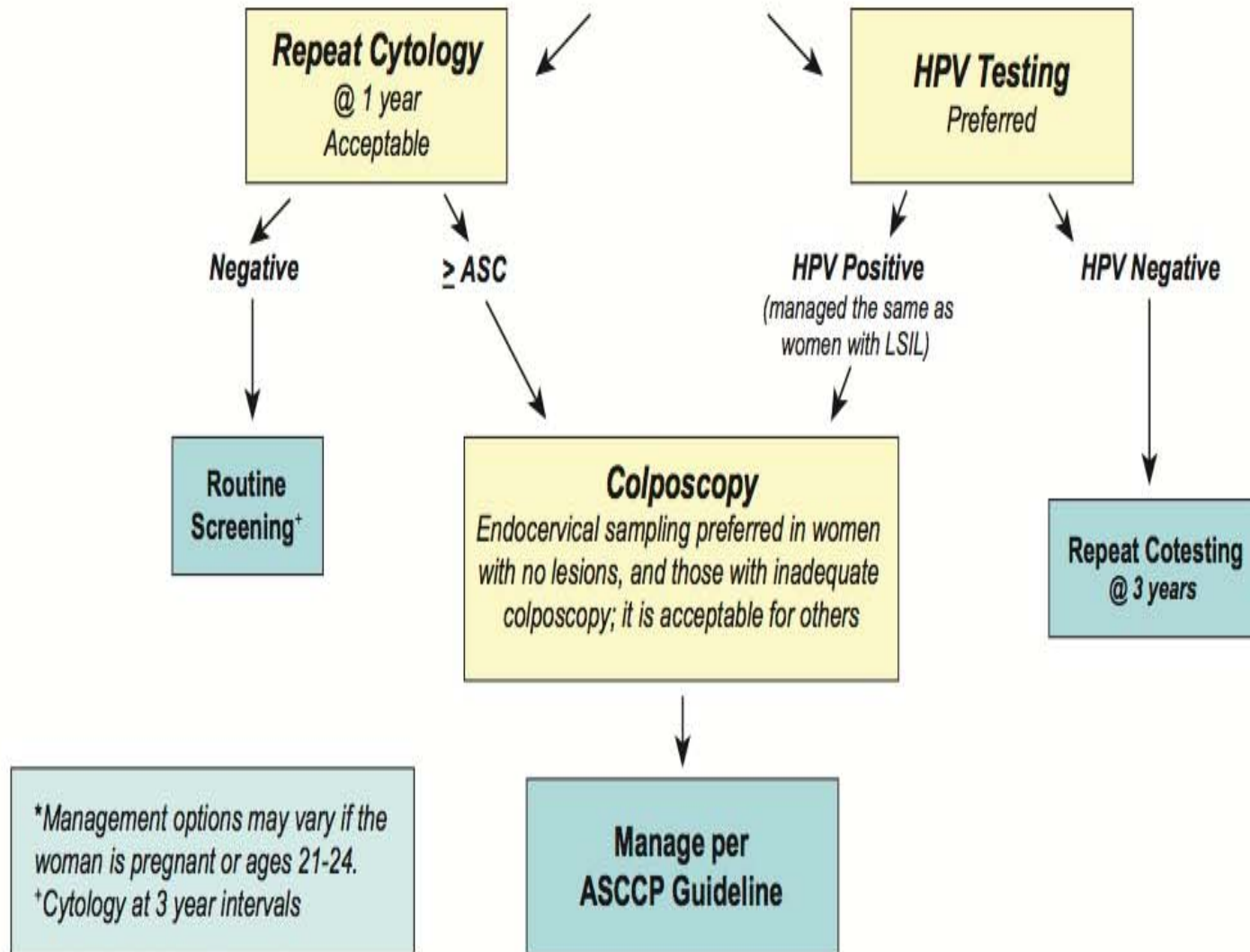


- Similar 90-95% efficacy as LEEP excision
- Must have satisfactory colposcopy and negative ECC
- N₂O versus CO₂
- Safe, low cost, available in low resource settings
- 3 min freeze-5 minute thaw-3 minute freeze vs 5 minute freeze

Managing ASCUS in adult women

- Up to 2/3 are HPV associated
- HPV+ more frequent in younger women
 - 60% age <25 vs 25% ages 45-55
- More frequent among those with multiple partners
- **HPV triage of ASCUS is more cost-effective than repeat cytology**

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

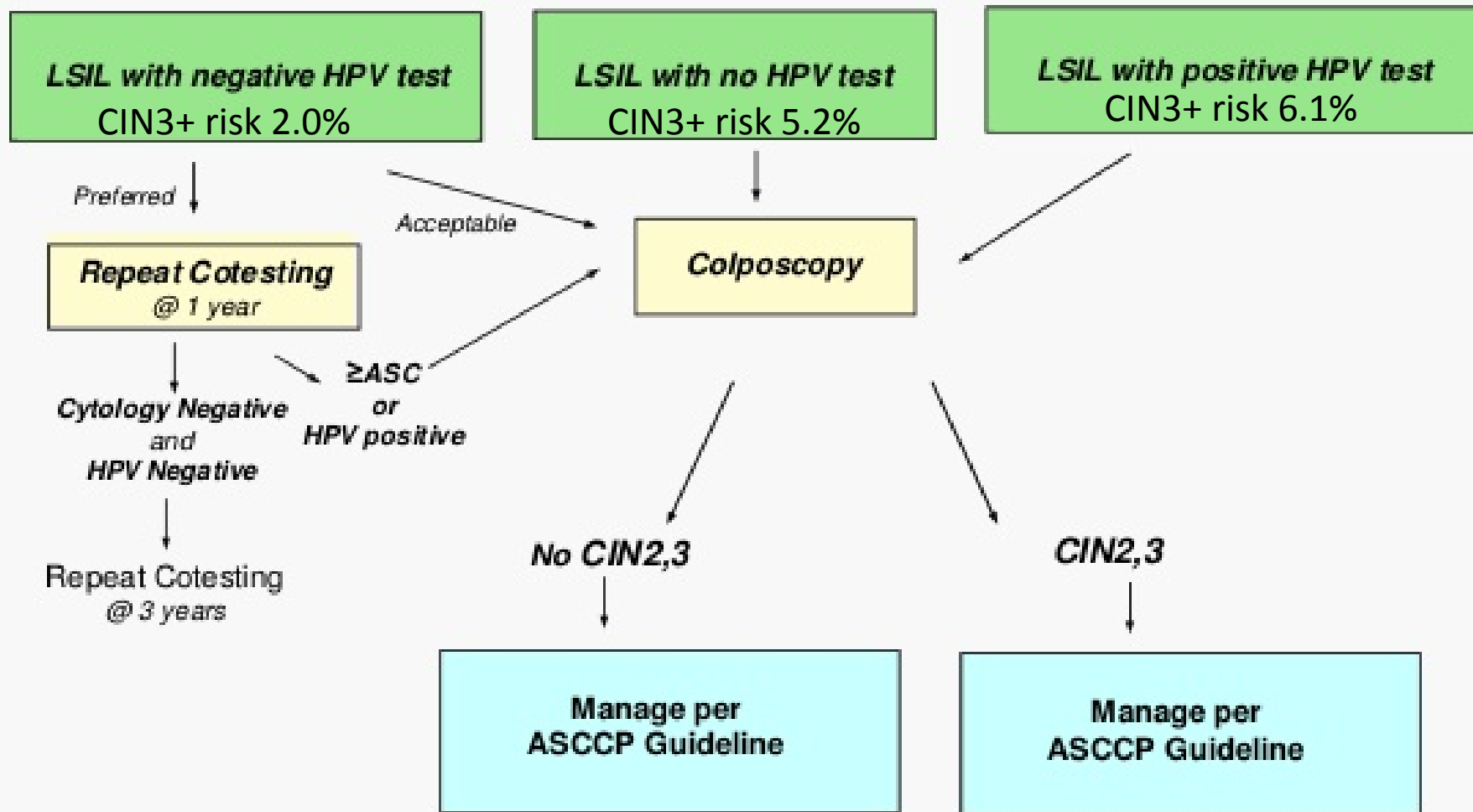


30 year old has had 3 normal Pap tests.
Pap shows LSIL and HPV test is negative.

What is the next step?

- Repeat co-testing in 3 years
- Colposcopy
- Repeat co-testing in 1 year
- Repeat Pap in one year

Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*



*Management options may vary if the woman is pregnant, postmenopausal, or ages 21-24 years (see text)

Figure 6

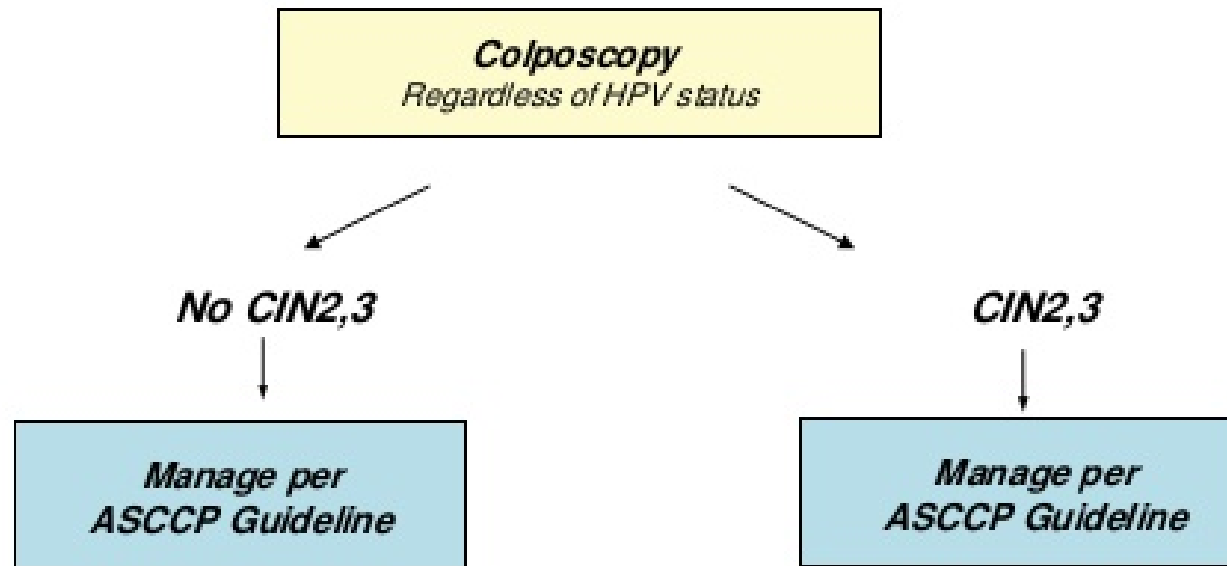
32 yo with history of abnormal Pap but records not available. Current ASC-H Pap and negative HPV. What is next step?

- Repeat co-testing in one year
- Repeat co-testing in 3 years
- Colposcopy
- Immediate see and treat

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

ASC-H/HPV- CIN3+ risk 3.5%

ASC-H/HPV+ CIN3+ risk 18%



**Management options may vary if the woman is pregnant or ages 21-24 years.*

HSIL in adult women

- Immediate CIN2+ risk is 60%
- Immediate CIN3+ risk is 36%
- CIN3+ risk increases to 47% at 5 years
- Colposcopy with endocervical assessment
- Immediate loop electrosurgical excision acceptable especially when future pregnancy not an issue
- 6% of women age 30-64 with HSIL will have cancer

Guidelines for Colposcopy

- Always recommend 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
 - Pap and HPV testing can be negative even when invasive cancer is present

Guidelines for Colposcopy

- Sensitivity of colposcopy is poor
 - The experts miss 18-36%
- Biopsies should be done with all colposcopies
 - If no lesions seen random biopsies+/-ECC
 - 20.9% of random biopsies show HSIL
- All visible lesions should be biopsied
- Sensitivity of colposcopy improves with every additional biopsy performed

Method of Diagnosing Women with CIN2+ (SPOCCS II)

Colpo biopsy	208/364 (57.1%)
Colpo biopsy + 2 o'clock	256/364 (70.3%)
Colpo biopsy + 2, 4 o'clock	297/364 (81.6%)
Colpo biopsy + 2, 4, 8 o'clock	329/364 (90.4%)
Colpo biopsy + 2, 4, 8, 10 o'clock	344/364 (94.5%)
Colpo biopsy + 2, 4, 8, 10 + ECC	364/364 (100%)

57.1% vs. 70.3% vs. 81.6% vs. 90.9% vs. 94.5% vs. 100%, Chi-Square = 326, df=5, P<.001

The accuracy of colposcopic biopsy: analyses from the placebo arm of the quadrivalent HPV vaccine clinical trials

LEEP Histology

	Neg	CIN1	CIN2	CIN3/AI S
Colpo Directed Biopsy				
Neg	195	82	29	54
CIN1	12	65	28	17
CIN2	1	2	21	25
CIN3/AI S	7	4	3	49
Total	215	153	81	145

CIN2+ called CIN1 or Neg 128/226 (57%)

CIN3/AIS called CIN1 or Neg 71/145 (49%)

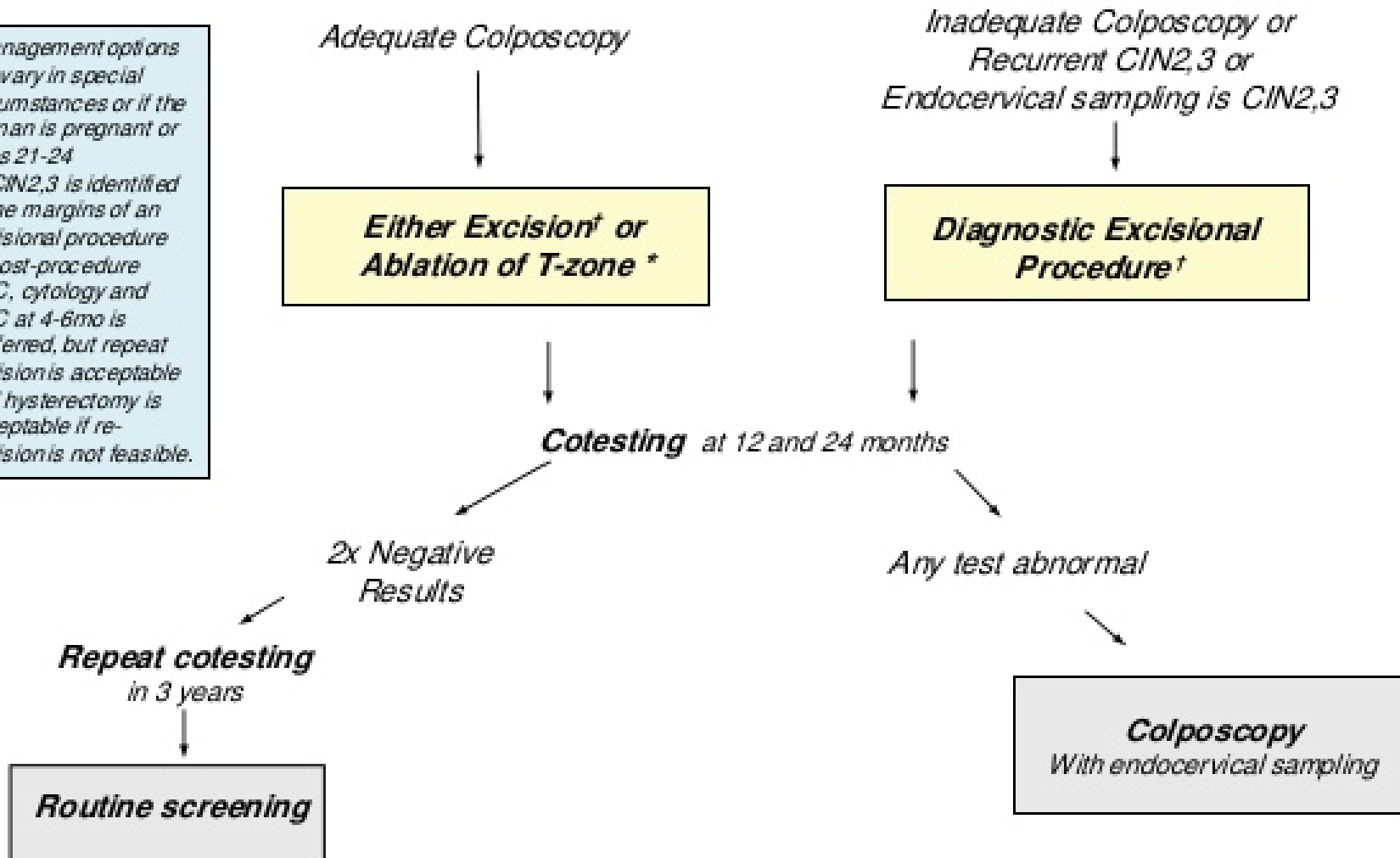
Stoler MH et al, Int J Cancer, 2010

40 year old had a LEEP for CIN 3. LEEP showed CIN 3. Margins negative. What is the next step?

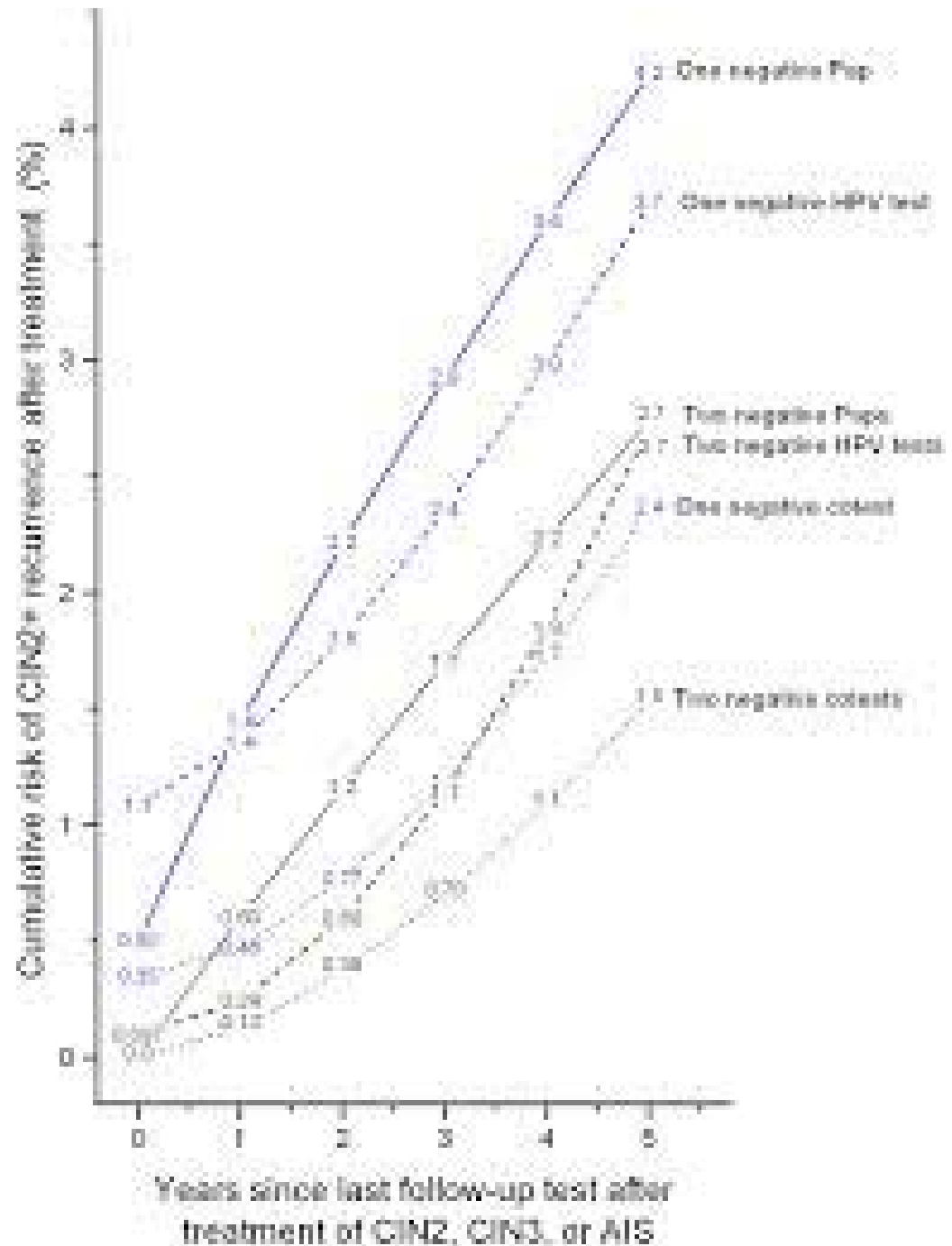
- HPV testing at 12 months
- Pap testing every 6 months
- Colposcopy and cytology at 6 and 12 months
- Co-testing at 12 and 24 months

Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2 and 3 (CIN2,3) *

**Management options will vary in special circumstances or if the woman is pregnant or ages 21-24
 † If CIN2,3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4-6mo is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.*



Cumulative risk of CIN2+ following subsequent negative follow up tests after treatment for CIN2,3, or AIS

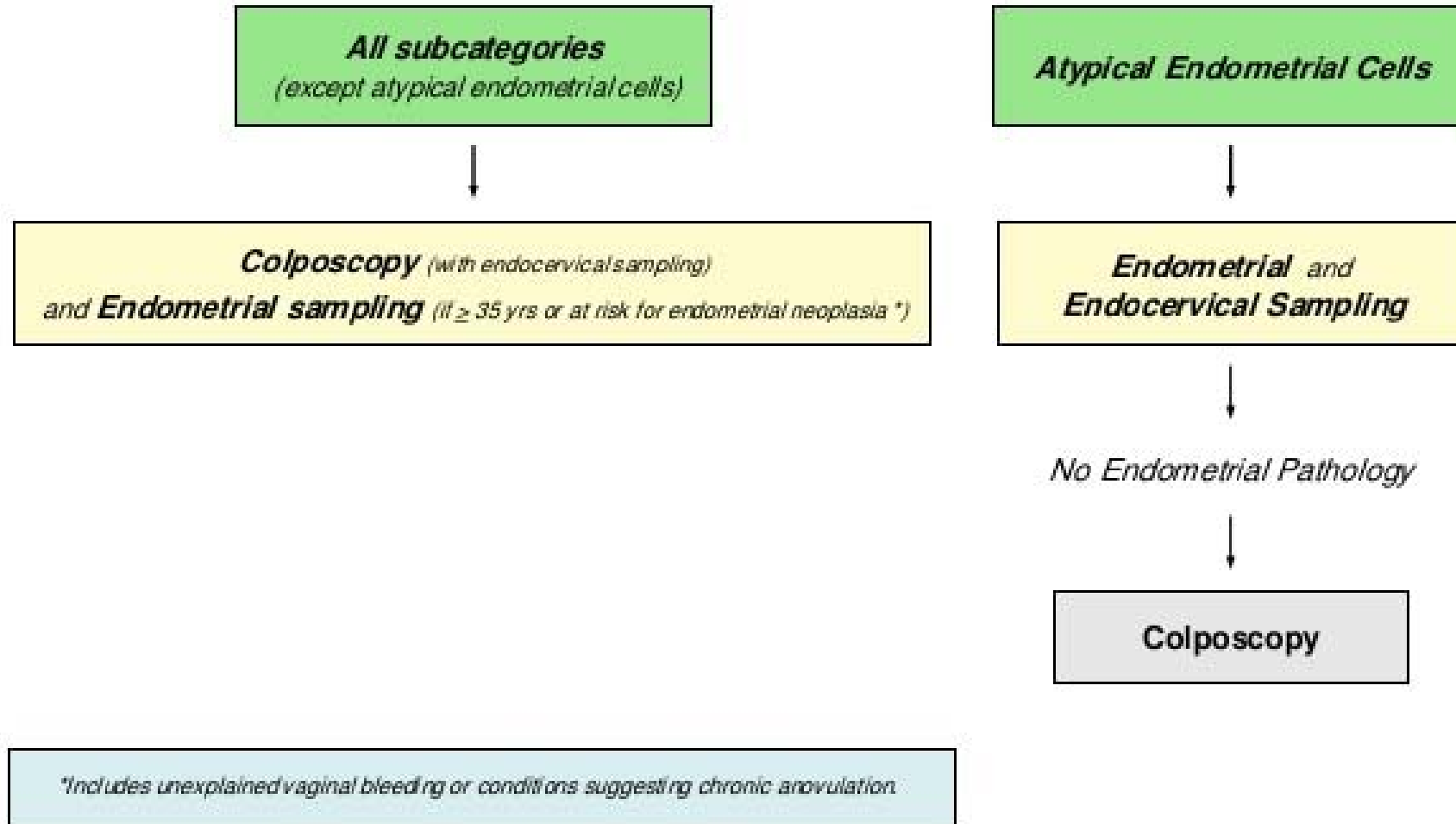


28 year old with a BMI of 68 and AUB-O has a Pap showing AGC-NOS. What is your next step?

1. Ask for reflex HPV testing
2. Repeat Pap in 6 months
3. Colposcopy with endocervical sampling
4. Endometrial sampling
5. Both colposcopy with ECC and endometrial sampling

Initial Workup of Women with Atypical Glandular Cells (AGC)

5 yr CIN3+ risk 8.5%



Review of 3,890 “AGCUS” Paps

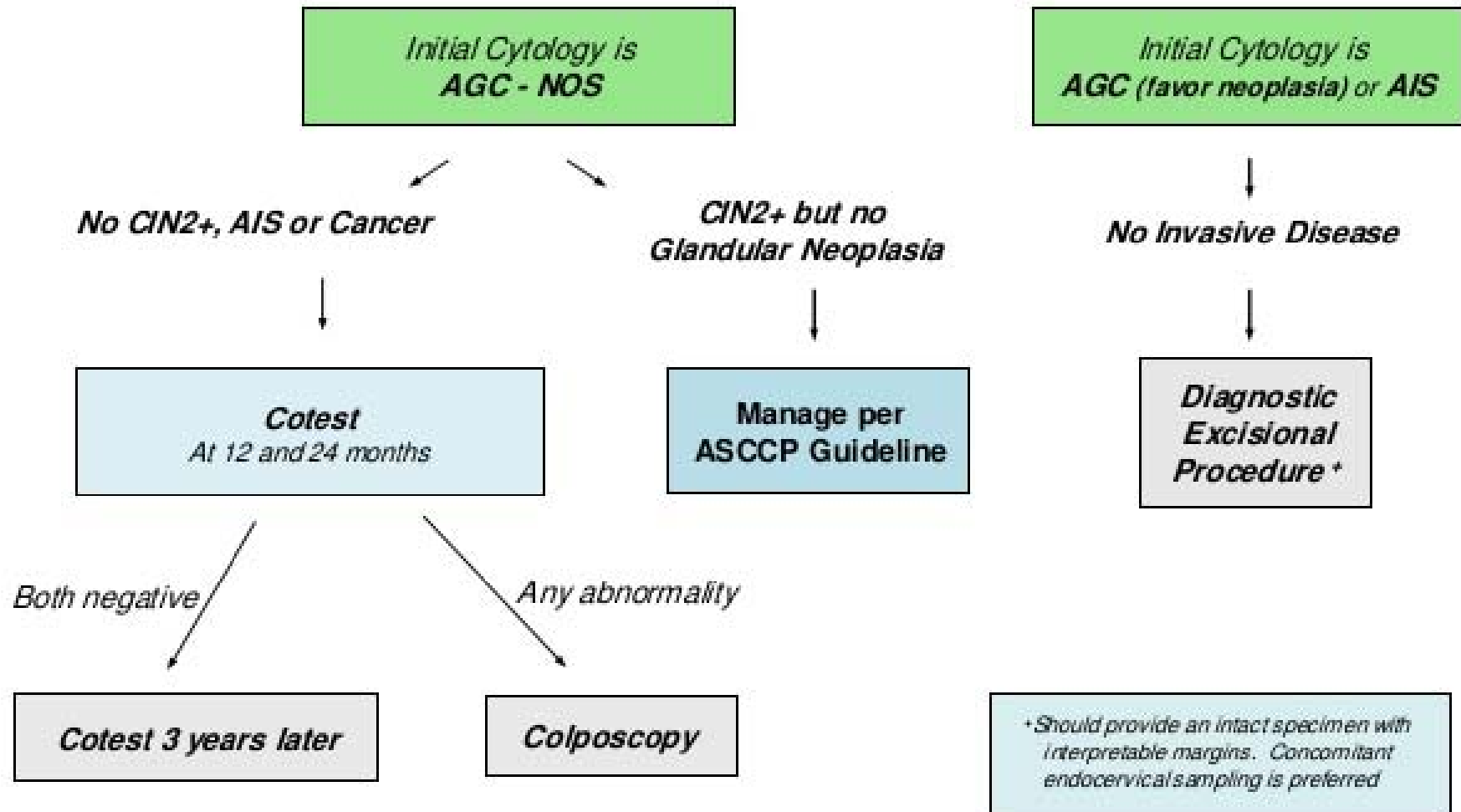
-5.2% had a malignancy

- 57.6% endometrial
- 23.6% cervical adenocarcinoma
- 6.9% other
- 5.4% cervical squamous cell carcinoma
- 5.4% ovarian
- 1% fallopian tube

– 23% had a significant finding

- 11.1% HSIL
- 8.5% LSIL
- 2.9% AIS
- 1.4% endometrial hyperplasia

Subsequent Management of Women with Atypical Glandular Cells (AGC)



Questions?



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