

Update on HPV Testing

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Disclosures

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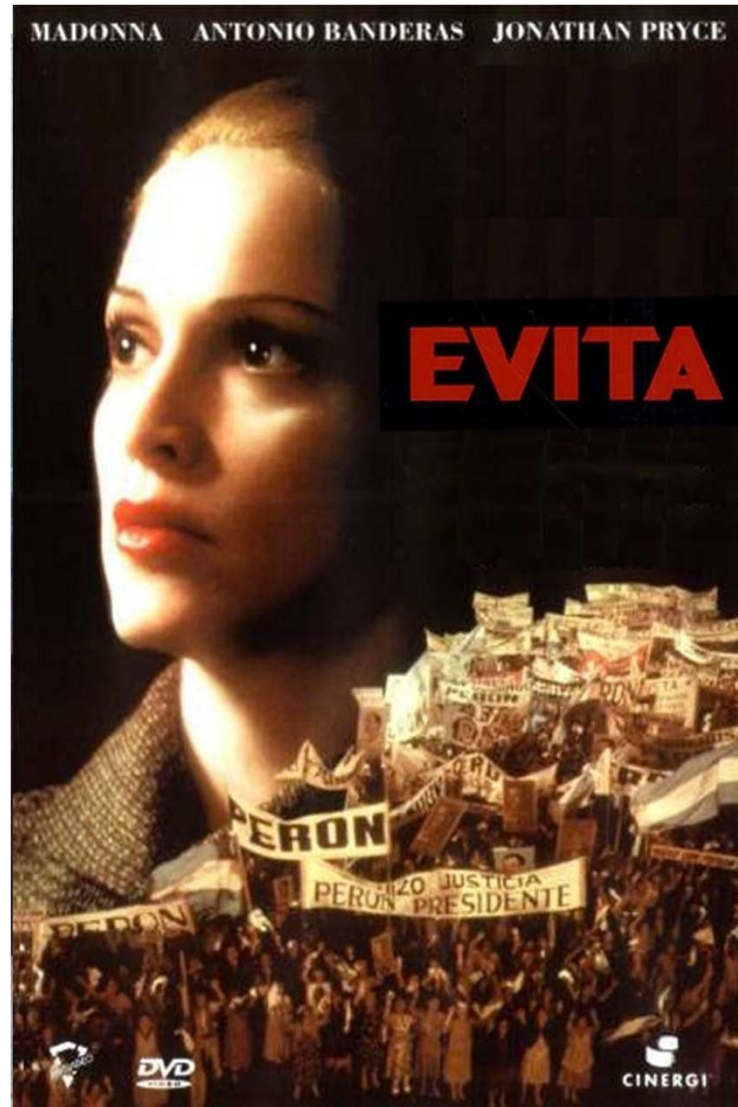
Robert Schlaberg, MD, MPH has disclosed the following financial relationships with commercial interests:

<u>Commercial Interest</u>	<u>What was Received</u>	<u>For What Role</u>
Roche Diagnostics	Honorarium	Advisor
Roche Diagnostics	Research Grants	PI
Hologic	Contract Research	PI
Hologic	Honorarium	Advisor
Epoch Biosciences	Contract Research	PI
Sanofi Pasteur	Contract Research	Co-PI
IDbyDNA	Stock	Co-Founder, CMO

Objectives

1. Understanding the biology and epidemiology of HR HPV
2. Understanding the performance of available cervical cancer screening tests
3. Reviewing recent changes to screening guidelines

Background



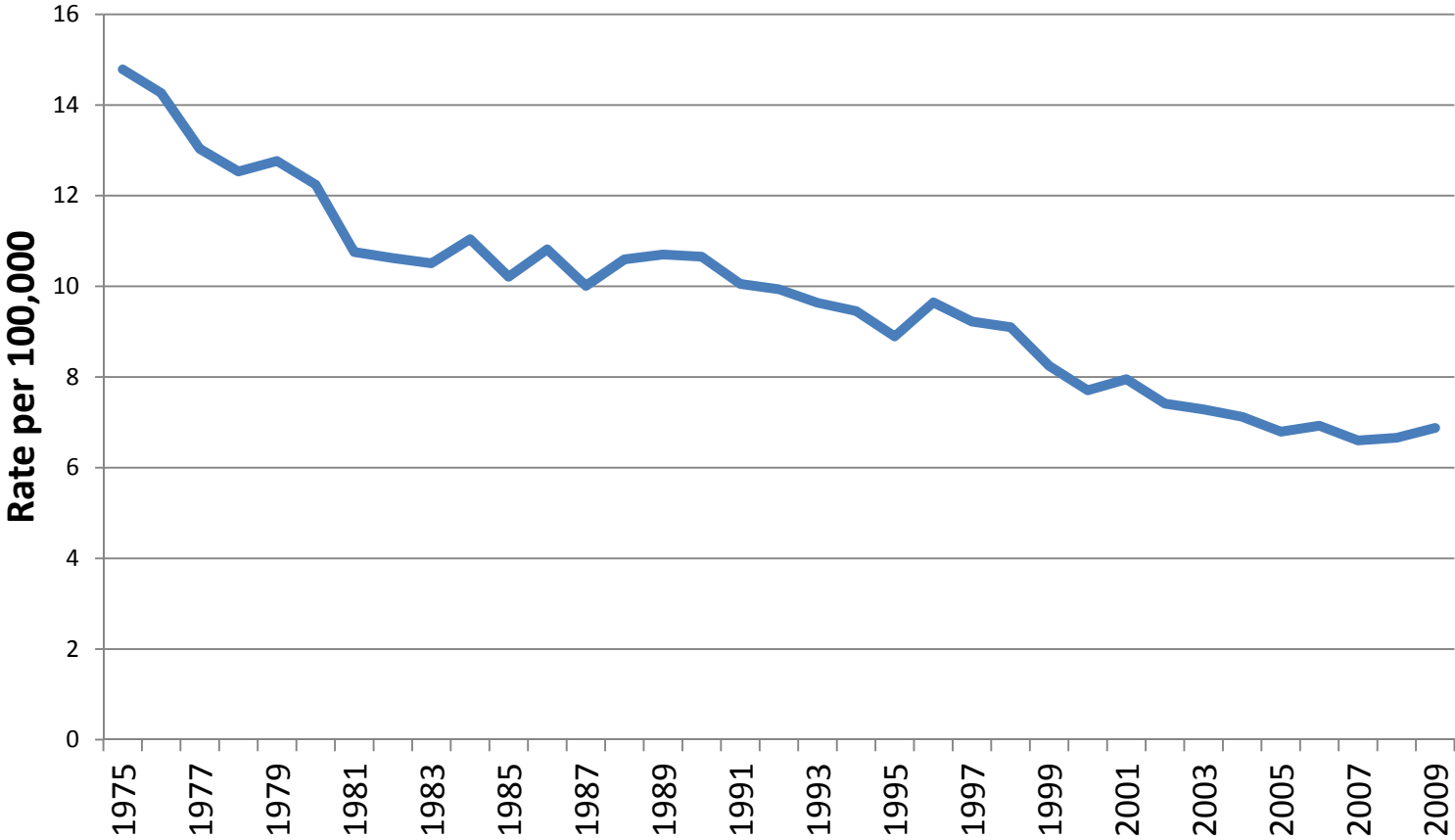
Eva and Juan Perón

See: Lancet 2000; 355: 1988–91

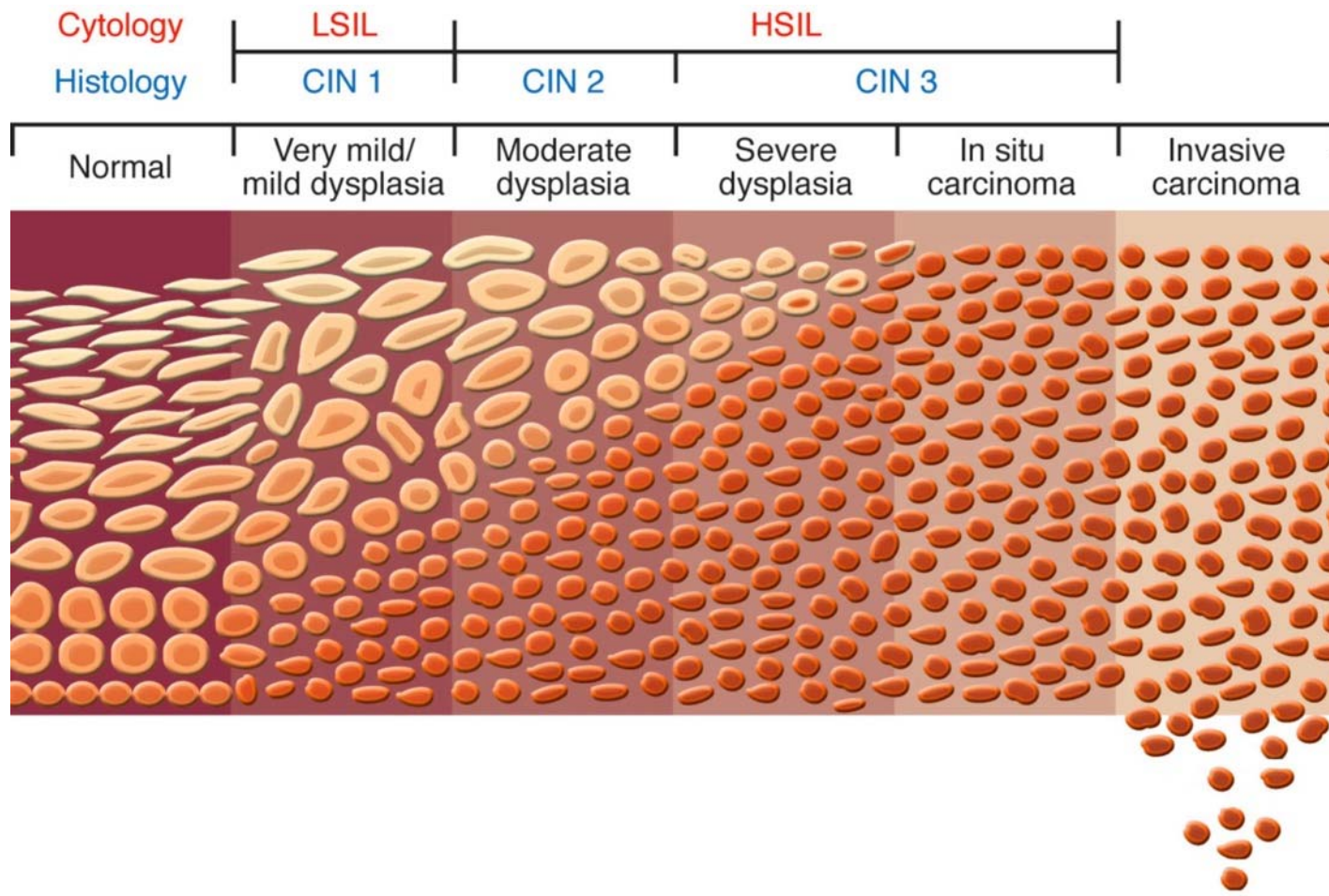
Cervical Cancer

- Incidence
 - Most frequent cancer death in women... now 14th
 - 12,000 cases, 4,200 deaths, 50% unscreened
- Persistent HR HPV infection
 - Almost 100% of cervical cancers HR HPV+
 - HPV16 (55-60%), HPV18 (10-15%)
- Cause all common/most rare histologic types
 - Squamous cell carcinoma (80-90%)

Cervical Cancer Trends - US



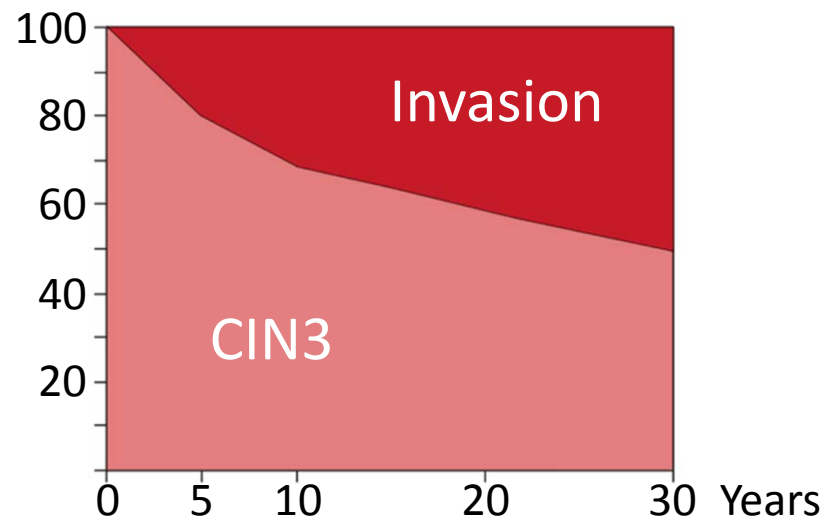
Squamous Cervical Precursor Lesions



Natural History of Cervical Precancer

Degree of Dysplasia	Regression (%)	Persistence (%)	Progression to CIN3 (%)	Progression to Invasive Cancer (%)
CIN I	57	32		
CIN II	43	35		
CIN III	32	56		

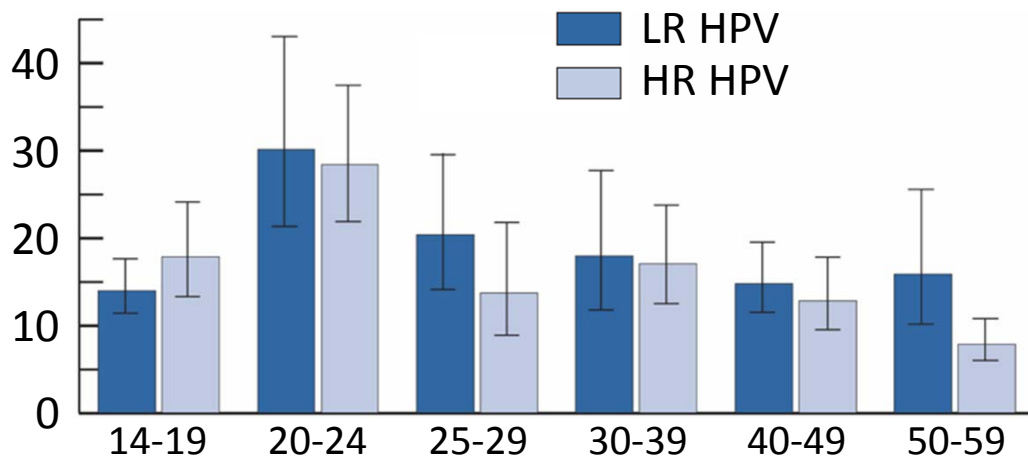
* Untreated



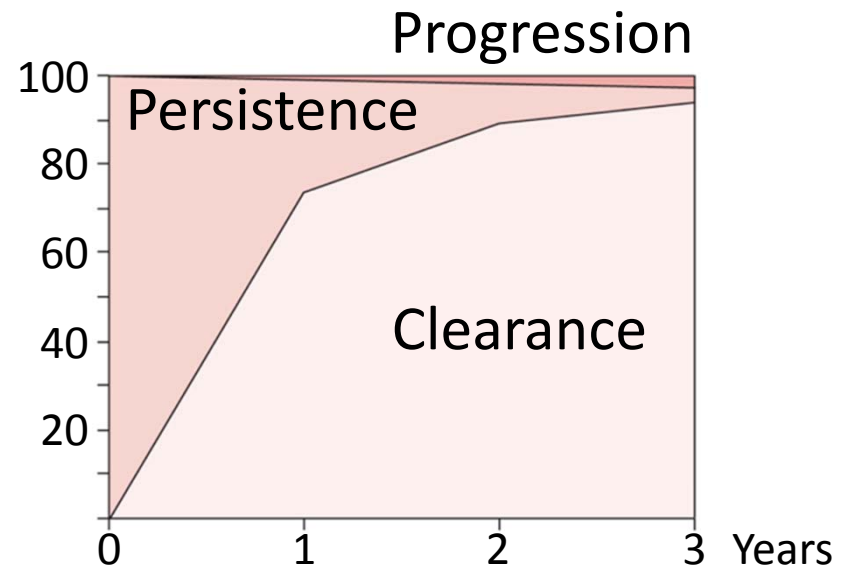
Lancet Oncol. 2008 May;9(5):425-34
 Lancet Oncol. 2008 May;9(5):404-6
 Int J Gynecol Pathol 1993; 12(2): 186-92

HPV Infection

- Most common viral STI
- Incidence ~ 6 million/y; prevalence ~20 million
- Lifetime risk ~ 50-75%
- Clearance 70% at 1 yr, 90% at 2 yrs

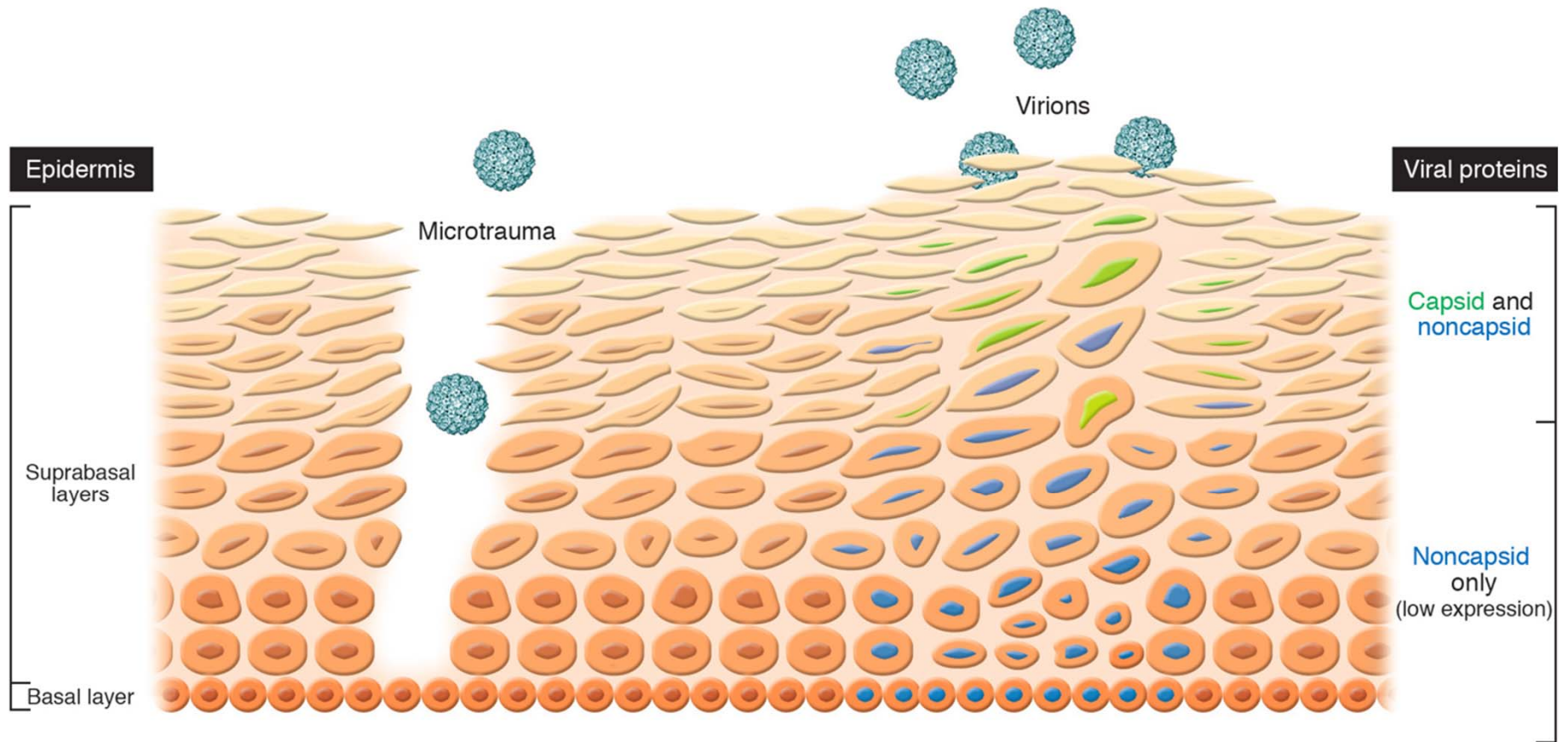


CDC, STD Surveillance, 2009

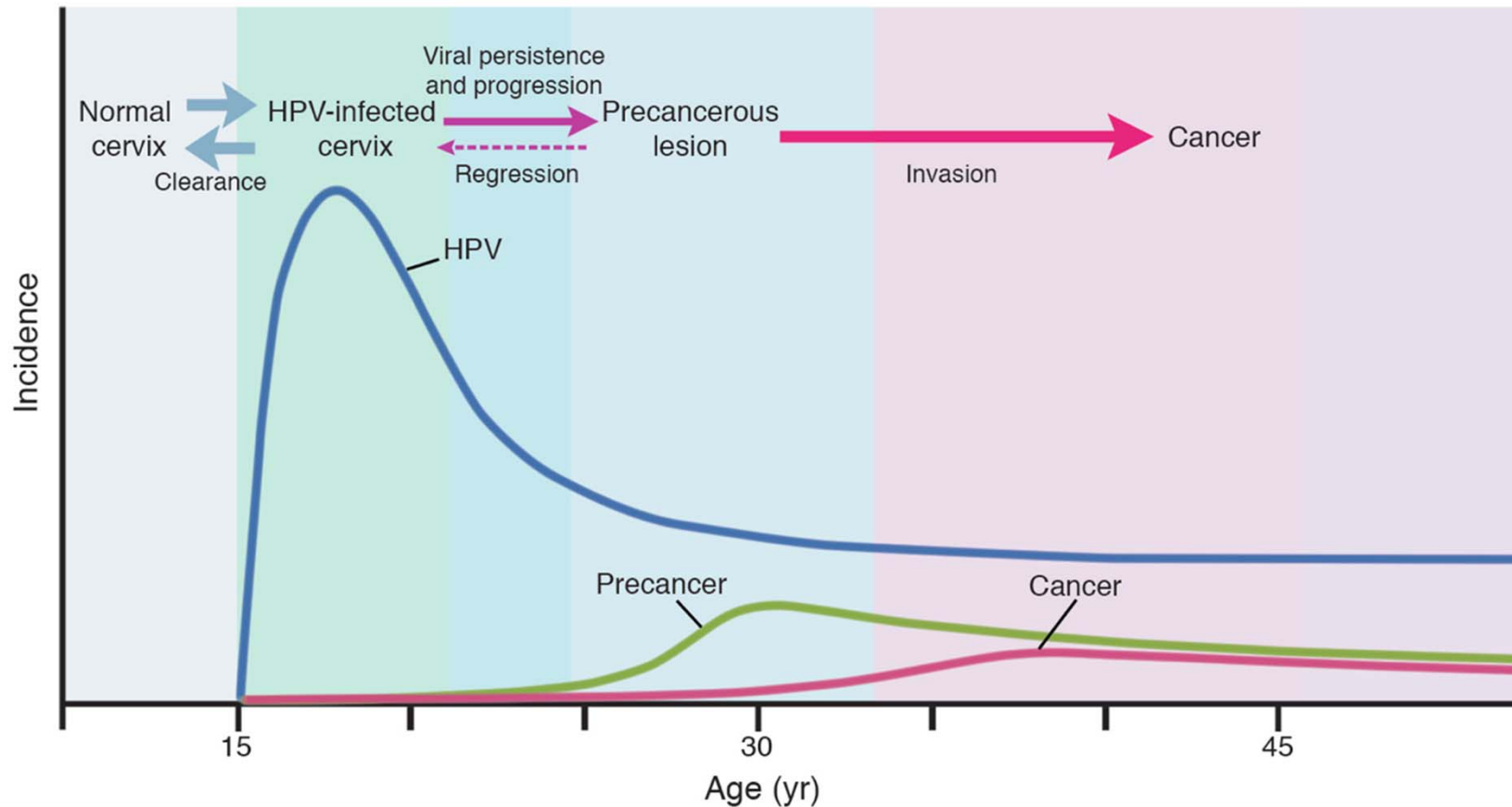


Lancet Oncol. 2008 May;9(5):404-6

HPV Replication

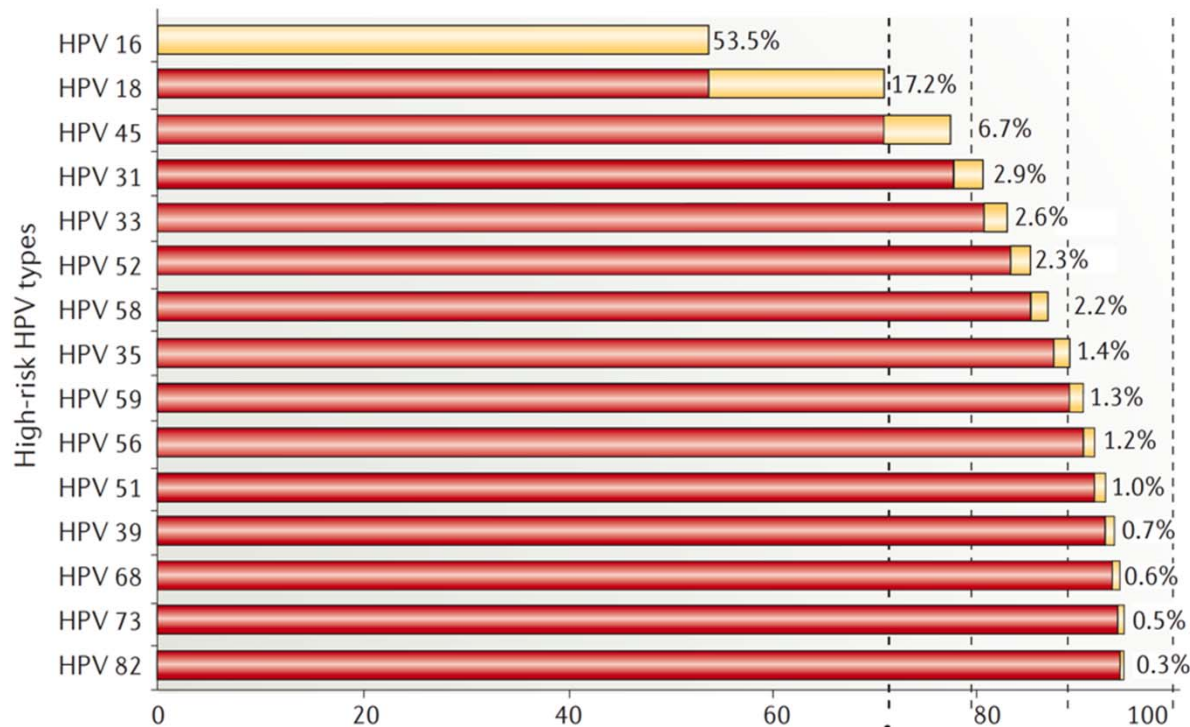


Role of HPV in Cervical Cancer

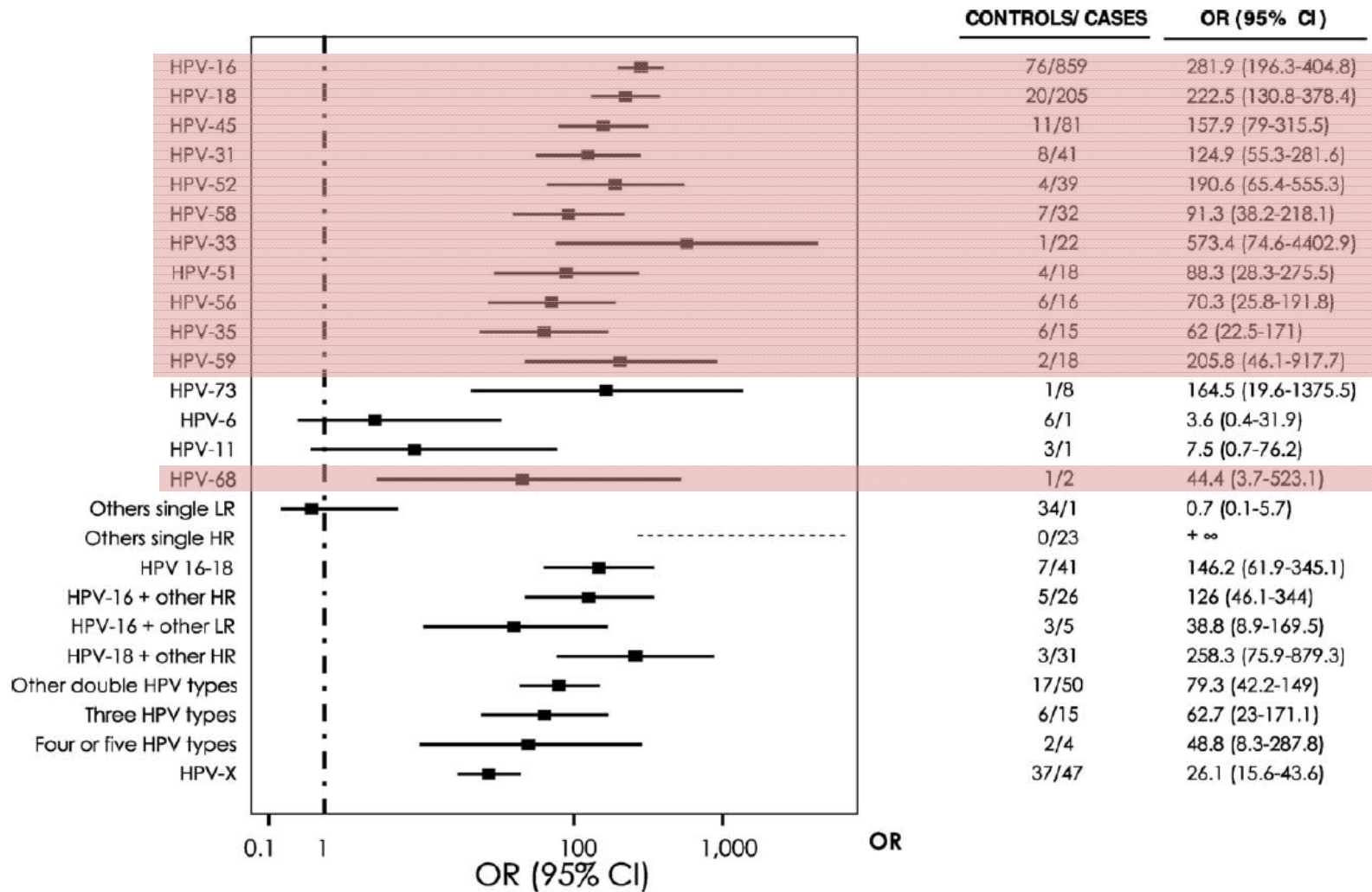


HPV Biology

- Double-stranded, circular DNA, ~8kb
- Oncogenes (E6, E7)
- >100 types, >40 infect genital tract



HPV Types – Association with Cancer



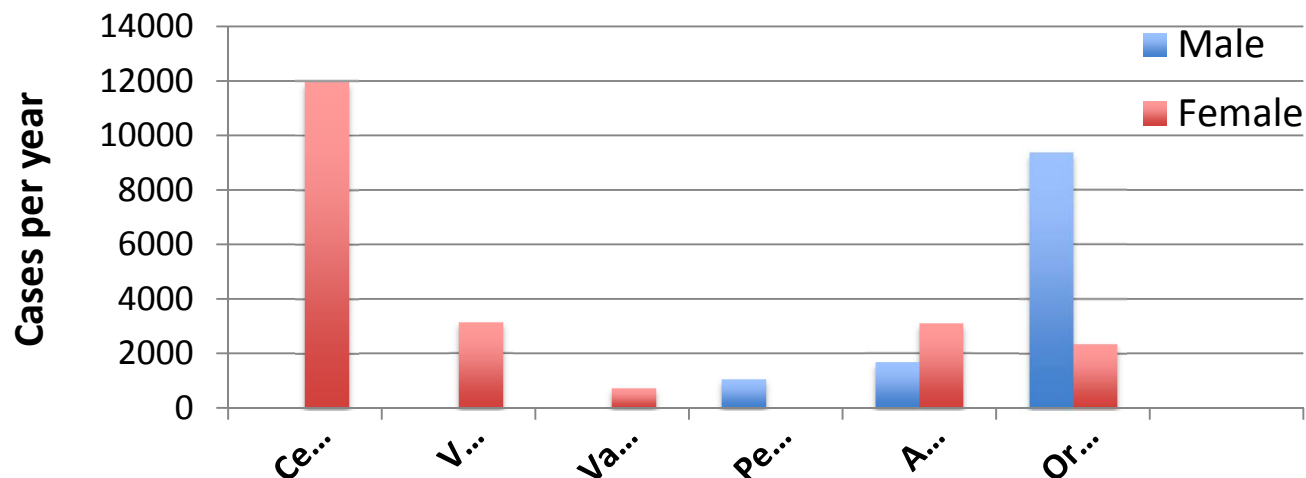
HPV – Pathogenic Spectrum

- **LR HPV**

- Genital warts, low-grade cervical abnormalities
- Recurrent respiratory papillomatosis

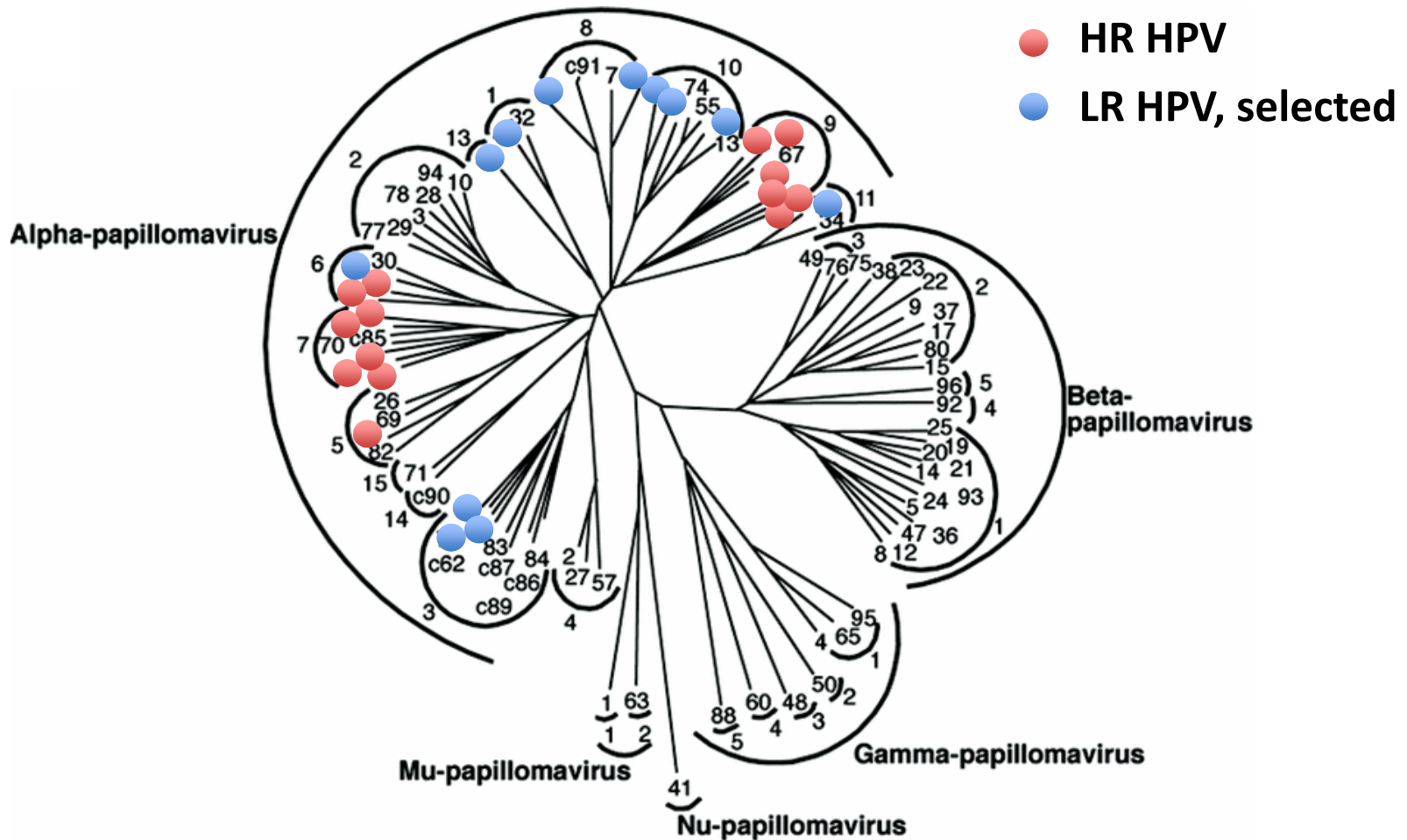
- **HR HPV**

- Uterine cervix, vulva, vagina, anus, (penis)
- Oropharynx (tonsil, base of tongue), esophagus



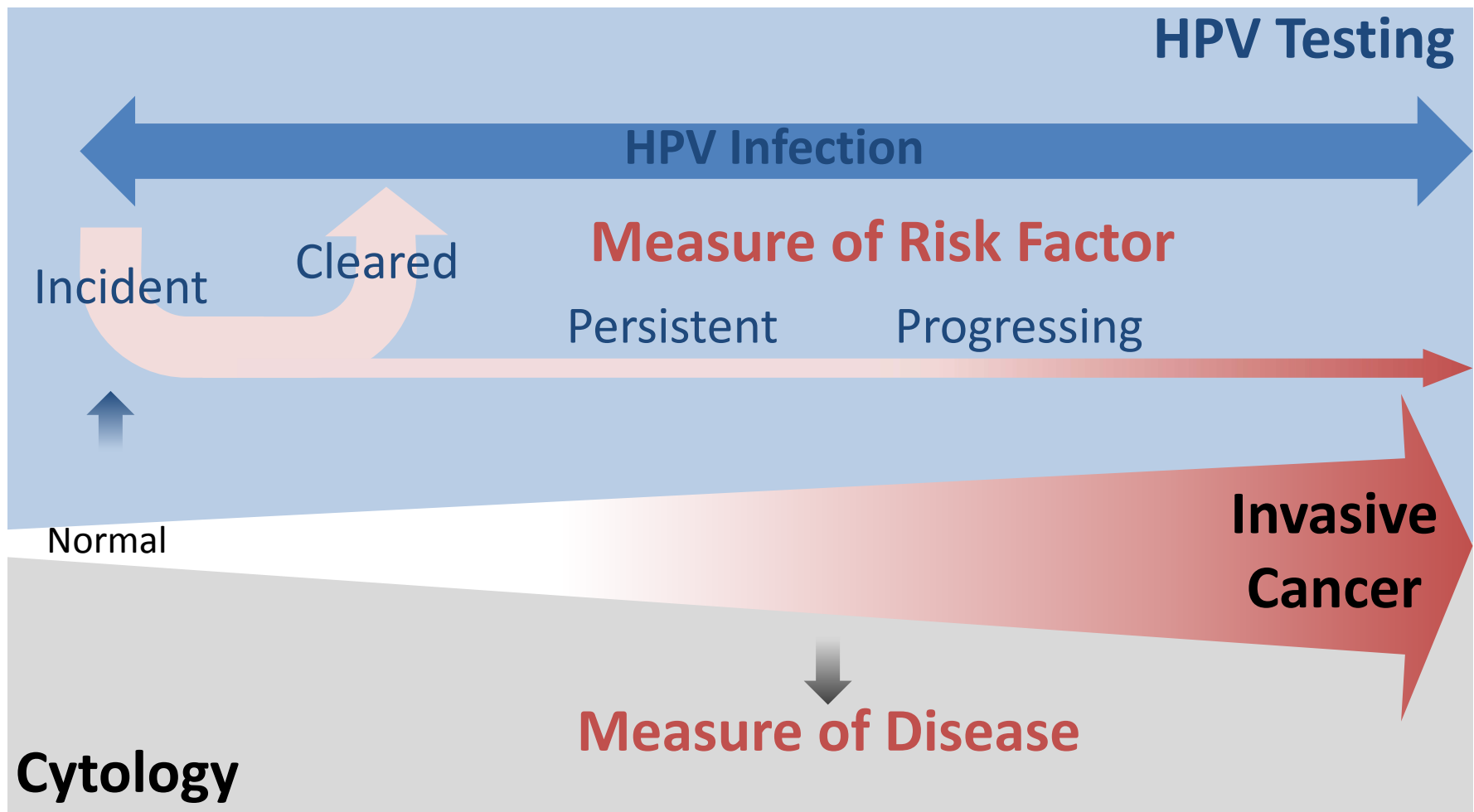
Challenges for HPV Tests I

I. Phylogeny



Challenges for HPV Tests III

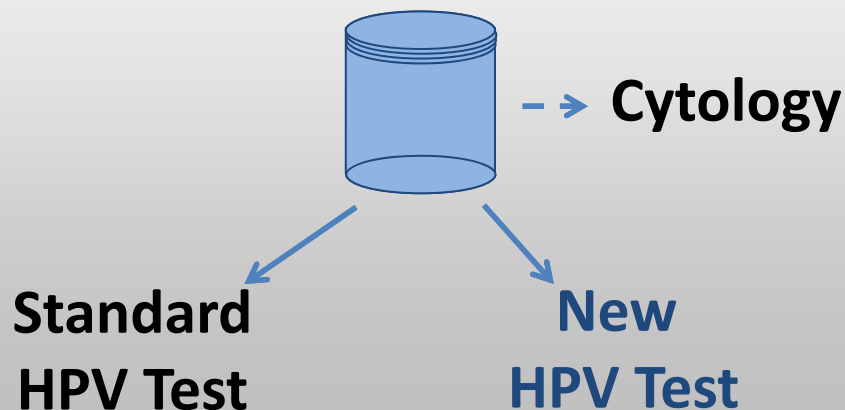
III. Analytical vs. Clinical Sensitivity



Clinical Cutoff For CIN2+

Participants: Women age 21+, routine screening (n~45,000)
61 sites, 23 states, 2 cervical specimens

Phase 1
(n ~ 29,000)



Determine Clinical Cutoff

Sensitivity ~ 90% for CIN2+
(pre-defined)

40.5 (HPV16)
40.0 (HPV18)
40.0 (12 HR HPV)

Confirm Clinical Cutoff: Phase 2 participants (n ~ 18,000)
Determine clinical performance

Screening



Georgios Papanikolaou



Harald zur Hausen

Cervical Cancer Screening

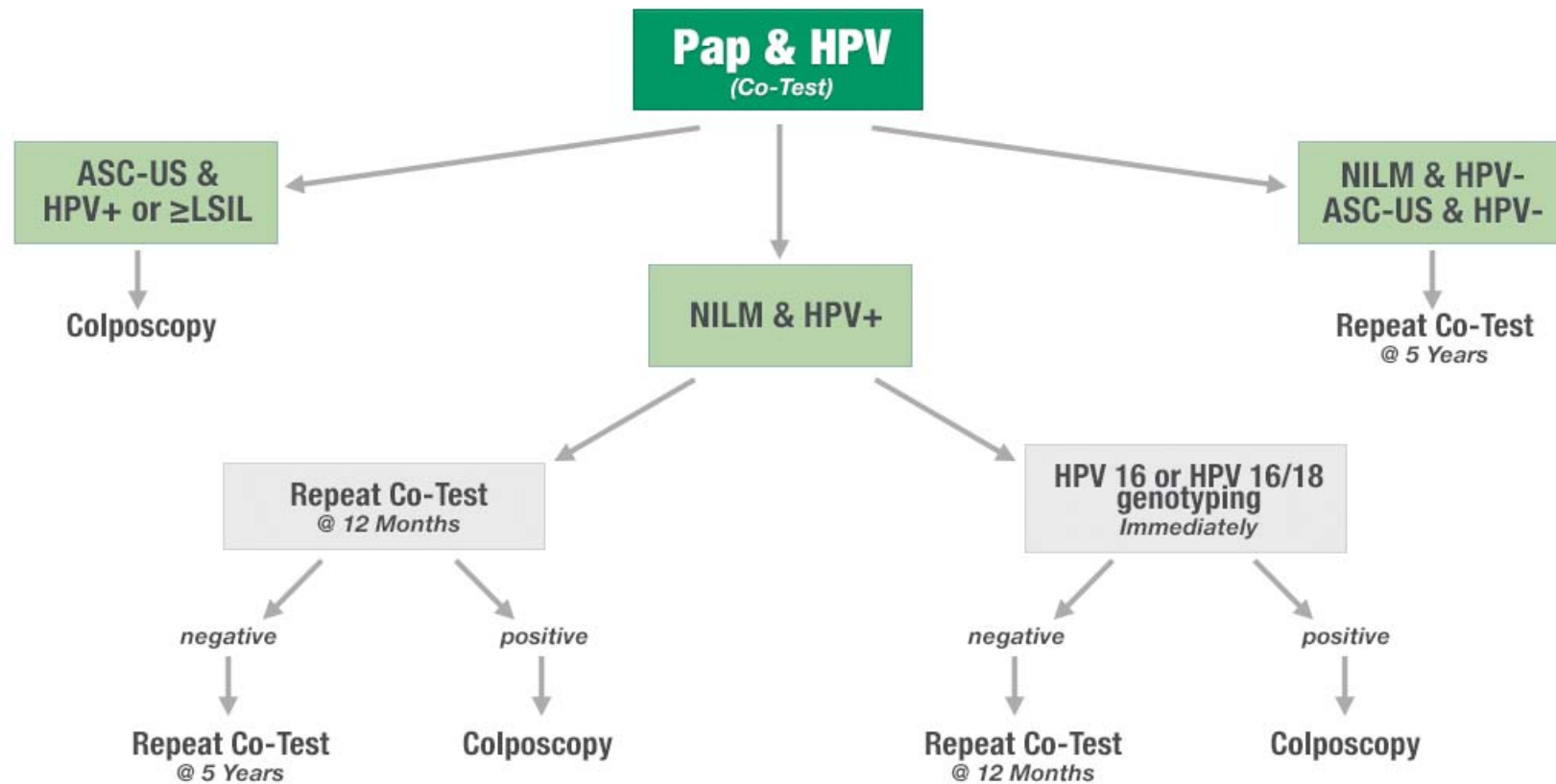
- **Pap test**
 - Identifies **dysplasia / pre-cancer / cancer**
 - High **specificity**
- **HPV test**
 - Identifies **women at risk**
 - High **negative predictive** value (CIN, cancer)
 - Higher **reproducibility**
- **Combined**
 - ASCUS-triage: follow-up interval (≥ 21 y)
 - Co-testing with cytology (≥ 30 y)

http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf

Cervical Cancer Screening Guidelines for Average-Risk Women^a

	American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) ¹ 2012	U.S. Preventive Services Task Force (USPSTF) ² 2012	American College of Obstetricians and Gynecologists (ACOG) ³ 2012	Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP): Interim clinical guidance for primary hrHPV testing ⁴ 2015
When to start screening^b	Age 21. Women aged <21 years should not be screened regardless of the age of sexual initiation or other risk factors.	Age 21. (<i>A recommendation</i>) Recommend against screening women aged <21 years (<i>D recommendation</i>).	Age 21 regardless of the age of onset of sexual activity. Women aged <21 years should not be screened regardless of age at sexual initiation and other behavior-related risk factors (<i>Level A evidence</i>).	Refer to major guidelines.
Statement about annual screening	Women of any age should not be screened annually by any screening method.	Individuals and clinicians can use the annual Pap test screening visit as an opportunity to discuss other health problems and preventive measures. Individuals, clinicians, and health systems should seek effective ways to facilitate the receipt of recommended preventive services at intervals that are beneficial to the patient. Efforts also should be made to ensure that individuals are able to seek care for additional health concerns as they present.	In women aged 30–65 years, annual cervical cancer screening should not be performed. (<i>Level A evidence</i>) Patients should be counseled that annual well-woman visits are recommended even if cervical cancer screening is not performed at each visit.	Not addressed.
Screening method and intervals				
Cytology (conventional or liquid based) ^c	21–29 years of age Every 3 years. ^d 30–65 years of age Every 3 years. ^d	Every 3 years (<i>A recommendation</i>). Every 3 years (<i>A recommendation</i>).	Every 3 years (<i>Level A evidence</i>). Every 3 years (<i>Level A evidence</i>).	Not addressed. Not addressed.
HPV co-test (cytology + HPV test administered together)	21–29 years of age 30–65 years of age HPV co-testing should not be used for women aged <30 years. Every 5 years; this is the preferred method.	Recommend against HPV co-testing in women aged <30 years (<i>D recommendation</i>). For women who want to extend their screening interval, HPV co-testing every 5 years is an option (<i>A recommendation</i>).	HPV co-testing ^g should not be performed in women aged <30 years. (<i>Level A evidence</i>) Every 5 years; this is the preferred method (<i>Level A evidence</i>).	Not addressed. Not addressed.
Primary hrHPV testing^f (as an alternative to cotesting or cytology alone) ^g	For women aged 30–65 years, screening by HPV testing alone is not recommended in most clinical settings. ^h	Recommend against screening for cervical cancer with HPV testing (alone or in combination with cytology) in women aged <30 years (<i>D recommendation</i>).	Not addressed.	Every 3 years. Recommend against primary hrHPV screening in women aged <25 years of age. ⁱ
When to stop screening	Aged >65 years with adequate negative prior screening* and no history of CIN2 or higher within the last 20 years. ^j <small>*Adequate negative prior screening results are defined as 3 consecutive negative cytology results or 2 consecutive negative co-test results within the previous 10 years, with the most recent test performed within the past 5 years.</small>	Aged >65 years with adequate screening history* and are not otherwise at high risk for cervical cancer ^k (<i>D recommendation</i>).	Aged >65 years with adequate negative prior screening* results and no history of CIN 2 or higher ^k (<i>Level A evidence</i>).	Not addressed.

ASCCP, ASCP, ACS



From: <https://www.hpv16and18.com/hcp/cervical-cancer-screening-guidelines/asccp-guidelines.html>
Saslow D et al, Journal of Lower Genital Tract Disease, Volume 16, Number 3, 2012

2012 Cervical Screening Guidelines

Population	Page Numbers	Recommended Screening Method [†]	Management of Screen Results	Comments
Aged <21 y		No screening		HPV testing should not be used for screening or management of ASC-US in this age group
Aged 21-29 y		Cytology alone every 3 y	HPV-positive ASC-US [†] or cytology of LSIL or more severe: Refer to ASCCP guidelines ² Cytology negative or HPV-negative ASC-US [†] : Rescreen with cytology in 3 y	HPV testing should not be used for screening in this age group
Aged 30-65 y		HPV and cytology "cotesting" every 5 y (preferred)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines ² HPV positive, cytology negative: Option 1: 12-mo follow-up with cotesting Option 2: Test for HPV16 or HPV16/18 genotypes <ul style="list-style-type: none"> • If HPV16 or HPV16/18 positive: refer to colposcopy • If HPV16 or HPV16/18 negative: 12-mo follow-up with cotesting Cotest negative or HPV-negative ASC-US: Rescreen with cotesting in 5 y	Screening by HPV testing alone is not recommended for most clinical settings
		Cytology alone every 3 y (acceptable)	HPV-positive ASC-US [†] or cytology of LSIL or more severe: Refer to ASCCP guidelines ² Cytology negative or HPV-negative ASC-US [†] : Rescreen with cytology in 3 y	
Aged >65 y		No screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 y
After hysterectomy		No screening		Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 y or cervical cancer ever
HPV vaccinated		Follow age-specific recommendations (same as unvaccinated women)		

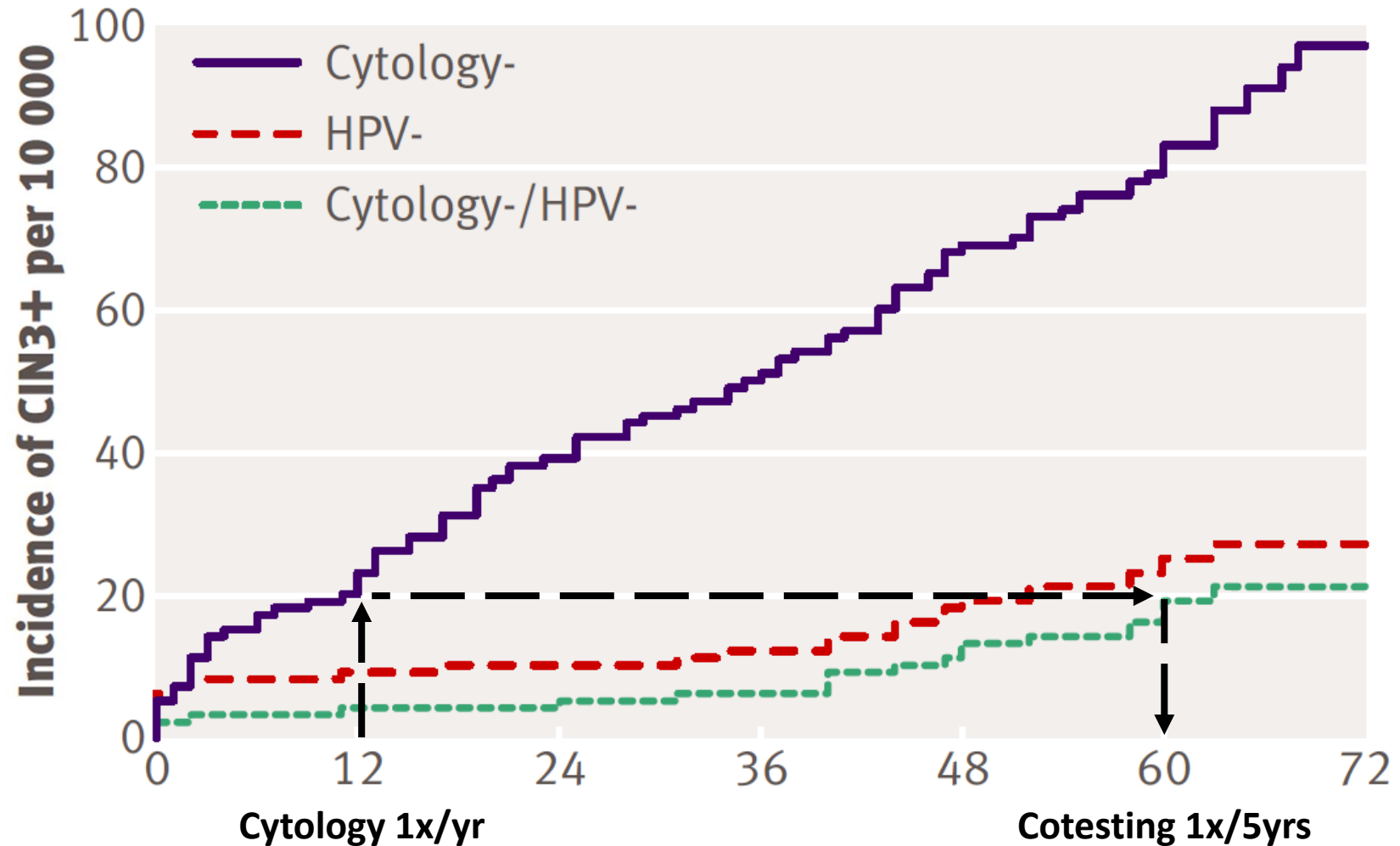
ACOG

- Screening should begin at age 21 years
- Cytology is recommended every 3 years for women aged 21-29 years
- Co-testing every 5 years is preferred for women aged 30-65 years
- In women post hysterectomy w/o history of CIN2+, screening should be discontinued
- Screening guidelines don't apply to women...
 - ...who have a history of cervical cancer
 - ...have HIV infection or are immunocompromised
 - ...who were exposed to diethylstilbestrol in utero
- Stop screening at age 65 in women with adequate negative prior screening and no history of CIN2+

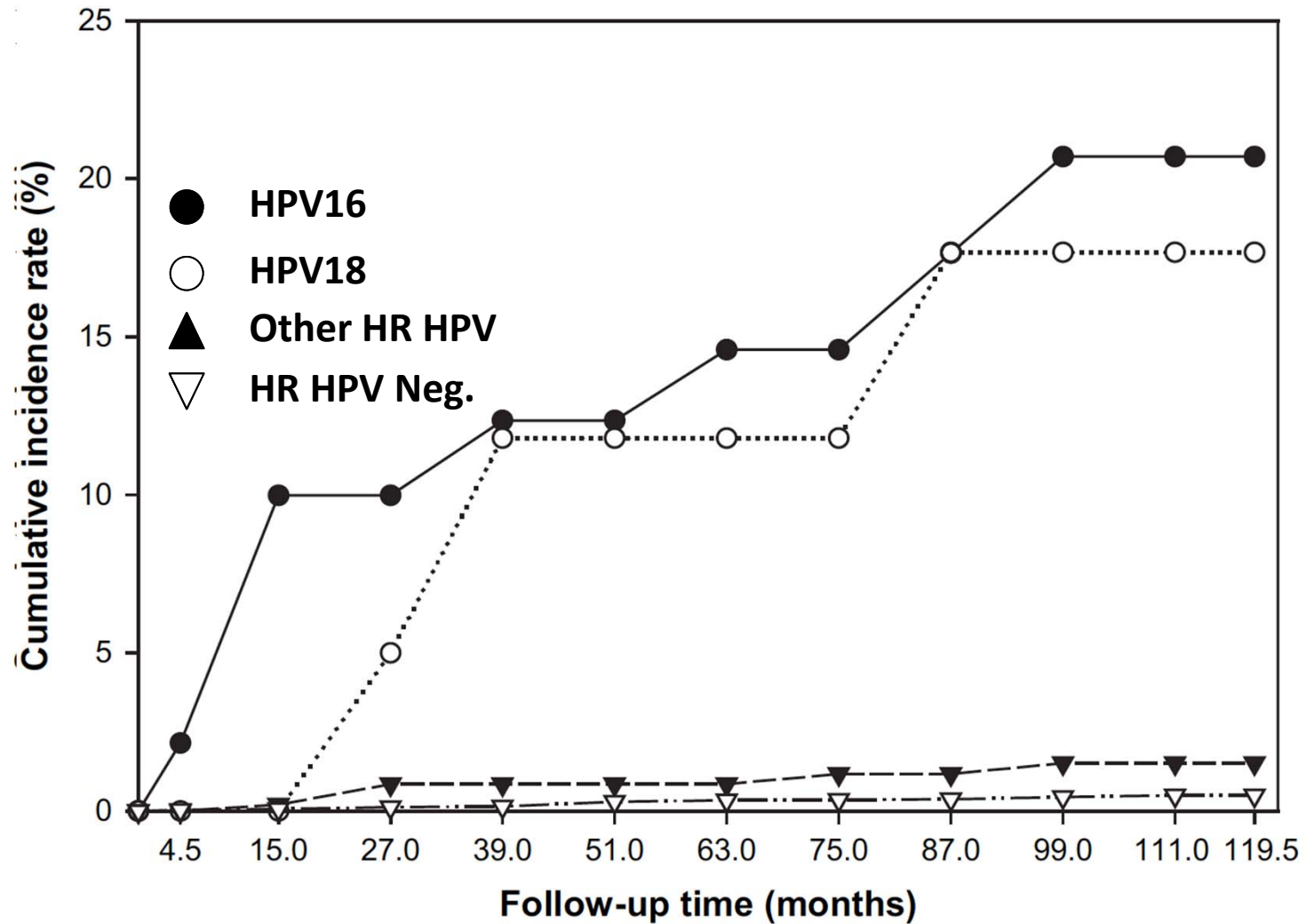
Table 1. Cervical-Cancer Screening Guidelines.*

Population	Screening Recommendation
Age group	
<21 yr	Do not screen.
21–29 yr	Perform cytologic testing alone every 3 years.
30–65 yr	Perform cytologic and HPV cotesting every 5 years (preferred), or perform cytologic testing alone every 3 years (acceptable). [†]
>65 yr	Discontinue screening if there has been an adequate number of negative screening results previously (3 consecutive negative cytologic tests or 2 consecutive negative cotests in the past 10 years, with the most recent test in the past 5 years) and if there is no history of HSIL, [‡] adenocarcinoma in situ, or cancer.
Women who have undergone hysterectomy	Discontinue screening if the patient has undergone a total hysterectomy with removal of cervix and if there is no history of HSIL, adenocarcinoma in situ, or cancer.

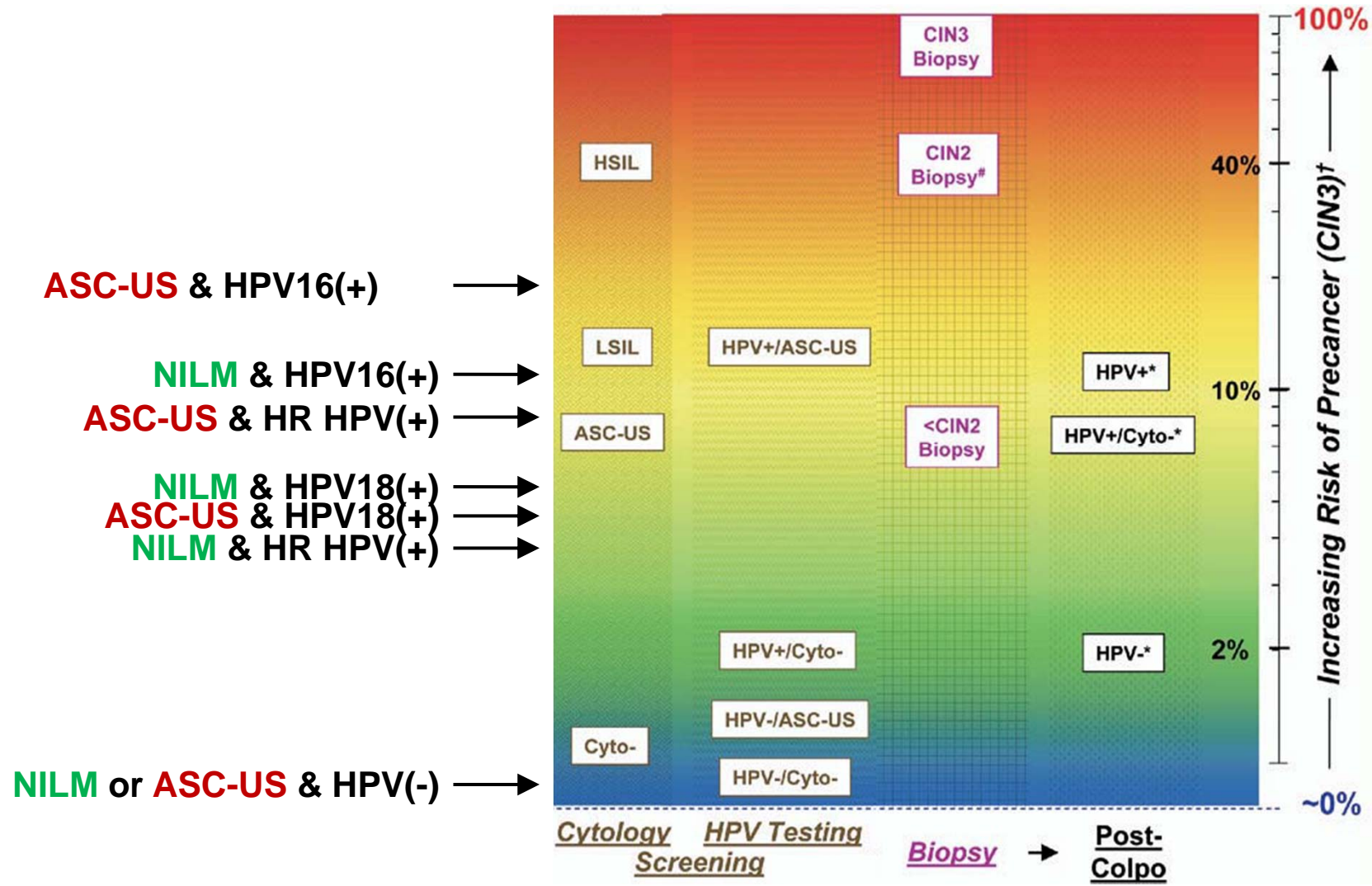
Rationale For Screening Interval



Rationale for Genotyping



Rationale for Genotyping, Cont.



Primary Screening, Age 25+

- HR HPV-neg. -> no retesting for at least 3 years
- HPV 16/18 pos. -> colposcopy
- Other HR HPV pos. -> cytology

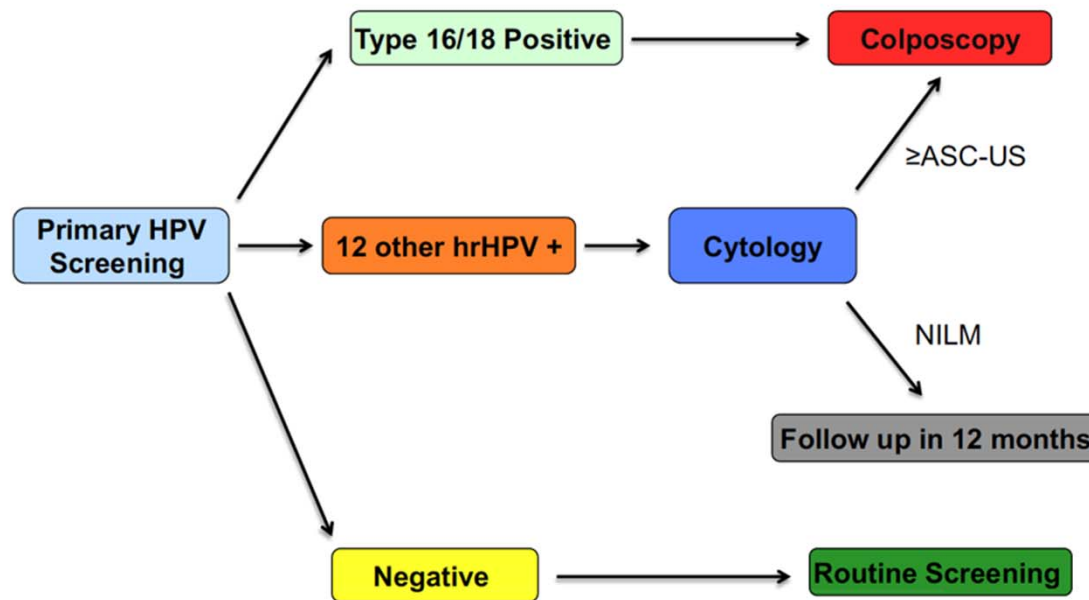


Fig. 1. Recommended primary HPV screening algorithm.

Results from the ATHENA Study

Table 3

Detection of cervical disease using different screening strategies and the number of screening tests and colposcopies that each strategy requires.

Strategy	Number of detected cases ^a (95% CI)			No. missed cases	No. screening tests (95% CI)	No. colposcopies (95% CI)	No. colposcopies to detect 1 case (95% CI)	
	Total	Detected at baseline	Detected years 1–3					
≥25 years								
CIN2+	Cytology	270 (239–303)	215 (187–245)	55 (41–70)	317 (282–350)	45,166 (44,931–45,392)	1934 (1809–2061)	7.1 (6.4–8.0)
	Hybrid strategy	384 (347–421)	215 (187–245)	169 (145–193)	203 (178–230)	82,994 (82,634–83,397)	3097 (2948–3264)	8.1 (7.4–8.9)
	HPV primary	471 ^{b,c} (430–514)	283 ^{b,c} (250–318)	188 (164–215)	116 ^{d,e} (97–136)	52,651 ^{b,e} (52,249–53,111)	3767 ^{b,c} (3617–3962)	8.0 ^b (7.4–8.8)
CIN3+	Cytology	179 (152–206)	143 (119–167)	36 (25–49)	168 (144–194)	45,166 (44,931–45,392)	1934 (1809–2061)	10.8 (9.4–12.6)
	Hybrid strategy	240 (209–270)	143 (119–167)	97 (79–115)	107 (89–126)	82,994 (82,634–83,397)	3097 (2948–3264)	12.9 (11.5–14.8)
	HPV primary	294 ^{b,c} (260–325)	197 ^{b,c} (169–226)	97 (78–115)	53 ^{d,e} (42–66)	52,651 ^{b,e} (52,249–53,111)	3769 ^{b,c} (3617–3962)	12.8 ^b (11.7–14.5)
≥30 years								
CIN2+	Cytology	185 (158–213)	144 (121–168)	41 (29–54)	192 (164–221)	37,312 (37,077–37,574)	1294 (1197–1390)	7.0 (6.1–8.1)
	Hybrid strategy	299 (267–331)	144 (121–168)	155 (133–178)	78 (64–94)	75,140 (74,684–75,614)	2457 (2316–2607)	8.2 (7.4–9.2)
	Primary HPV	299 ^b (266–332)	178 ^{b,c} (152–205)	121 (101–143)	78 ^d (63–94)	42,425 ^{b,e} (42,030–42,847)	2522 ^{b,c} (2376–2667)	8.4 ^b (7.6–9.4)
CIN3+	Cytology	128 (105–152)	106 (87–127)	22 (13–31)	100 (82–121)	37,312 (37,077–37,574)	1294 (1197–1390)	10.1 (8.6–12.2)
	Hybrid strategy	189 (163–215)	106 (87–127)	83 (67–99)	39 (30–49)	75,140 (74,684–75,614)	2457 (2316–2607)	13.0 (11.5–15.0)
	Primary HPV	192 ^b (165–218)	136 ^{b,c} (113–160)	56 (42–71)	36 ^d (27–48)	42,425 ^{b,c} (42,030–42,847)	2522 ^{b,c} (2376–2667)	13.1 ^b (11.5–15.2)

Independent Results

Table 1
Performance of different cervical cancer screening algorithms for the detection of CIN2 or worse.

Strategy	Initial test performed	Colposcopies performed	Colposcopies needed to be performed	Colposcopies to detect 1 CIN2 +	CIN2 + identified	Sensitivity(%) (n/N CIN2 + identified)	Sensitivity relative to cytology	FPR relative to cytology	Specificity relative to cytology
1 Cytology alone	3993	141	210	6.4	22	53.7 (22/41)	1.00	1.00	1.00
2 Cytology with reflex HPV test (ASCUS triage)	4111	109	145	5.0	22	53.7 (22/41)	1.00	0.74	1.01
3 Co-testing with reflex for ASCUS	7986	109	145	5.0	22	53.7 (22/41)	1.00	0.74	1.01
4 Co-testing with genotyping and cytology triage: HPV 16/18 and ASCUS HPV + threshold	7986	196	261	5.8	34	82.9 (34/41)	1.54	1.39	0.99
5 Co-testing with genotyping and cytology triage: HPV 16/18 and LSIL threshold	7986	161	222	5.0	32	78.0 (32/41)	1.45	1.10	1.00
6 HPV alone	3993	409	507	10.0	41	100.0 (41/41)	1.86	3.13	0.93
7 HPV with cytology triage	4500	96	113	4.4	22	53.7 (22/41)	1.00	0.61	1.01
8 HPV with genotyping triage	3993	119	153	5.0	24	58.5 (24/41)	1.09	0.81	1.01
9 HPV with genotyping and reflex cytology: ASCUS threshold	4347	183	229	5.4	34	82.9 (34/41)	1.54	1.26	0.99
10 HPV with genotyping and cytology (LSIL cut off) triage	4347	148	190	4.6	32	78.0 (32/41)	1.45	0.97	1.00

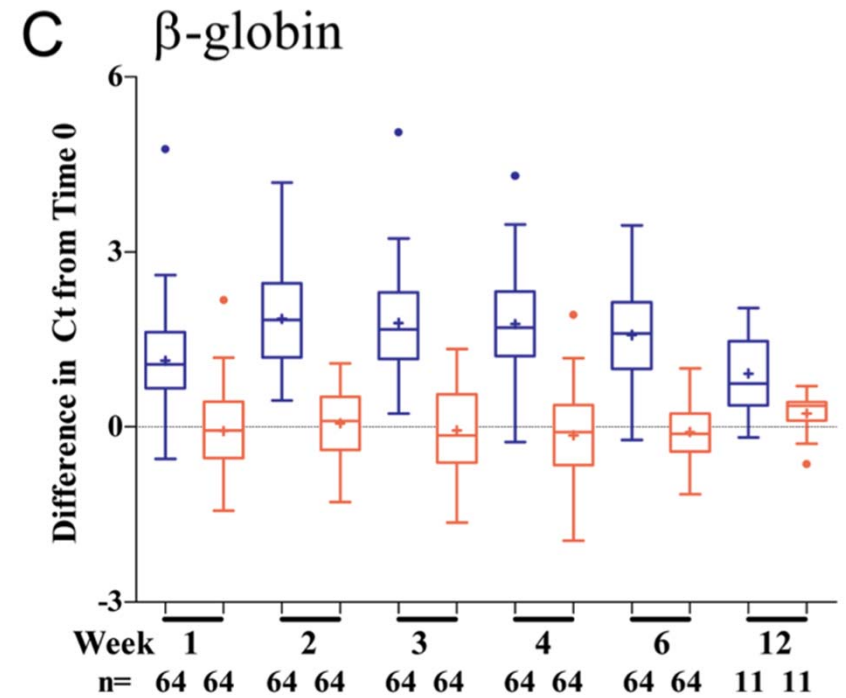
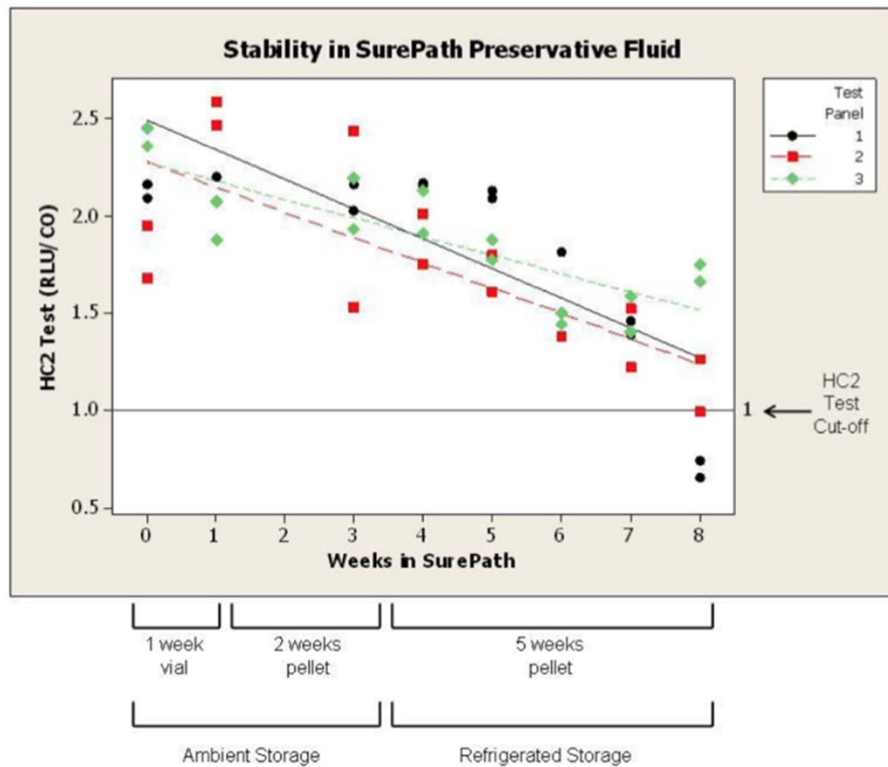
HPV: Human Papillomavirus, MO: Months, NILM: Negative for Intraepithelial Lesion or Malignancy, ASCUS: Atypical Squamous Cells of Undetermined Significance, LSIL: Low-grade Squamous Intraepithelial Lesion, CIN2 +: Cervical Intraepithelial Neoplasia grade 2 or worse, FPR: False Positive Rate

Different HPV Tests, Hard to Compare

Table 1 Digene HC2 and Roche COBAS agreement at baseline

		COBAS		
		All ages		
		Positive	Negative	Total
HC2	Positive	410	106	516
	Negative	132	5,524	5,656
	Total	542	5,630	6,172
Overall agreement (95 % CI)		96.1 % (95.6, 96.6)		
Kappa (95 % CI)		0.75 (0.72, 0.79)		
Positive agreement (95 % CI)		77.5 % (74.7, 80.3)		
Negative agreement (95 % CI)		97.9 % (97.6, 98.2)		

HPV Testing from SurePath

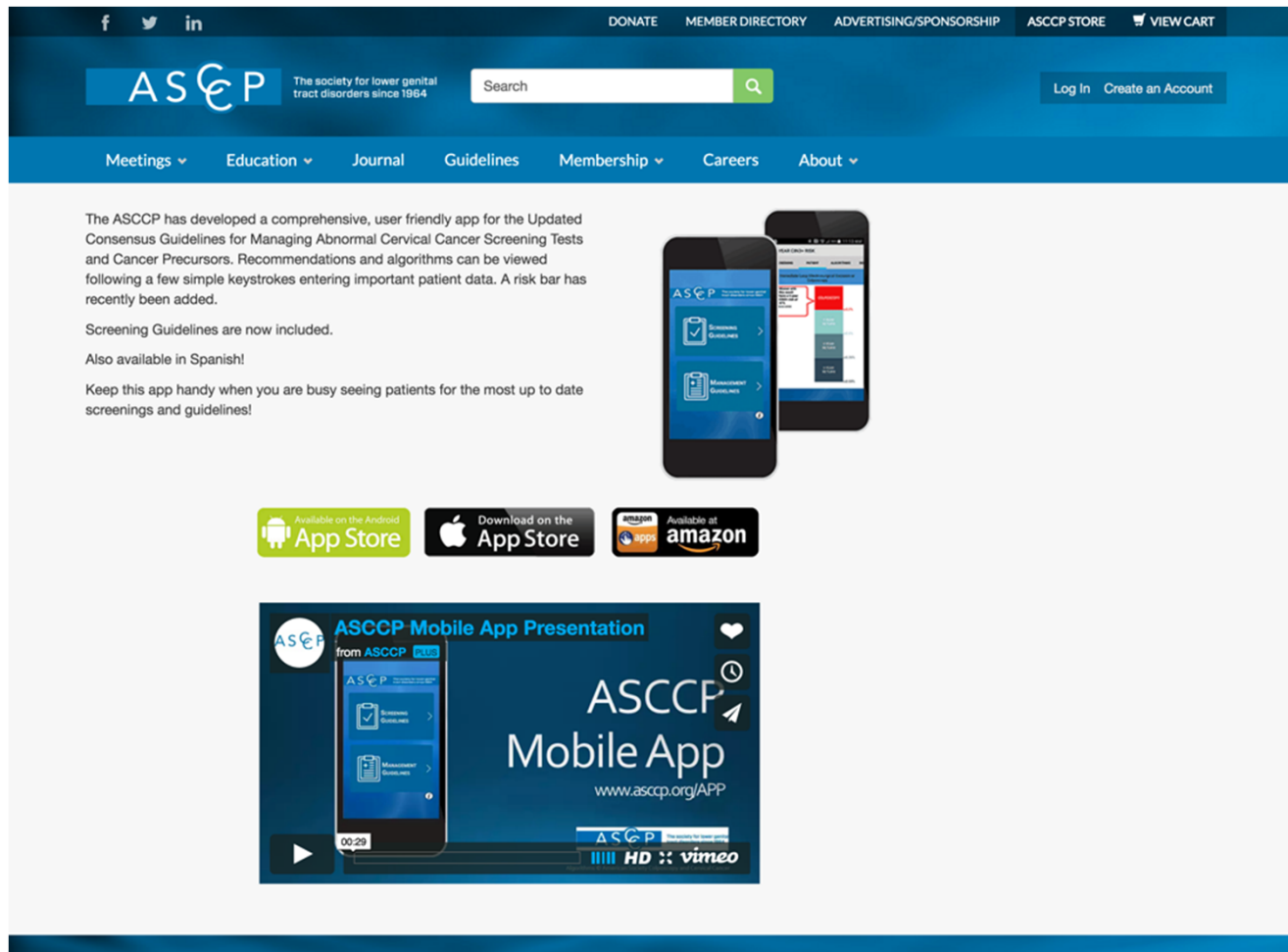


HPV Testing from SurePath

First FDA approval for SurePath (7/7/2016)

- ASC-US triage
- Co-testing with cytology for women 30+
- Not approved for primary screening

Help with Complicated Algorithms



The screenshot shows the ASCCP website with a dark blue header. The header includes social media icons for Facebook, Twitter, and LinkedIn, and navigation links for DONATE, MEMBER DIRECTORY, ADVERTISING/SPONSORSHIP, ASCCP STORE, and VIEW CART. The main content area features the ASCCP logo and tagline "The society for lower genital tract disorders since 1964", a search bar, and "Log In" and "Create an Account" buttons. A secondary navigation bar lists Meetings, Education, Journal, Guidelines, Membership, Careers, and About. The main text describes a mobile app for the Updated Consensus Guidelines for Managing Abnormal Cervical Cancer Screening Tests and Cancer Precursors, highlighting its user-friendly interface and ability to view recommendations and algorithms. It also mentions that the app is available in Spanish and is useful for busy clinicians. To the right of the text are two smartphones displaying the app's interface. Below the text are three download buttons: "Available on the Android App Store", "Download on the App Store", and "Available at amazon". At the bottom is a video player titled "ASCCP Mobile App Presentation" with a play button, a progress bar, and a "vimeo" logo.

The ASCCP has developed a comprehensive, user friendly app for the Updated Consensus Guidelines for Managing Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Recommendations and algorithms can be viewed following a few simple keystrokes entering important patient data. A risk bar has recently been added.

Screening Guidelines are now included.

Also available in Spanish!

Keep this app handy when you are busy seeing patients for the most up to date screenings and guidelines!

Available on the Android App Store | Download on the App Store | Available at amazon

ASCCP Mobile App Presentation
from ASCCP
ASCCP Mobile App
www.asccp.org/APP
vimeo

<http://www.asccp.org/store-detail2/asccp-mobile-app>

Cervical Cancer Screening – ARUP Consult

Human Papillomavirus - HPV

Primary Author [Schlaberg, Robert, MD, MPH.](#)

Key Points

Dx

Screen

Monitor

Background

Lab Tests

Key Points

HPV Testing in Men

- Summary of recommendations

HPV Testing in Women

- [Cervical Cancer Screening Recommendations](#) (ASCCP Powerpoint, 2012)
- Updated disease management guidelines – [algorithms and FAQs](#)
- [ACS, ASCCP, ASCP Screening Guidelines for the Prevention and Early Detection of Cervical Cancer](#)
- [2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors](#)
- Video – Spotlight on Test Utilization: Clinical Performance Comparison of FDA-Cleared HPV Tests (ARUP, Schlaberg, 2013)
- Screening recommendations
 - Women <21 years
 - Women 21-29 years
 - Women 30-65 years
 - Women >65 years
 - Post hysterectomy
 - Post HPV vaccination

<http://www.arupconsult.com/Topics/HPV.html>

Estimated Cervical Cancer Mortality Worldwide in 2008



GLOBOCAN 2008, International Agency for Research on Cancer