

Cervical Cancer Screening

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Cervical Cancer Screening

- Learning Objectives
 - Describe the etiology, natural history, and usage of the human papillomavirus (HPV) in cervical cancer screening
 - Discuss the rationale for the currently available cervical cancer screening modalities
 - Give examples of the management of abnormalities identified during cervical cancer screening

Cervical Cancer Screening

- Disclosures
 - I have no financial interest or other conflict of interest in relation to this program/presentation.

Cervical Cancer Screening

Top 5 Cervical Cancer Screening Take Home Messages

Cervical Cancer Screening

1. “Most cases of cervical cancer occur in women who were either never screened or screened inadequately”

Cervical Cancer Screening

2. “Liquid-based and conventional methods of cervical cytology specimen collection are acceptable for screening”

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3. “Infection with oncogenic HPV is a necessary but not sufficient factor for the development of squamous cervical neoplasia.

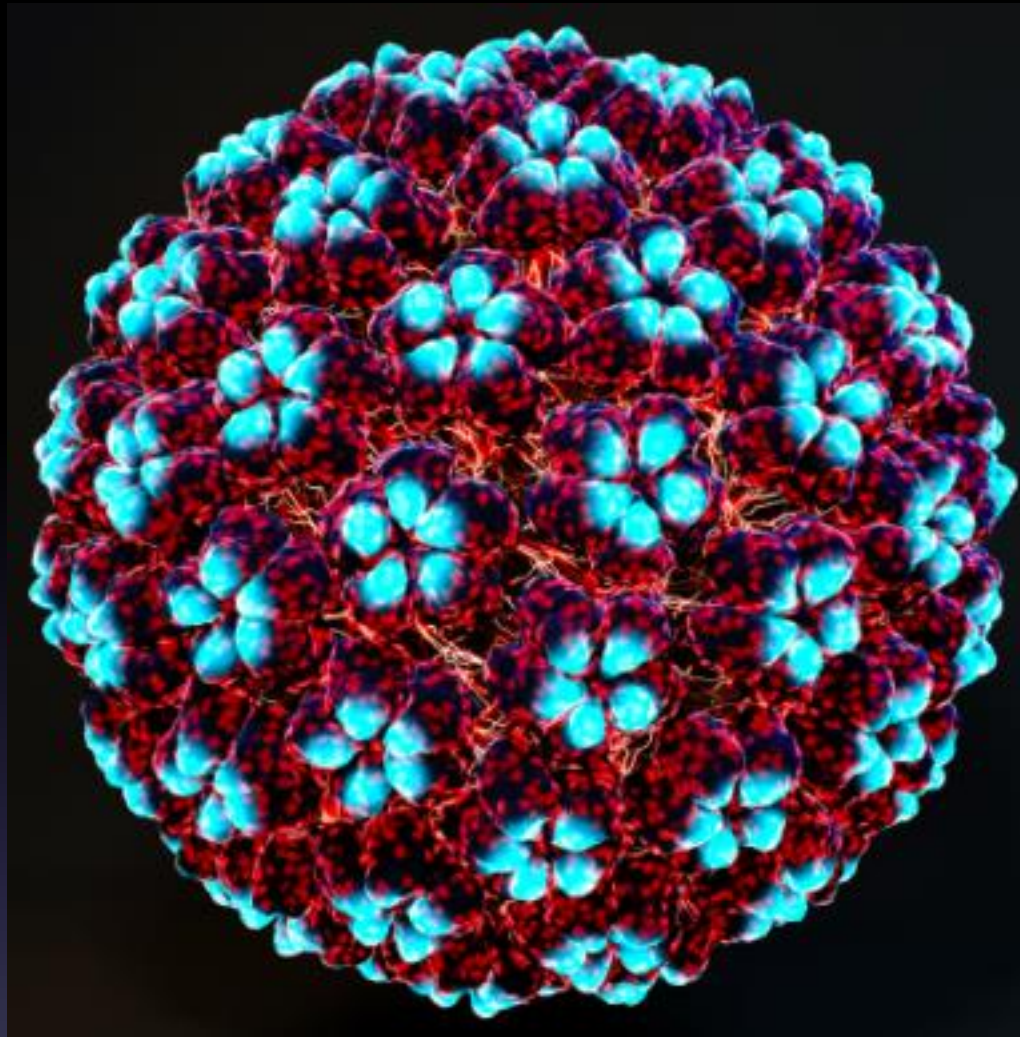
Cervical Cancer Screening

4. “The shift from cytology to HPV testing will be a significant change-from an oncologic screening paradigm to a communicable disease paradigm”

Cervical Cancer Screening

5. Screening and management algorithms are too complicated to remember...GET THE APP!





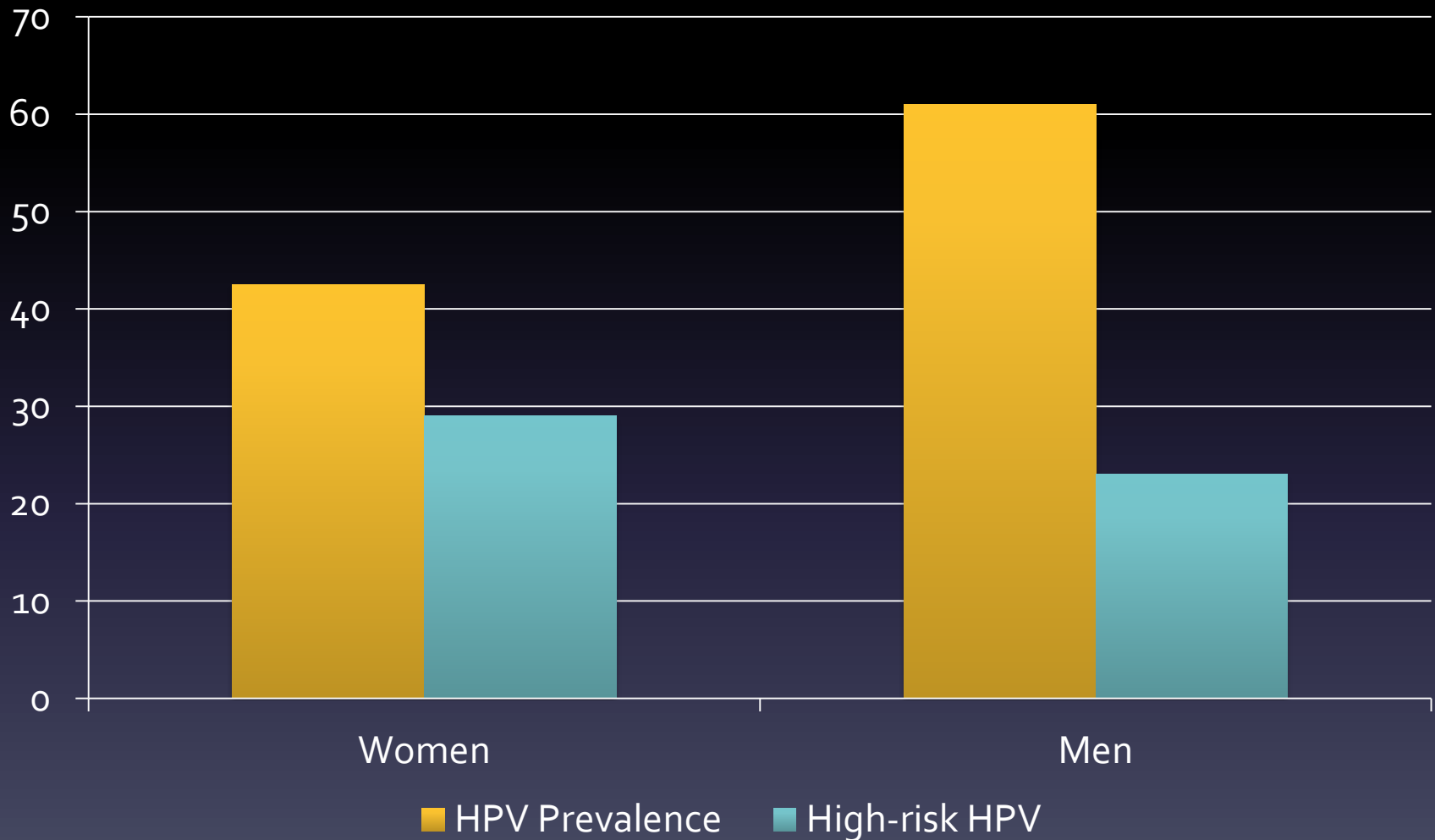
HUMAN PAPILLOMAVIRUS (HPV)
HARALD ZUR HAUSEN – ISOLATED HPV 16 IN 1983

HPV

- **HPV Transmission**

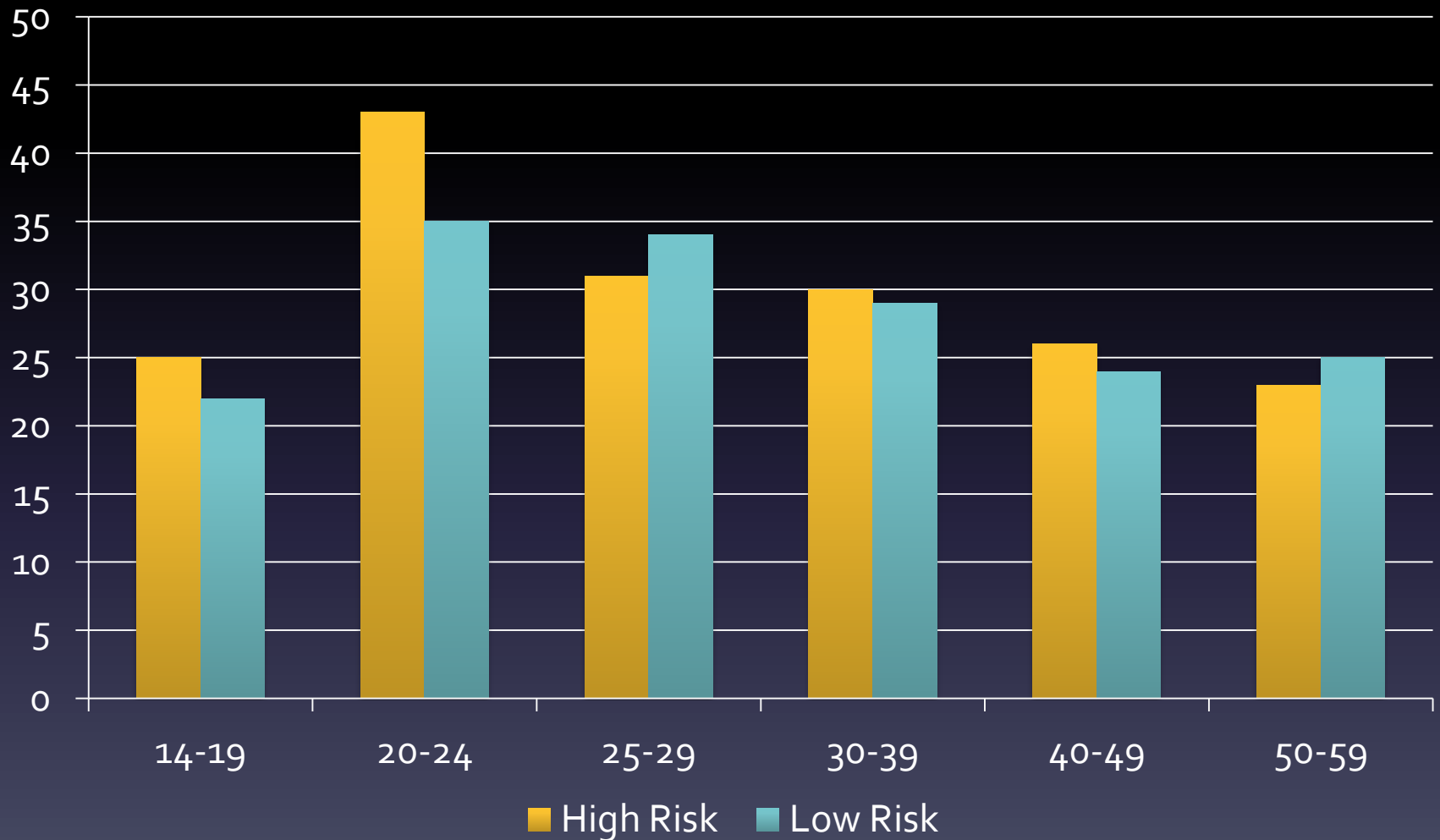
- Almost exclusively acquired from sexual exposure
- Concordance among partners varies from 40-60%
- HPV detected from multiple sites: cervix, anus, penis, hands, scrotum, vulva, and oropharynx
- Vertical transmission occurs in 20-30% of patients
 - Majority of neonatal infections are cleared by the first year of life

HPV Prevalence



Hariri S et al. J Infect Dis. 2011. Aug 15;
204(4): 566-573.

HPV Prevalence



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HPV

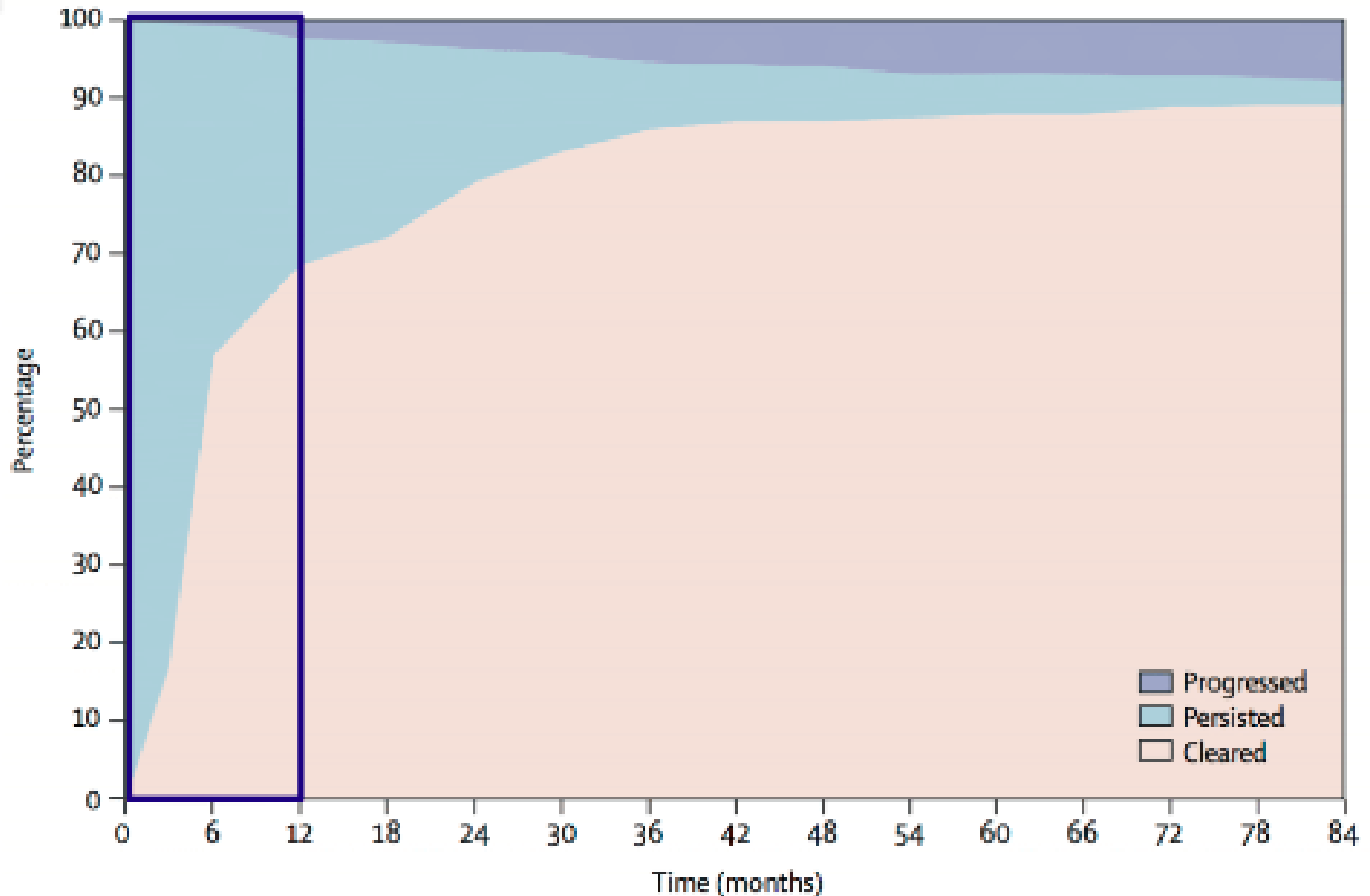
- Natural History of Infection
 - “The majority of HPV infections are cleared and only a minority persist and progress to CIN or invasive cancer”
 - Young women are more likely to clear infections than older women
 - Low risk HPV infections clear more quickly than high-risk HPV infections
 - Men have higher rates of HPV clearance

HPV Clearance vs. Progression

Gender	Time Frame	Clearance Rate
Women	1 year	40-70%
	2-5 year	70-100%
Men	1 year	75%

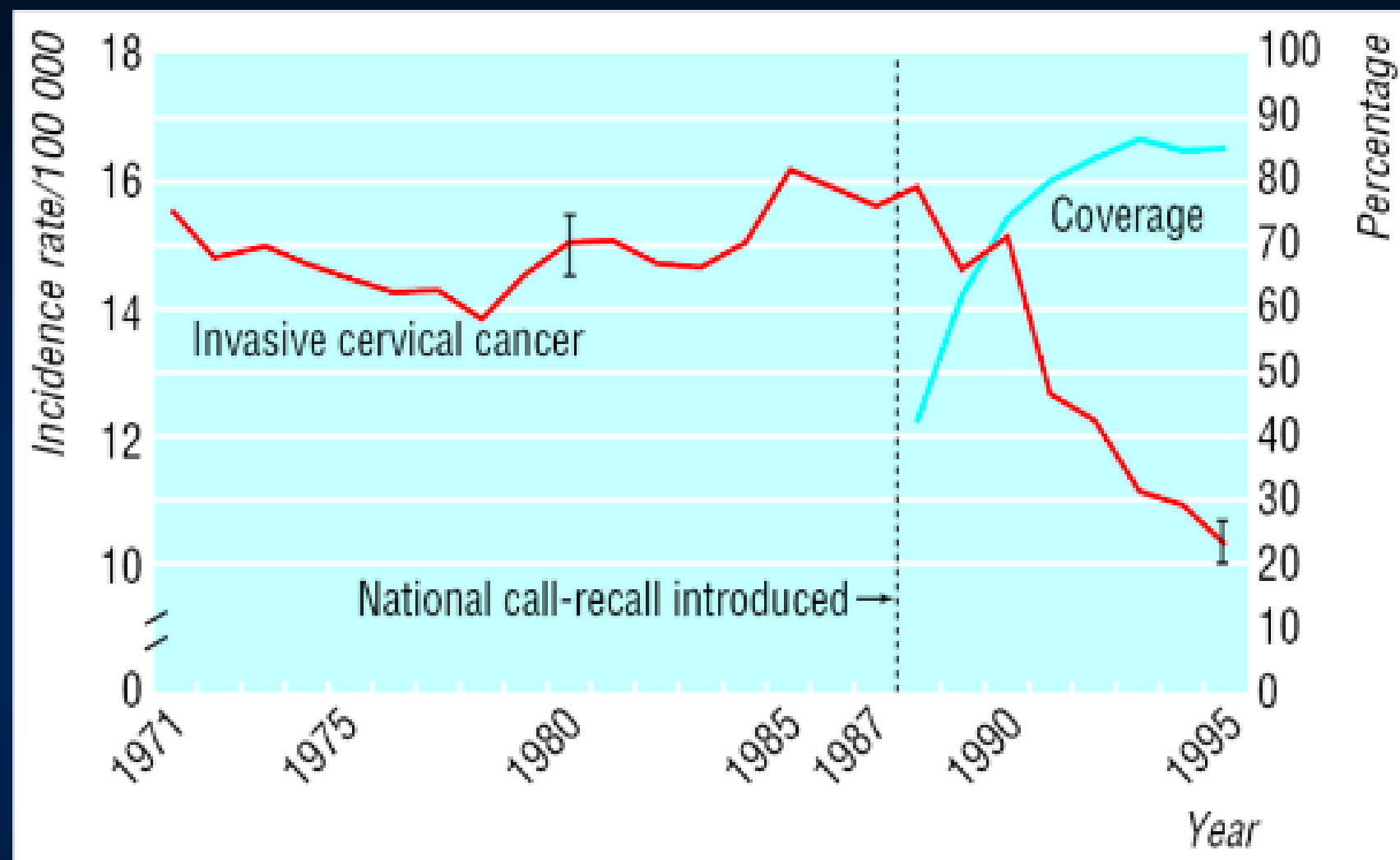
Among Women Who Do Not Clear Their Infection	
CIN 2-3	8-28%
Cervical cancer	3-5%

Natural History of HPV



HPV Testing

- Indications for HPV Testing
 - Women > 21 with an ASCUS Pap smear
 - Co-testing with cytology in women > 30
 - Follow-up after excisional procedures or ablation of CIN_{2,3}
 - Management of postmenopausal women with LSIL
 - Management of women with AGC
 - Follow-up of CIN 1 when it was preceded by LSIL, ASCUS, and ASC-H



Age standardized incidence of invasive cervical cancer and coverage of screening, England, 1971-95
(Quinn *et al.*, *BMJ* 1999; 318: 9048)

Cervical Cytology (Pap)

- Why did we move away from cytology alone?
 - Very subjective
 - Low reproducibility rate
 - Not as sensitive for CIN₂, ₃ as previously thought
 - Identifies women with lesions; not those at risk for developing lesions

Cervical Cytology (Pap)

Variability of Cervical Cytology

	<u>LAB A</u>	<u>LAB B</u>	<u>LAB C</u>	<u>LAB D</u>
Number	12,294	4,218	16,979	12,442
Median Age	40.9	37.9	39.3	40.1
≥ASCUS	3.8%	5.2%	8.1%	9.9%

Very Subjective with Low Reproducibility

Cervical Cytology (Pap)

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Sensitivity of cytology	42.0%	51.0%	60.5%	73.0%

In Athena Trial, 53.5% of women with CIN 3 or >, had NORMAL liquid based cytology

Cervical Cytology (Pap)

Comparative Sensitivity Cross Sectional Studies

Author	Year	#	Endpt	Pap	HPV	Cotest
Petry	2003	8466	CIN2+	44%		
Ronco	2006	16706	CIN2+	74%		
Kulasingham	2002	4075	CIN3+	61%		
Bigras	2005	13842	CIN2+	59%		
Mayrand	2007	10153	CIN2+	58%		
Ikenberg	2013	19250	CIN2+	66%		
ATHENA	2014	40901	CIN3+	43%		

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Cervical Cytology (Pap)

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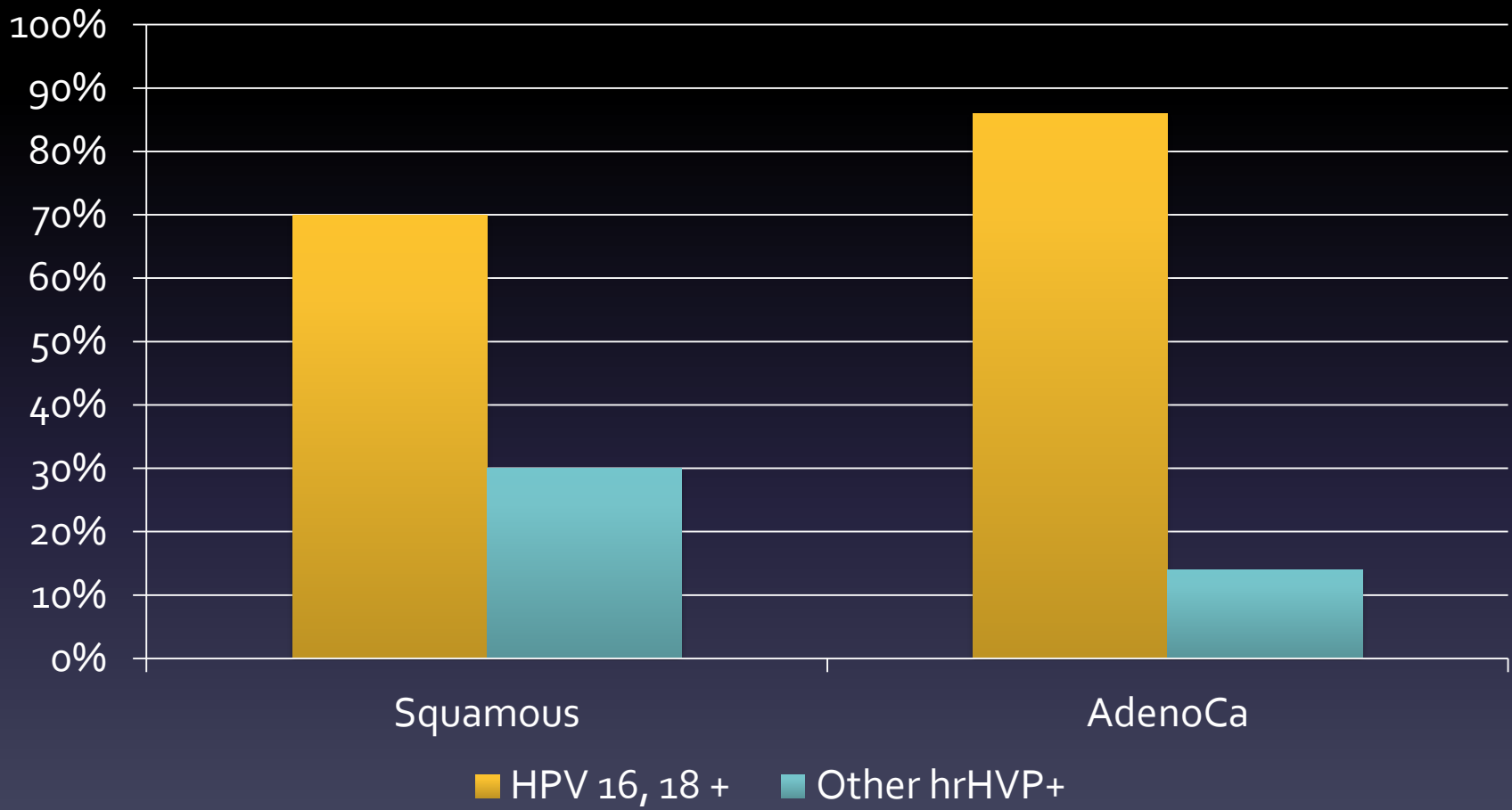
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Sensitivity of cytology	42.0%	51.0%	60.5%	73.0%
Sensitivity of HPV	90.1%	88.2%	88.4%	88.9%

Cervical Cytology Co-Testing



Cervical Cancer Screening

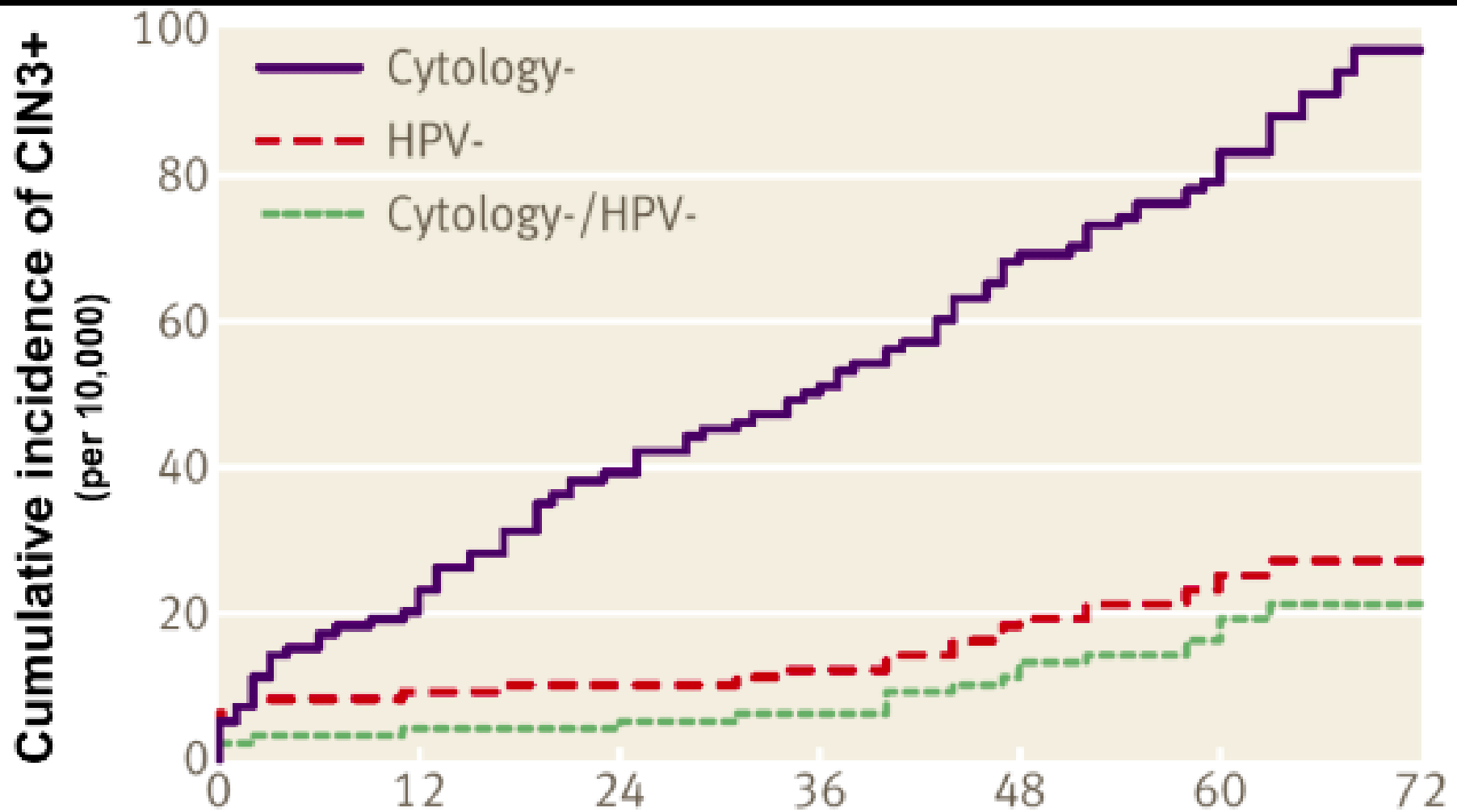
- **Advantages of Screening with Co-testing**
 - More sensitive for CIN₂, ₃ than cytology alone
 - Allows interval extension to 5 years
 - Using HPV allows us to identify women at-risk for cervical disease in the future
 - Identifies a higher rate of adenocarcinoma

Primary HPV Screening

Comparative Sensitivity Cross Sectional Studies

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Cervical Cancer Screening



Primary HPV Screening

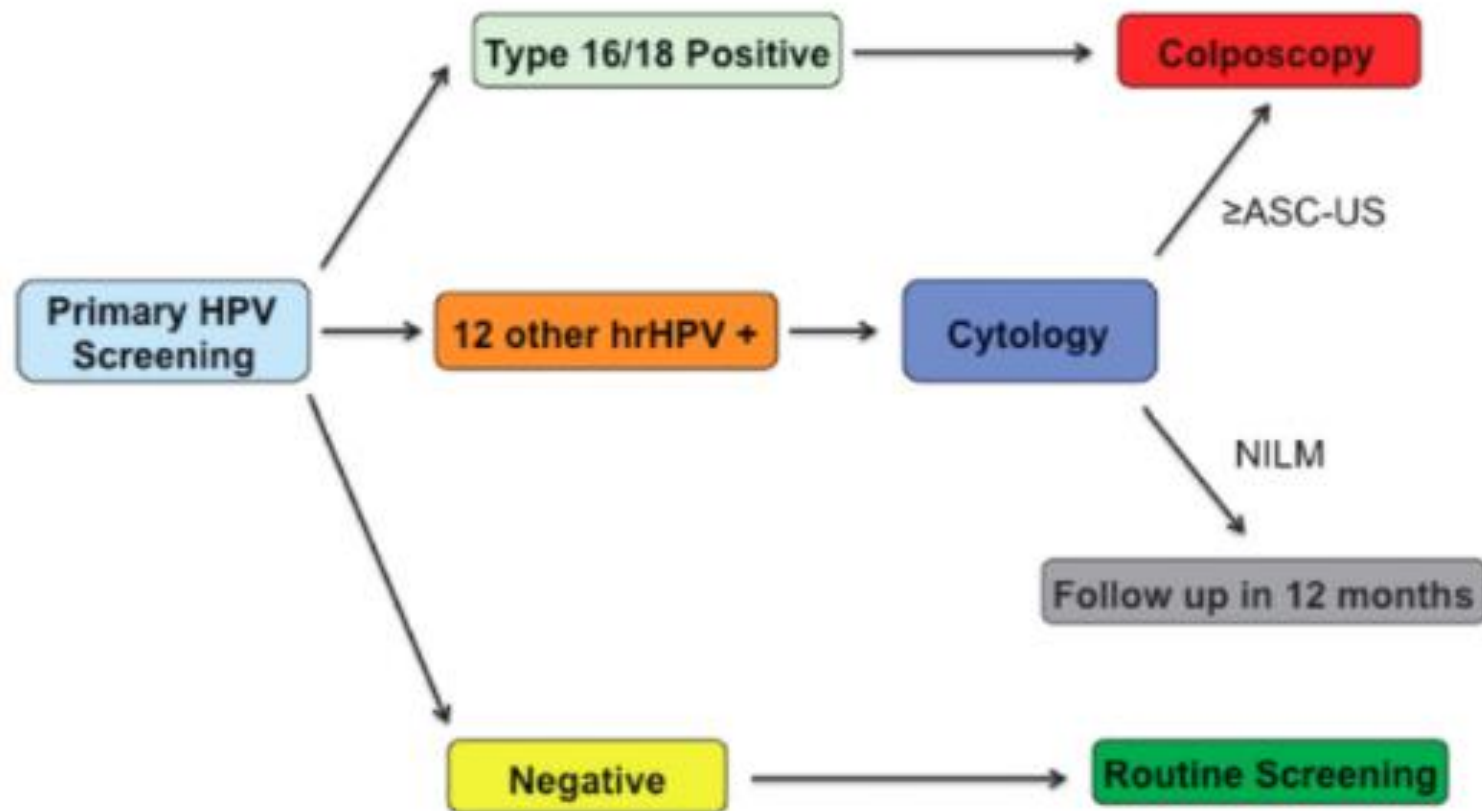


FIGURE 1. Recommended primary HPV screening algorithm. HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ASC-US, atypical squamous cells of undetermined significance; NILM, negative for intraepithelial lesion or malignancy.

HPV Screening

<u>HPV Type Matters</u>	
<u>HPV Results</u>	<u>10-Year Risk of CIN 3</u>
HPV 16+	17%
HPV 18+	14%
Other hrHPV (+)	3%
hrHPV (-)	<1%

“HPV Persistence is perhaps the most important risk factor for cervical cancer”.

Huh WK et al. Am J Obstet Gynecol.
2017;216(3):206-207.

Primary HPV Screening

<u>Primary HPV Screening</u>		
<u>Method</u>	<u>Sensitivity</u>	<u>Specificity</u>
Cytology	53%	96%
Primary HPV	96%	90%

Primary HPV Screening

Comparison of Strategies in Women > 25

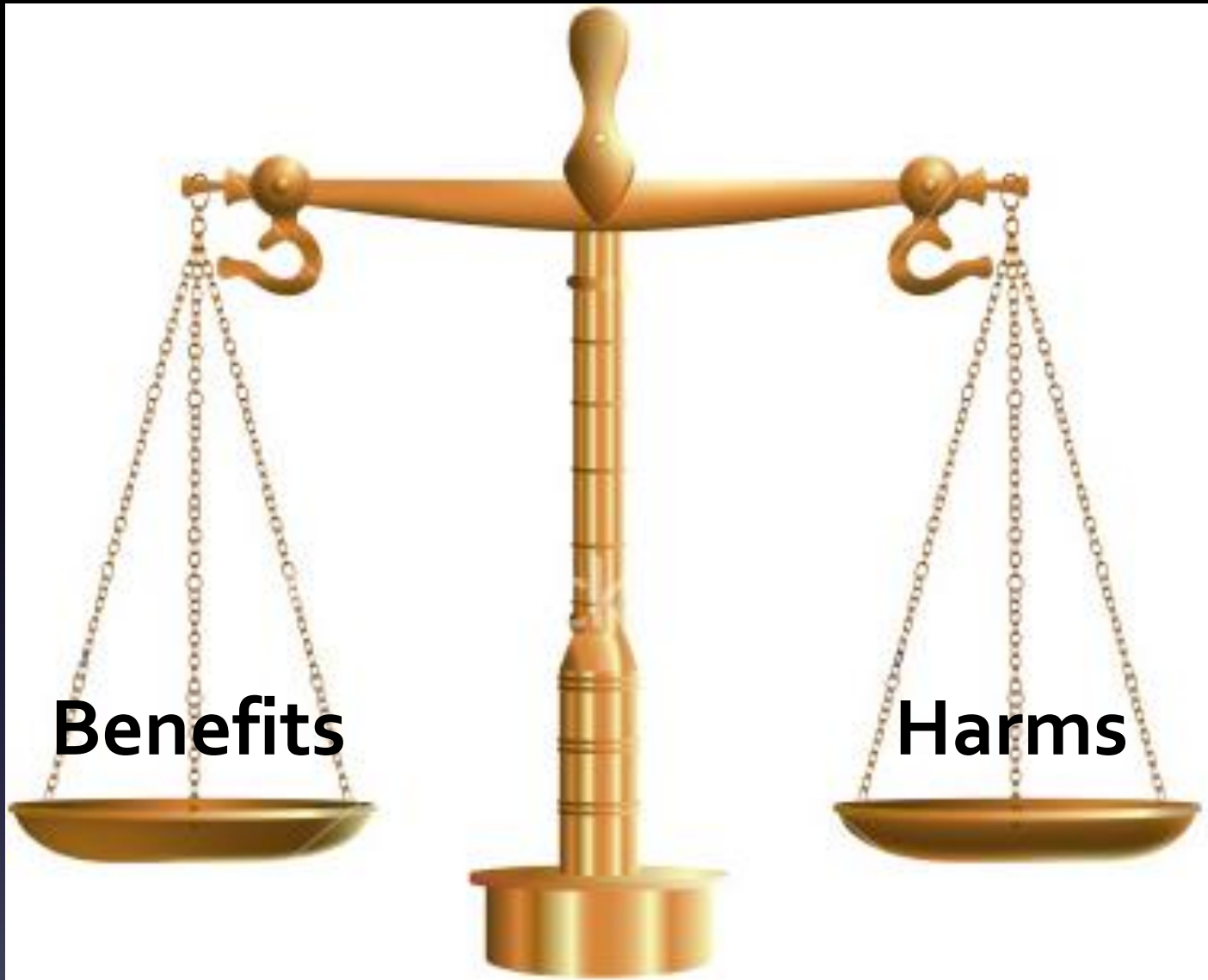
Strategy	# Tests	CIN ₃ Baseline	CIN ₃ + Yrs 1-3	CIN ₃ + Missed	Colpos	Colpos Per CIN ₃
Cytology	45,166	143	36	168	1934	10.8
Cotesting	82994	143	97	107	3097	12.4
HPV only	52651	197	97	53	3769	12.8

Tradeoff between CIN₃ detected and number of colposcopy procedures

Cervical Cancer Screening

USPSTF Draft Recommendations for Cervical Cancer Screening

<u>Age</u>	<u>Recommendation</u>
21-29	Cytology alone every 3 years
30 - 65	Cytology alone every 3 years OR HPV-testing alone every 5 years



SCREENING GUIDELINES

Cervical Cancer Screening



Adolescent (< 21 Years of Age)

Cervical Cancer Prevention

- Safe sexual practices to limit exposure to sexually transmitted infections
- HPV vaccination
- Initiation of reproductive health care should not be predicated on screening



Cervical Cancer Screening

- Cancer screening should begin at age 21
 - Why?
 - 1-2 cases of cervical cancer per year per 1,000,000 females aged 15-19
 - Screening younger women has not decreased the rate of cervical cancer
 - Nearly all cases of HPV are cleared by the immune system within 1-2 years without producing neoplastic change

Cervical Cancer Screening

- Cancer screening should begin at age 21
 - Exception
 - Women who are infected with HIV or who are otherwise immunocompromised should be screened

Cervical Cancer Screening



Women Age 21 - 29

Cervical Cancer Screening

21-29 years

- **Women aged 21-29 years should be tested with cervical cytology alone**
- Screening should be performed every 3 years
- HPV co-testing should **NOT** be performed
 - Very high prevalence of high risk HPV infection
 - Low incidence of cervical cancer in this population
 - Transient infection without carcinogenic potential

Cervical Cancer Screening

21-29 years

Why only screen every 3 years?

Comparison of Cervical Cancer Screening

<u>Frequency</u>	<u>Cancer Detected</u>	<u># of Colpo</u>
2 Years	37/100,000	176/100,000
3 Years	39/100,000	134/100,000

Cervical Cancer Screening

30 - 65 years




**Pap+HPV
Together™**
She's worth it

Learn about **Pap+HPV Together™**
(co-testing), the preferred
cervical cancer screening method
for women ages 30 to 65.

Cervical Cancer Screening

30 - 65 years

- Women aged 30 – 65
 - Preferred: Co-testing with cytology and HPV testing
 - Acceptable: Cytology alone every 3 years

Screening Results	5-Year Risk of CIN 3 or >
Negative cytology alone	0.26%
Negative co-testing	0.08%

Cervical Cancer Screening



Women > 65

Cervical Cancer Screening

- Women aged > 65
 - Screening should be discontinued in women with:
 - Evidence of adequate negative prior screening test results
 - No history of CIN 2 or higher
 - What is adequate negative screening?
 - 3 consecutive negative cytology results or
 - 2 consecutive negative co-testing results within the previous 10 years.

Cervical Cancer Screening

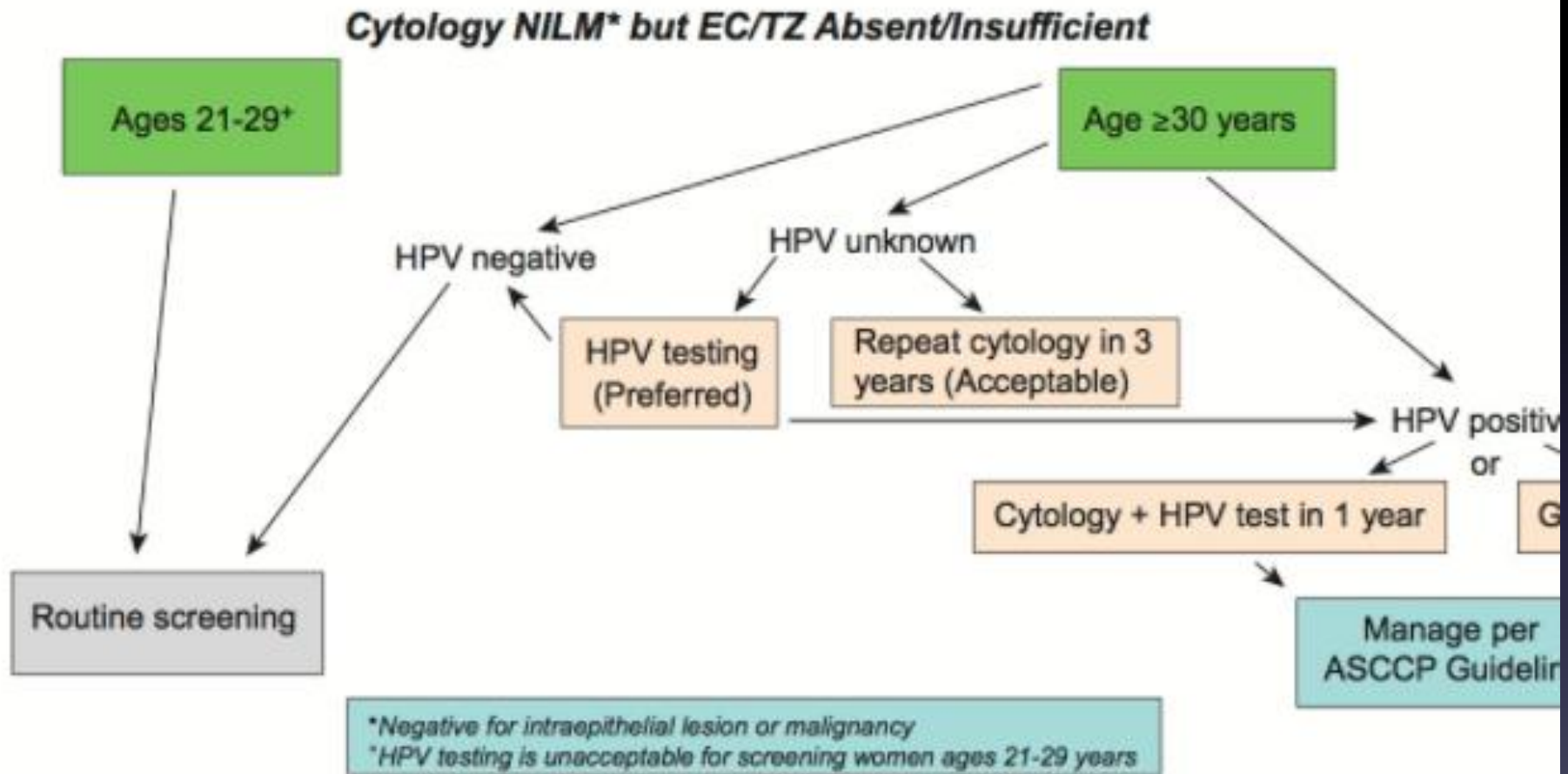
- Women aged > 65
 - Represent 14.1% of the population but account for 19.6% of the new cases of cervical cancer
 - Why do we stop screening?
 - Most cases occur in unscreened women
 - Cervical cancer occurs 15-25 years after HPV infection
 - Screening between 65 and 90 every 3 years would prevent 1.6/1000 cases of cancer
 - Increased false positive cytology results due to atrophy

Cervical Cancer Screening

- Women with a previous hysterectomy
 - If they have never had a h/o CIN2 or >, routine screening should be discontinued and not restarted for any reason
 - For those with a history of CIN2 or >, screen with cytology alone every 3 years for 20 years

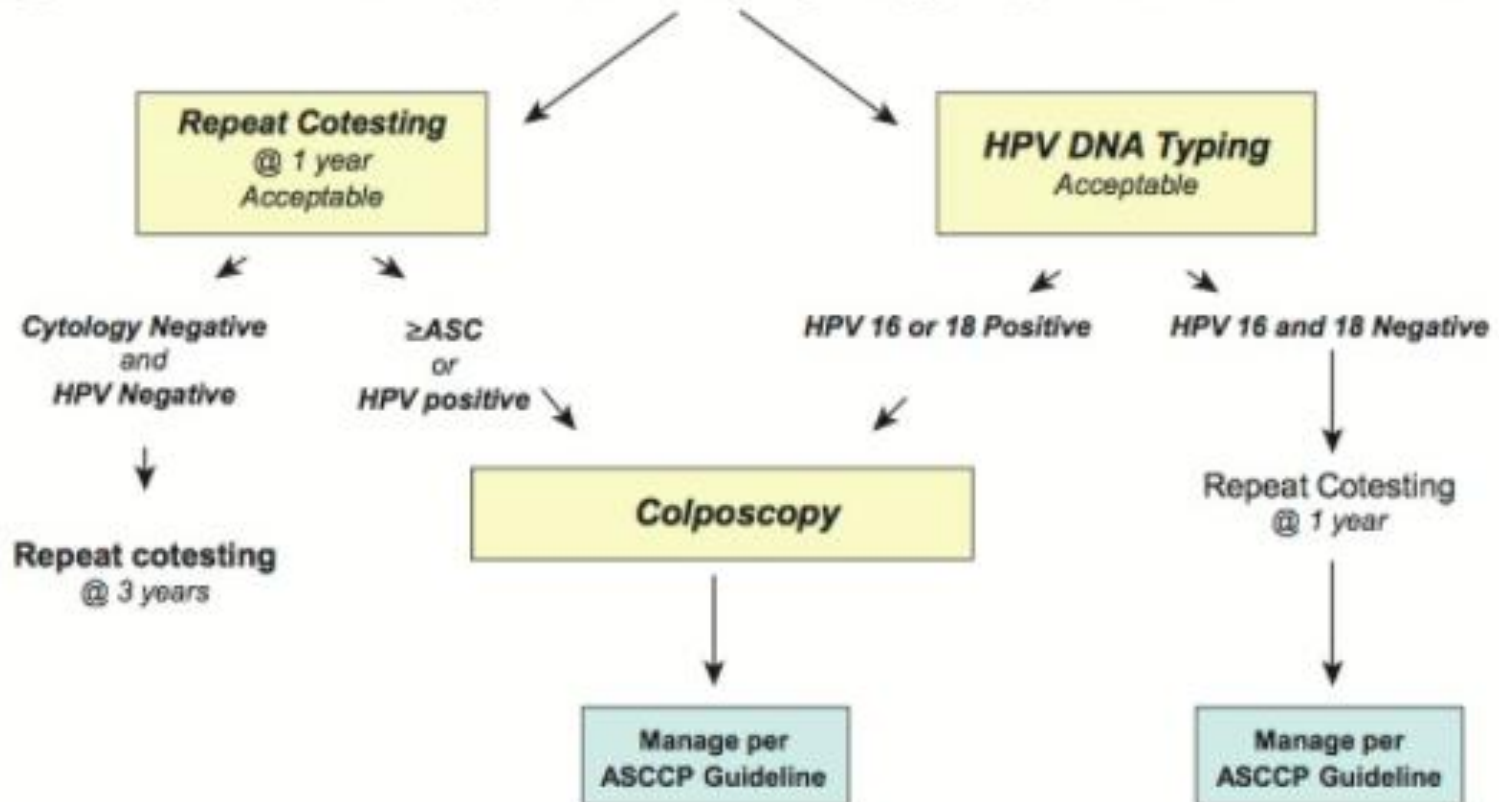
MANAGEMENT OF CERVICAL CANCER SCREENING RESULTS

Absent Endocervical Cells



Cytology Negative/HPV Positive

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



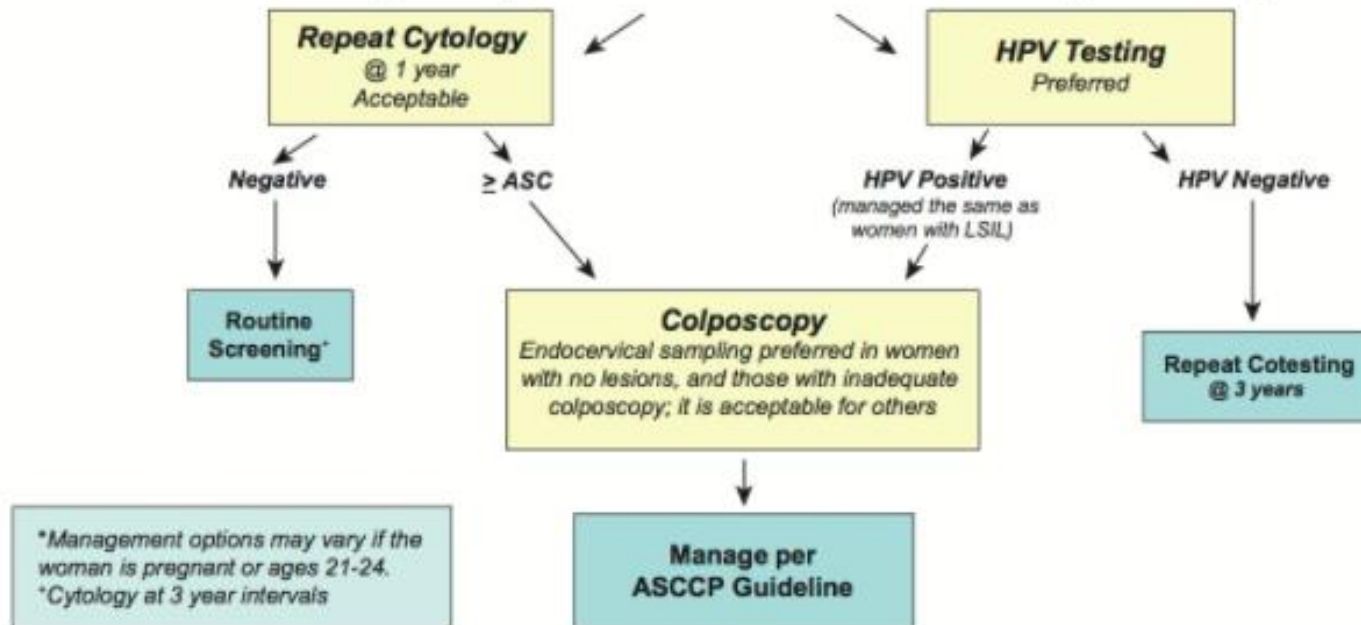
Cytology Negative/HPV Positive

Kaiser Permanente Northern California Study		
<u>Screening Test</u>	<u>5-Year - CIN₃</u>	<u>5-Year - Cancer</u>
Negative Co-test	0.08%	0.011%
ASCUS-HPV (-)	0.43%	0.05%
Negative-HPV (+)	4.5%	0.34%

“Repeat cotesting in 1-year allows most women with transient infection and no carcinogenic risk sufficient time for the HPV infection to clear and identifies a smaller group at risk of precancerous lesions to undergo colposcopy.”

ASCUS Cytology Results

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



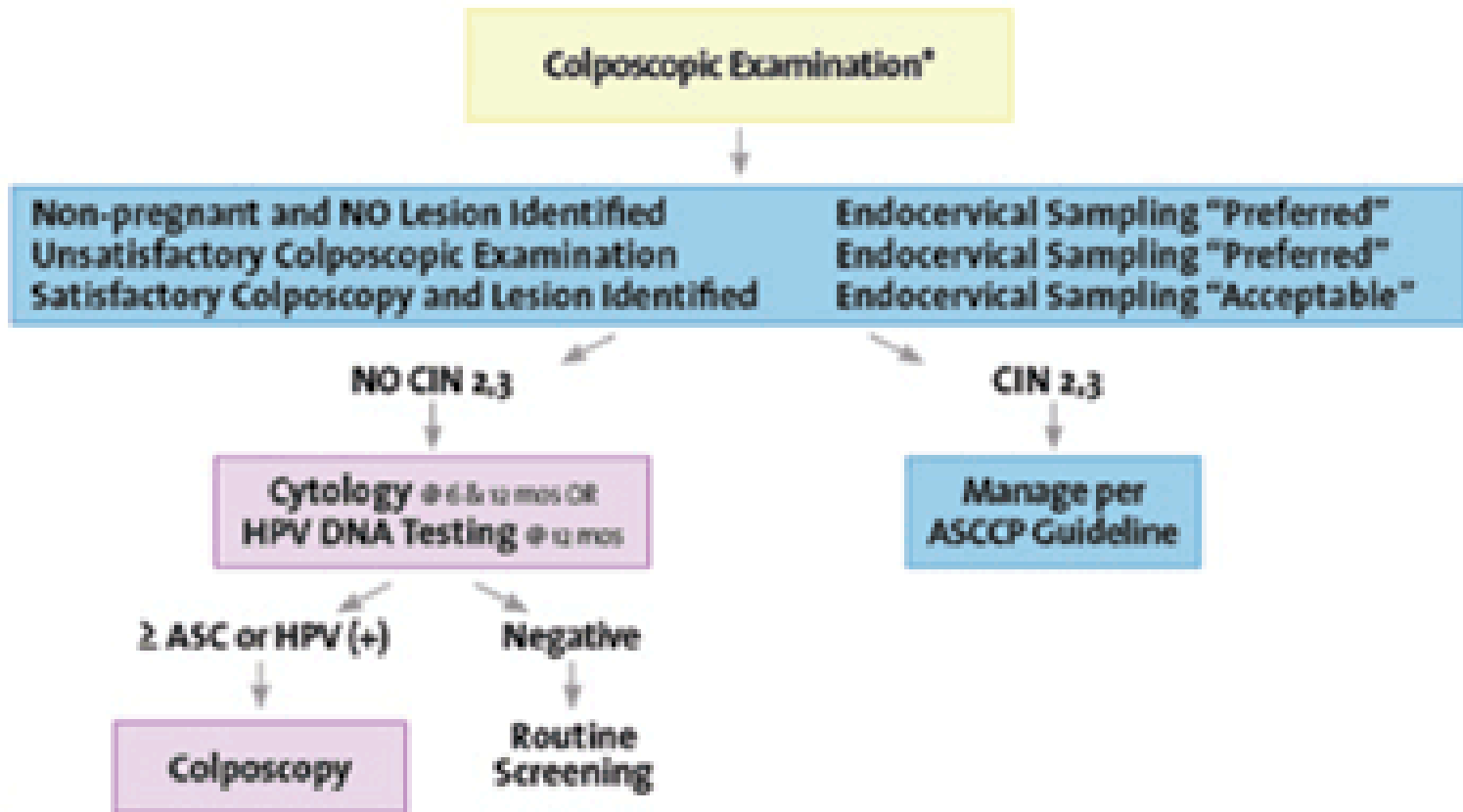
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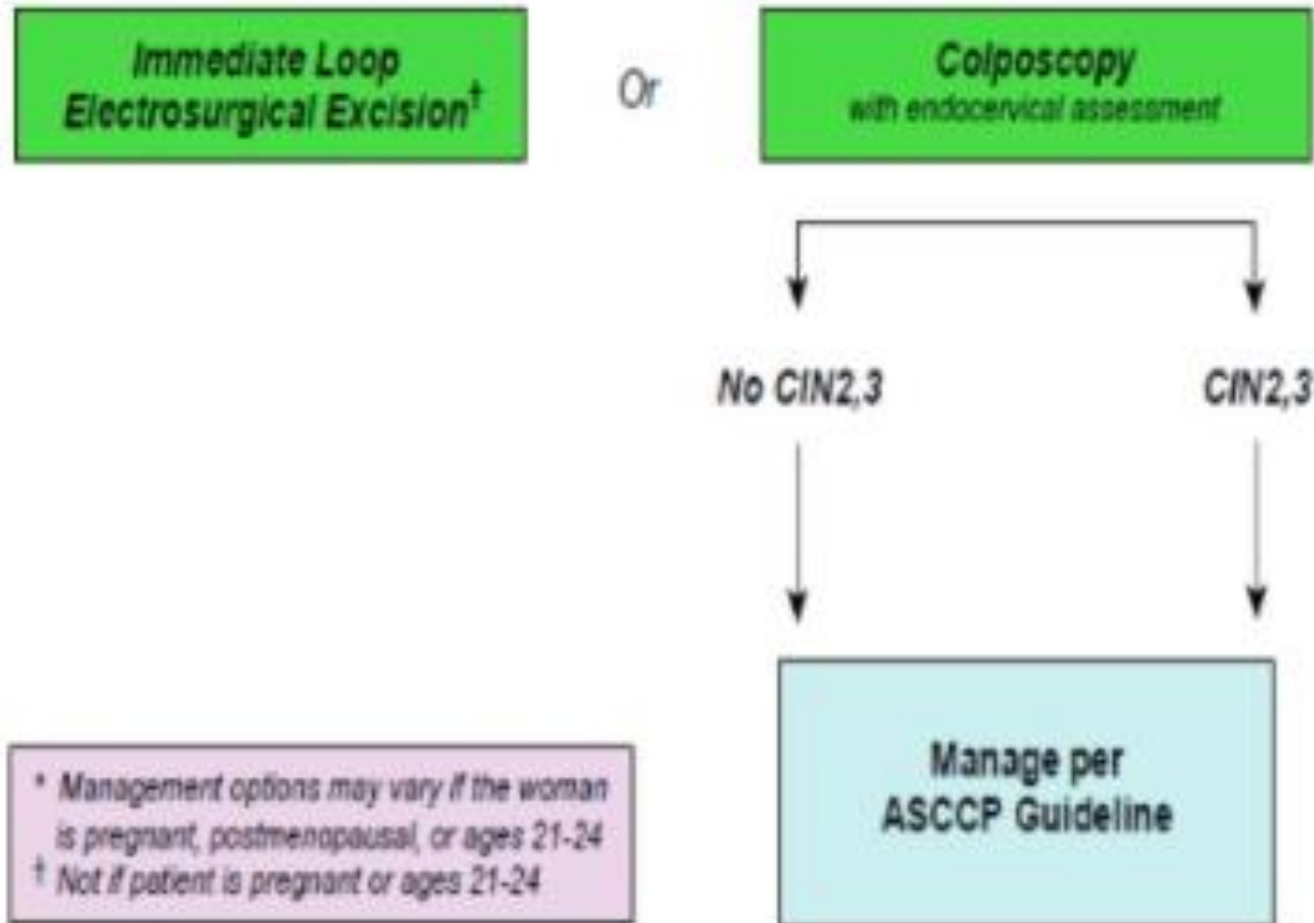
“Women aged 30-65 with ASCUS-HPV (-) cytology results should have follow-up co-testing in 3 years rather than in 5 years”

LSIL Cytology Results

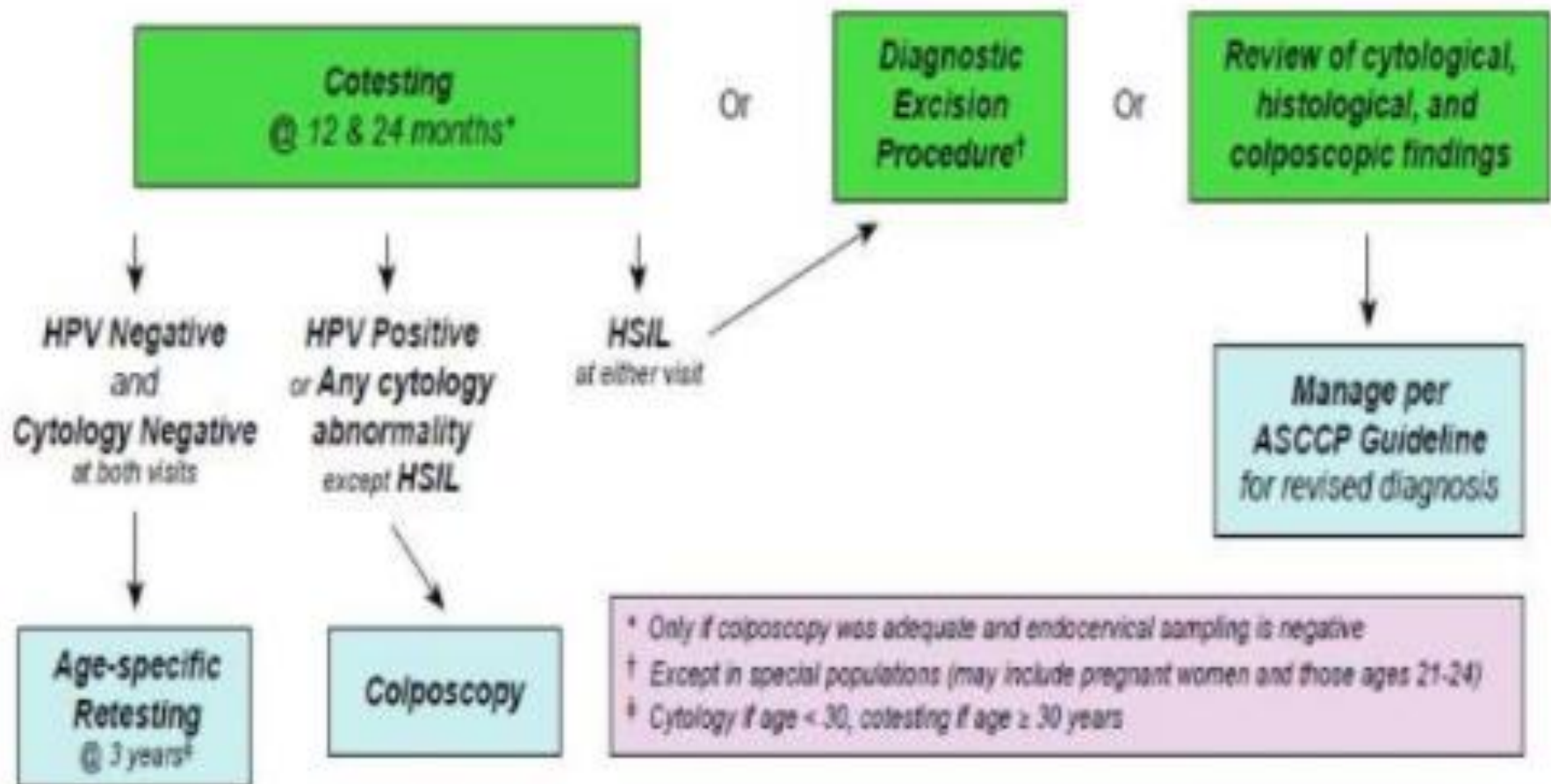
Management of Women with Low-grade Squamous Intraepithelial Lesion (LSIL) *



HSIL Cytology Results

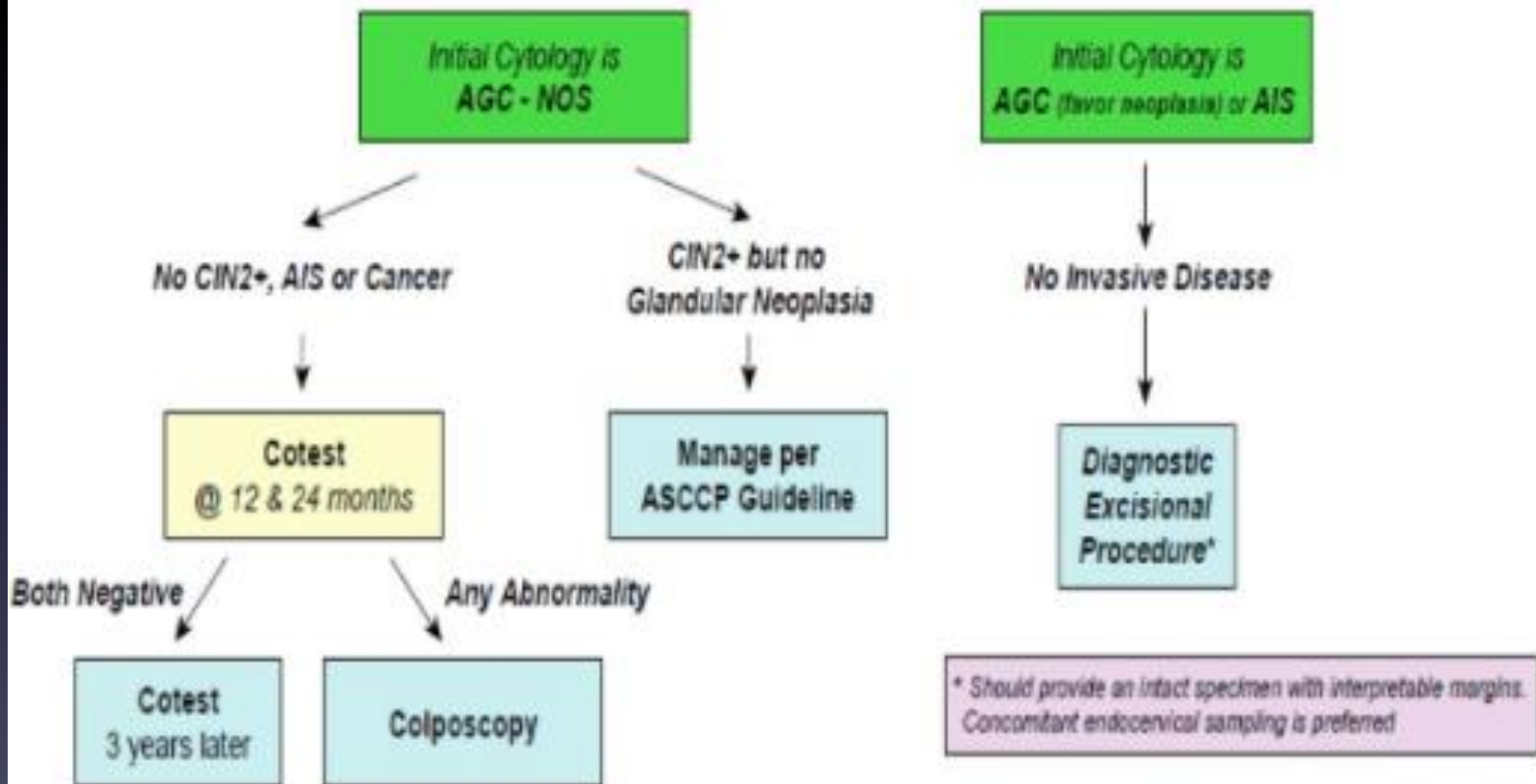


Management of women with No lesion or Biopsy – confirmed cervical intraepithelial Neoplasia – grade 1 (CIN1) preceded by ASC-H or HSIL cytology



Atypical Glandular Cells Results

Subsequent management of women with Atypical Glandular Cells (AGC)



Cervical Cancer Screening

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