HPV Molecular Diagnostics and Cervical Cytology

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American Society for Clinical Pathology (ASCP)
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Disclosures & Disclaimers

- I serve on a Merck Data and Safety Monitoring Board (Compensated).
- I have a non-disclosure agreement with Roche to help analyze data from the ATHENA trial.
- I have received HPV assays/testing for research from Qiagen and Roche at a reduced cost or no cost.
- The views expressed are my own and do not represent those of the ASCP or any other organization.

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

BMJ, 2006

Today's Talk

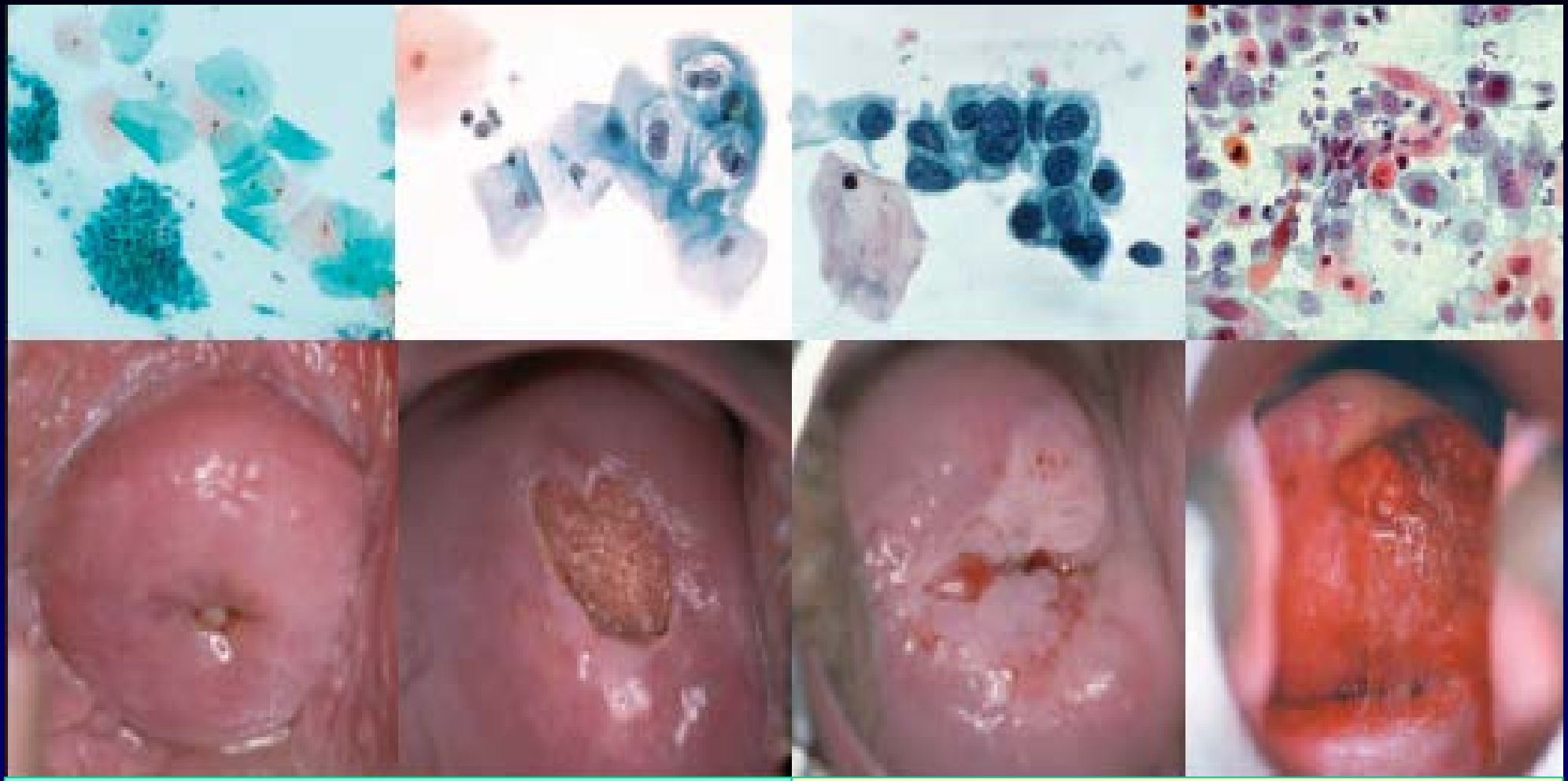
1. Natural History of HPV: Rational Basis for Cervical Cancer Prevention

2. Evidence for HPV Testing in Screening

3. Management of HPV-Positive Women

4. Reaching those who do not come through the clinic doors

New Model of Cervical Carcinogenesis



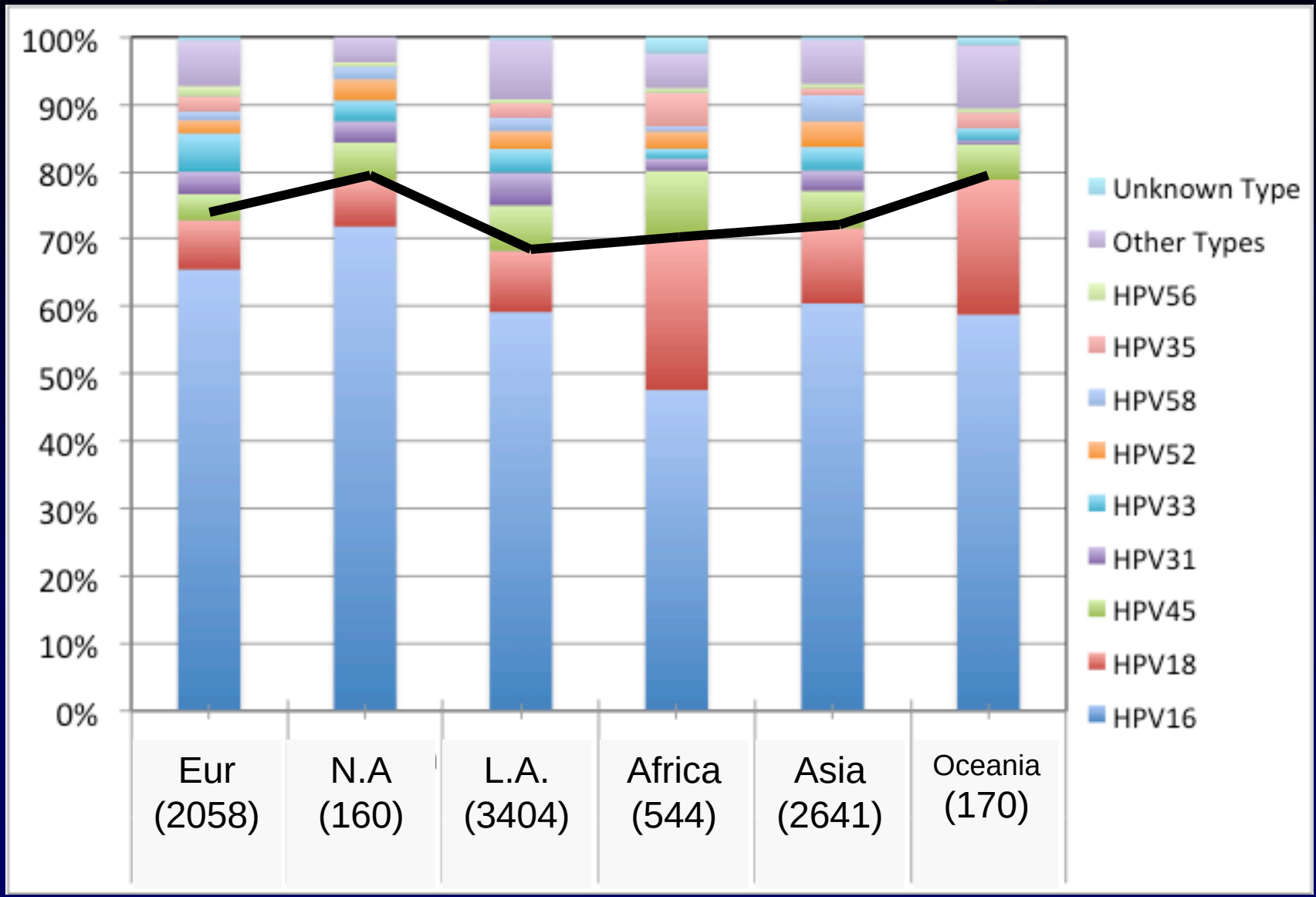
Transient infection | Persistent HPV

Normal cervix → INFECTION → HPV-infected cervix → PROGRESSION → Precancer → INVASION → Cancer

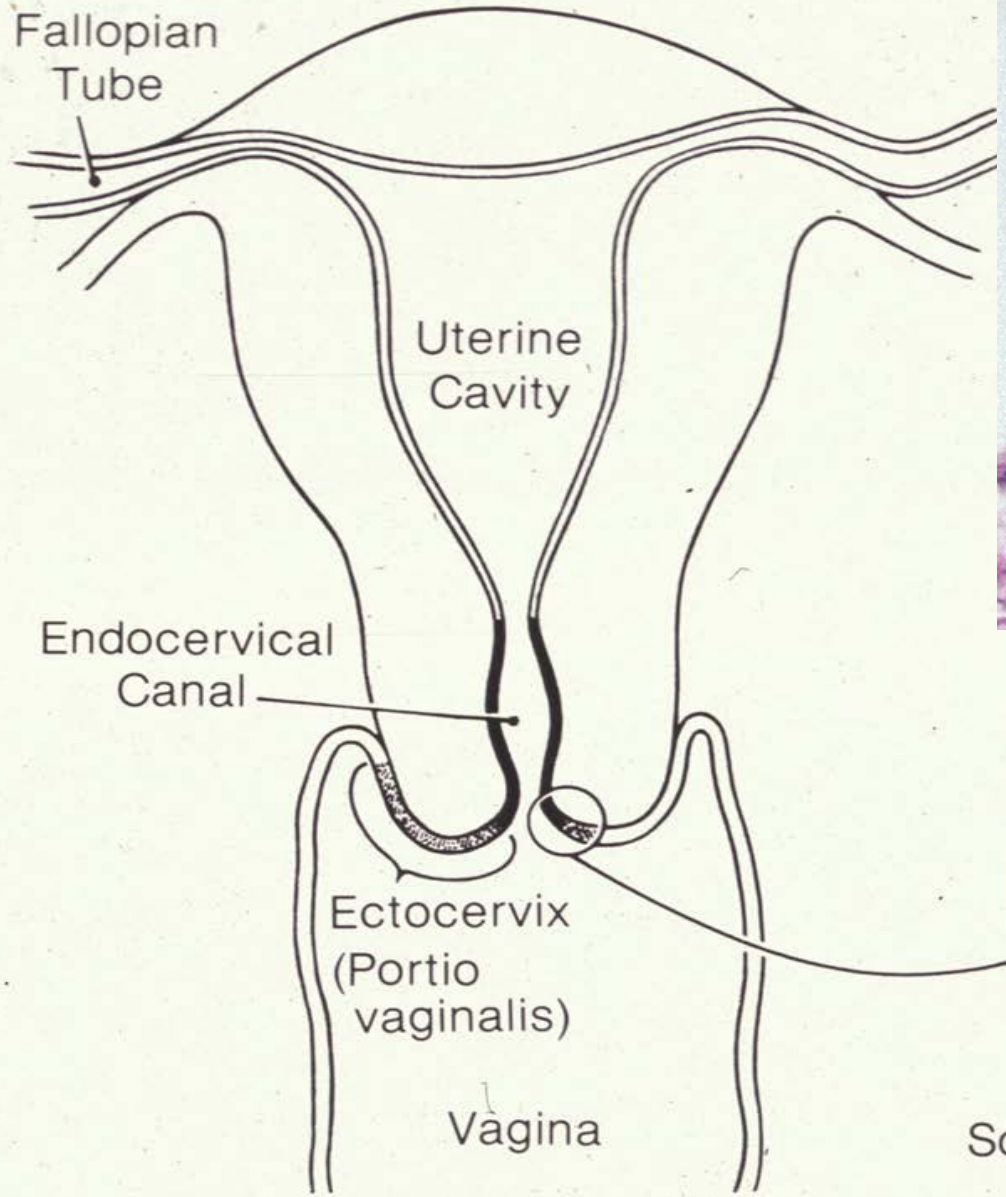
HPV-infected cervix → CLEARANCE → Normal cervix

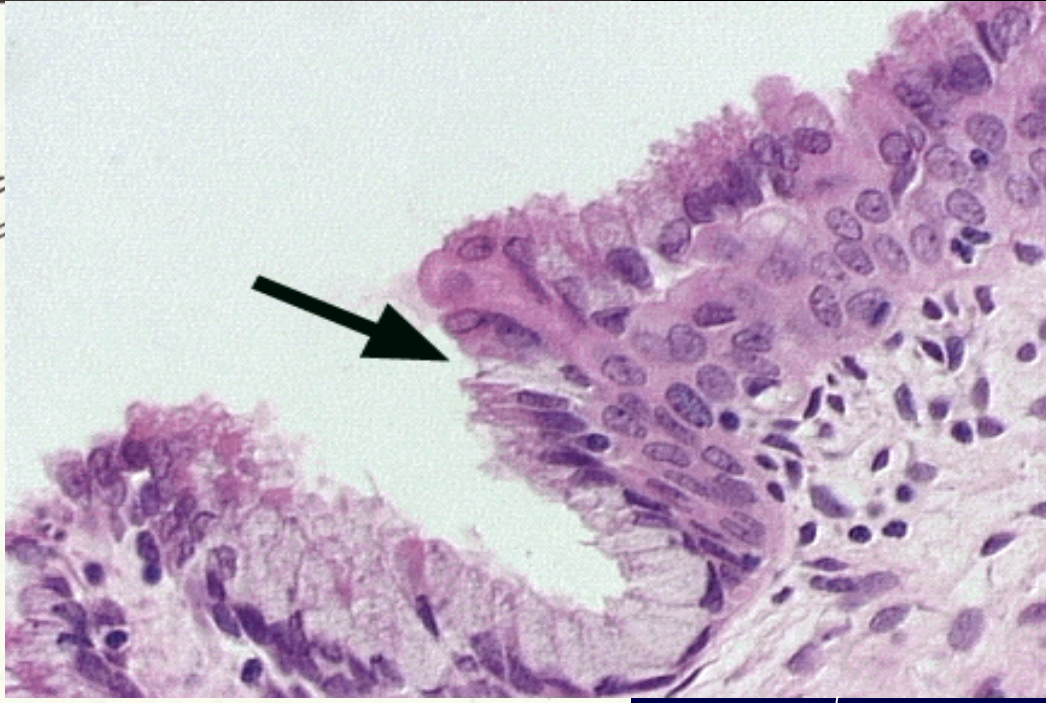
Precancer → REGRESSION? → HPV-infected cervix

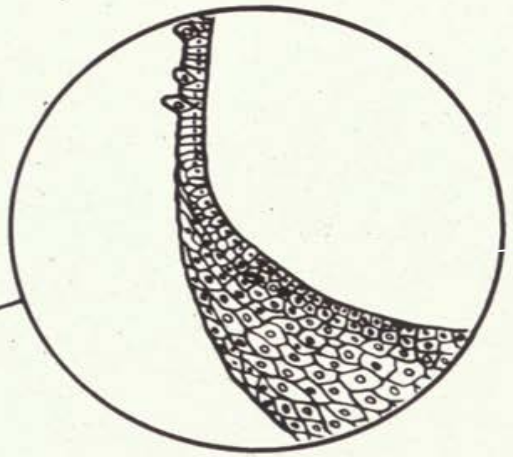
Regional Variation of HPV Genotypes in CxCa



de Sanjose *et al*., Lancet Oncol, 2010

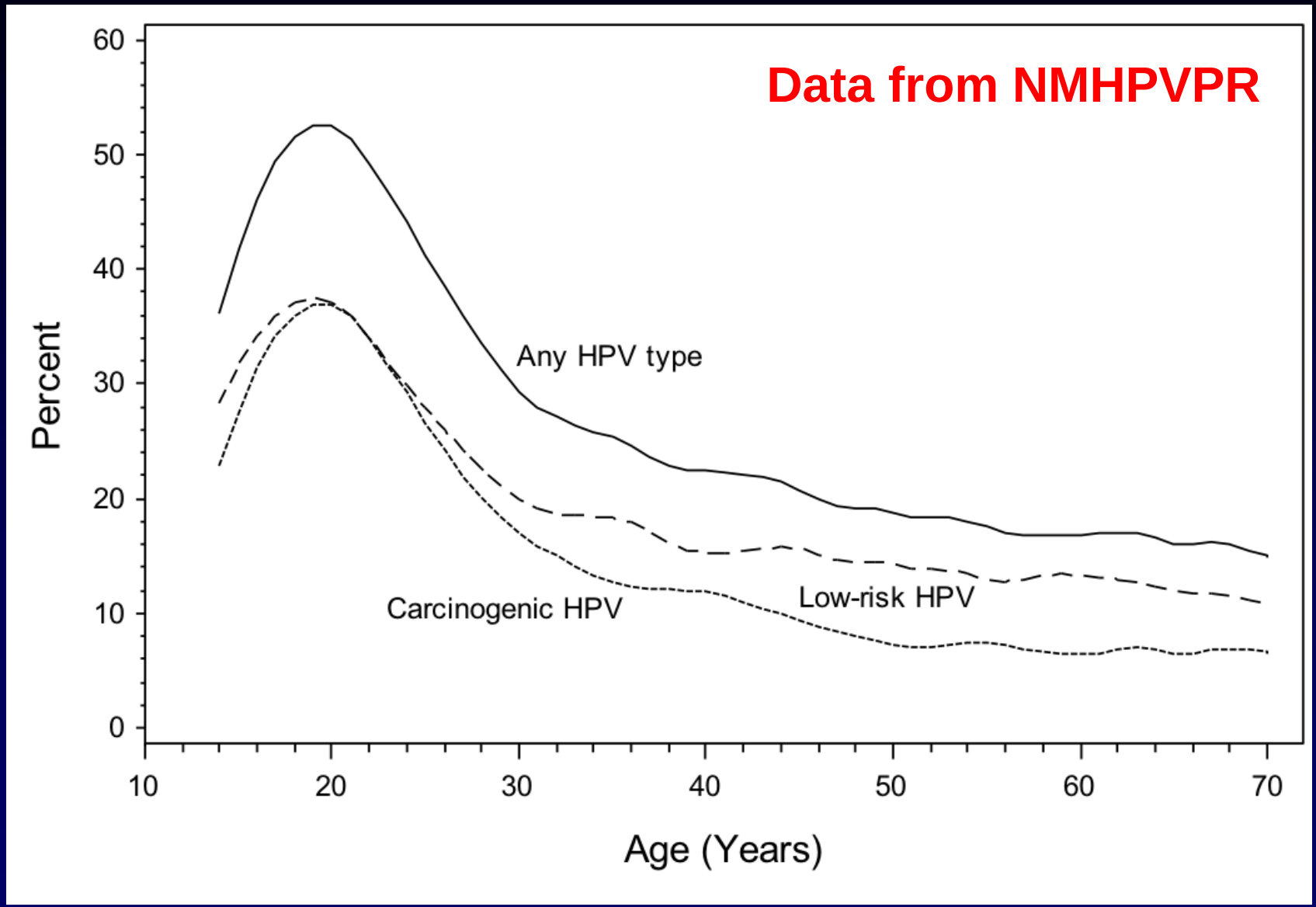






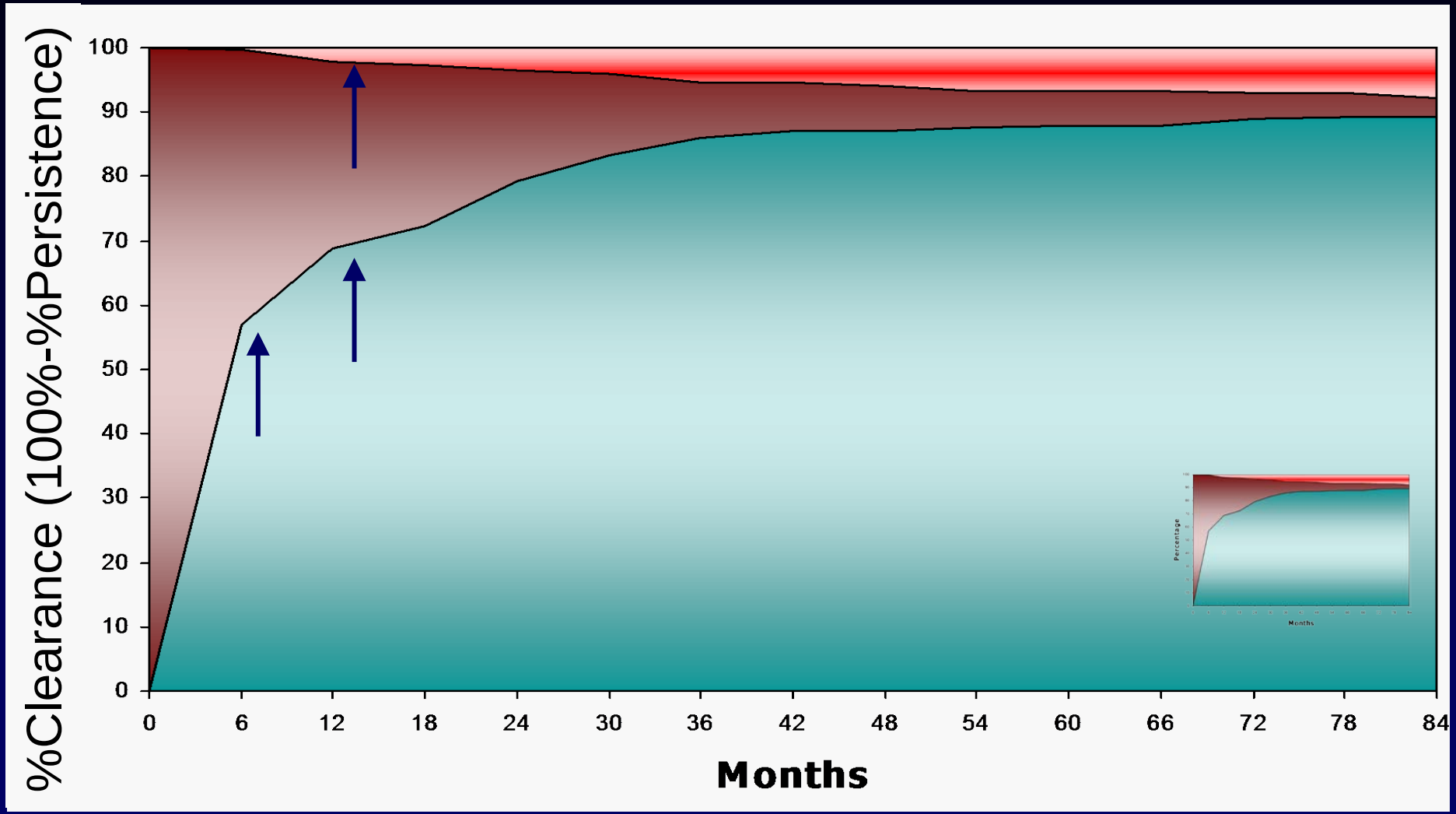
Squamocolumnar Junction
(Transformation Zone)

Age-Specific HPV Prevalence



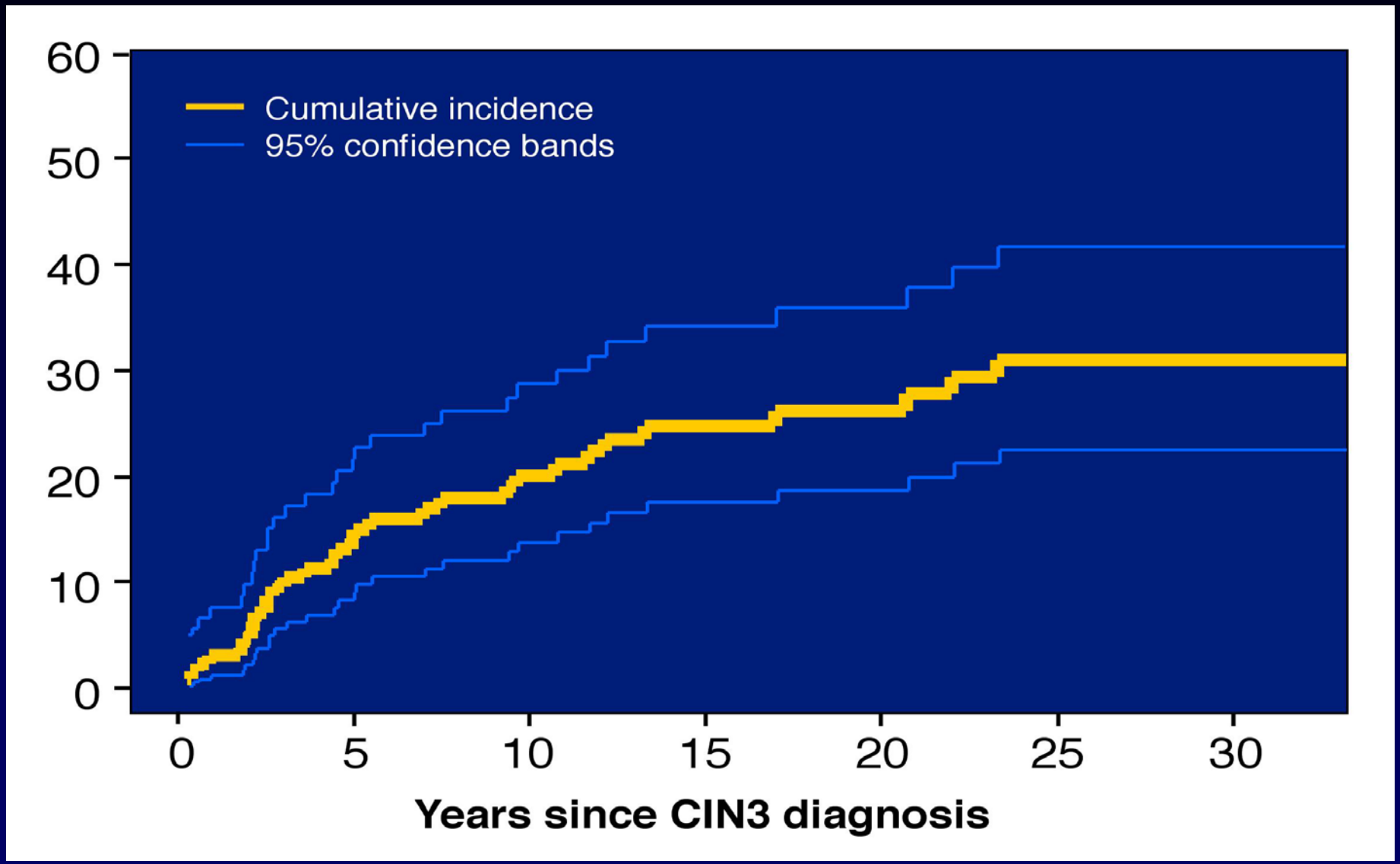
Wheeler *et al*., submitted

Natural History Profile of Prevalent HPV



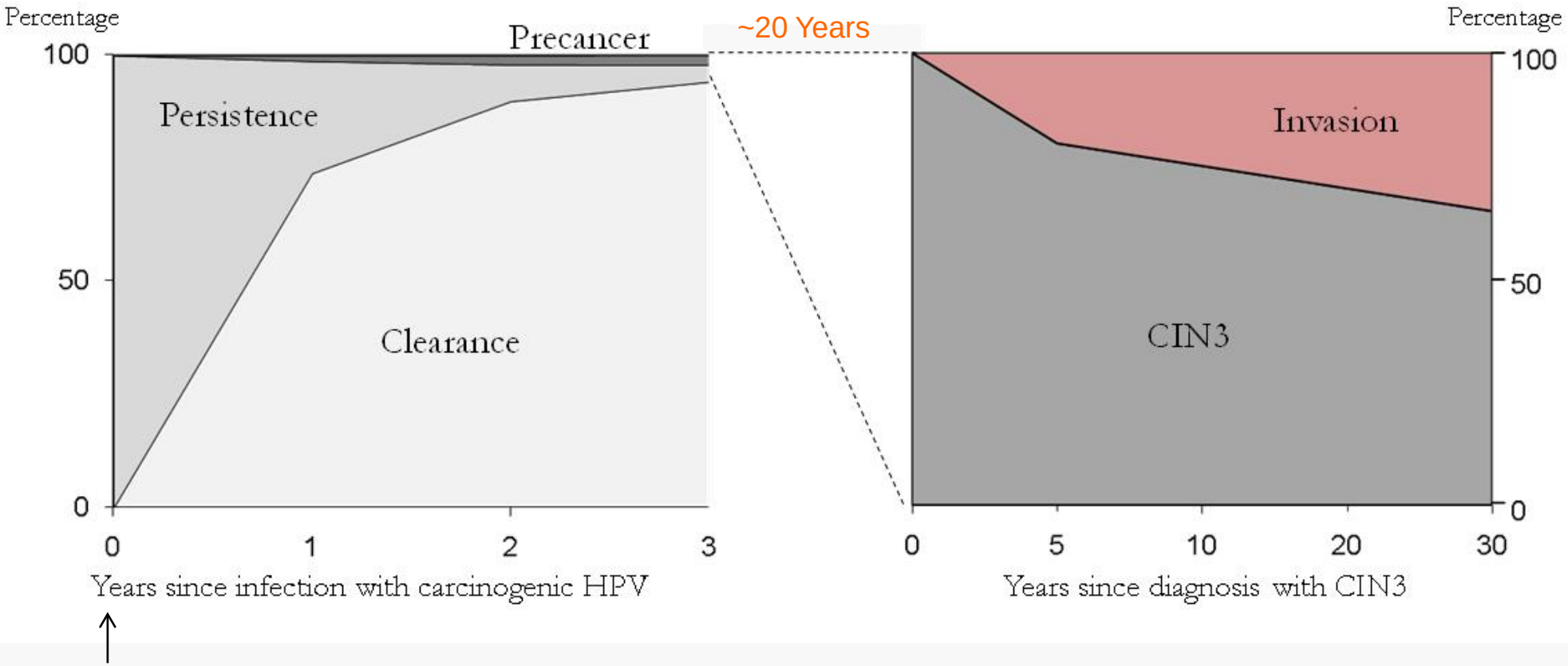
Schiffman *et al*., Lancet, 2007

An Unfortunate Experiment



McCredie *et al*., Lancet Oncology, 2008

Persistence, Progression, and Invasion



Courtesy of Mark Schiffman

Today's Talk

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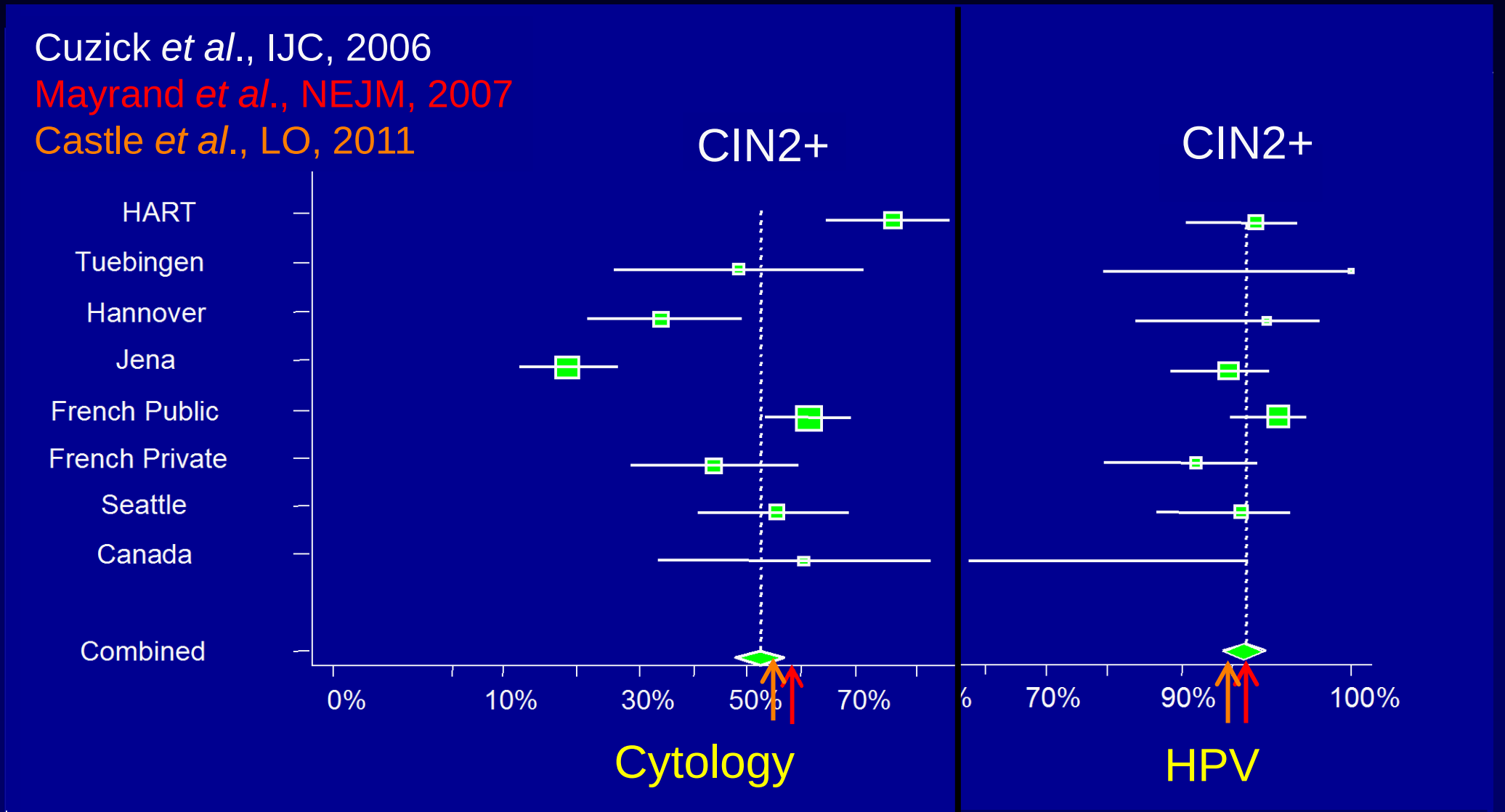
My Basic Principles of Screening

1. The goal of screening is not to find disease. Most diseases are too rare to succeed. Rather, screening is to rule out disease in the generally healthy population and identify a subset who need further evaluation. If the screen is good, the subset will be very enriched for disease i.e., better PPV.

2. In the case of cervical cancer prevention, we want a positive screen to identify those women who have or may develop CIN3, which can be treated before it becomes invasive. CIN3 itself is **NOT** disease. It marker of cancer risk.

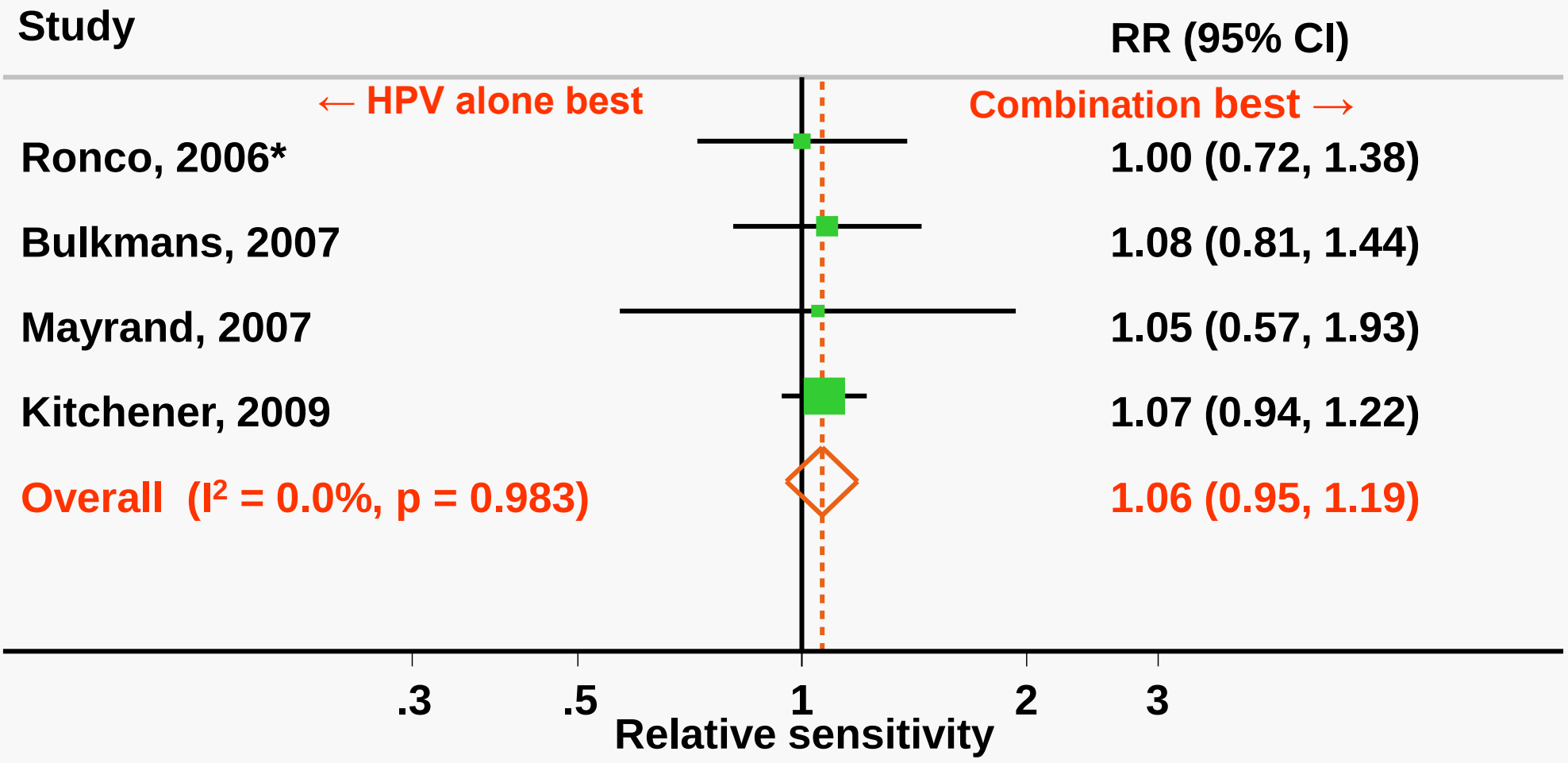
3. We want a negative screen to provide an acceptable degree of reassurance against cancer until the next screen.

Sensitivity: CIN2+



(HPV & cyto) vs HPV alone

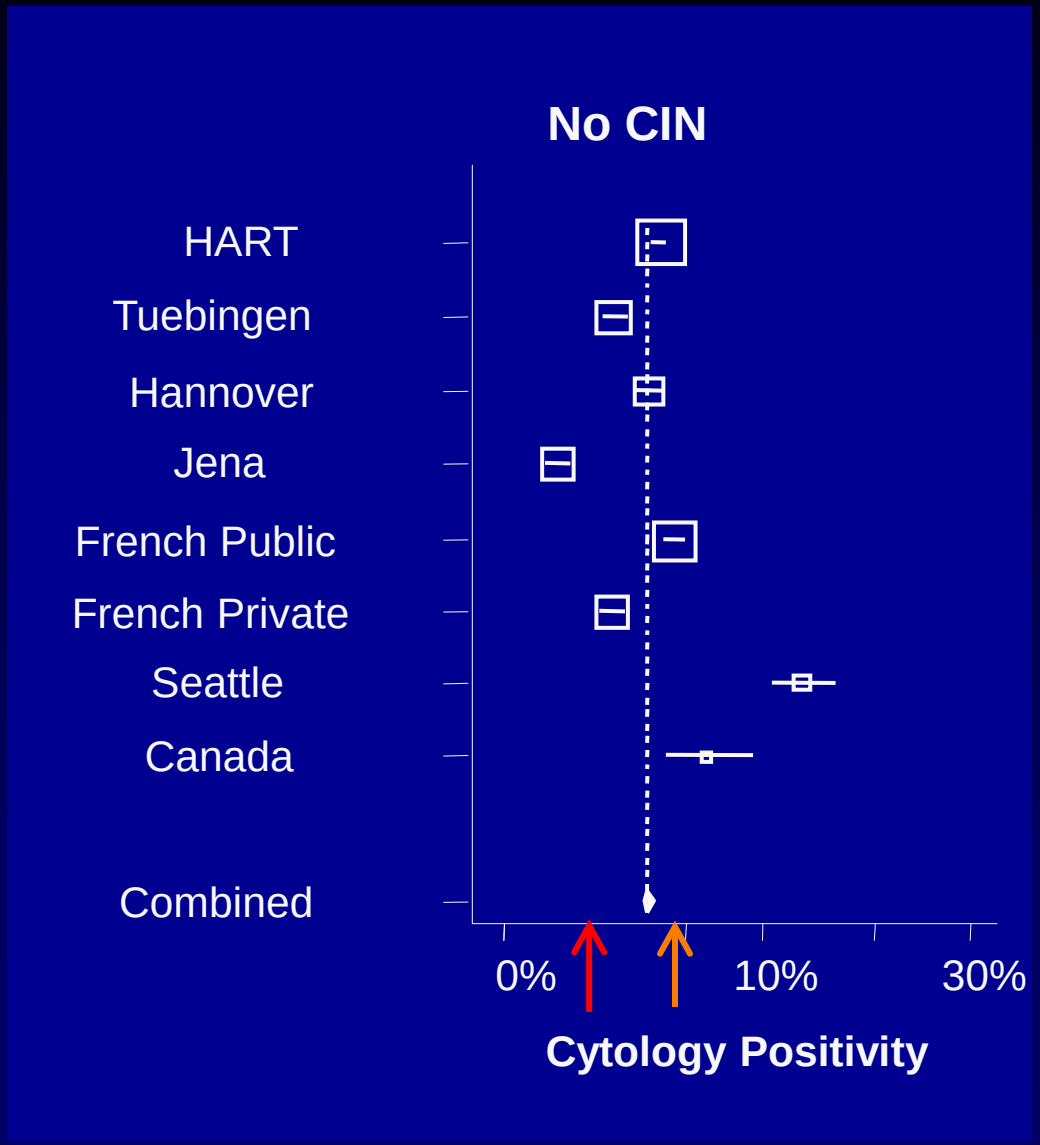
Detection of CIN2+, 1st screening round

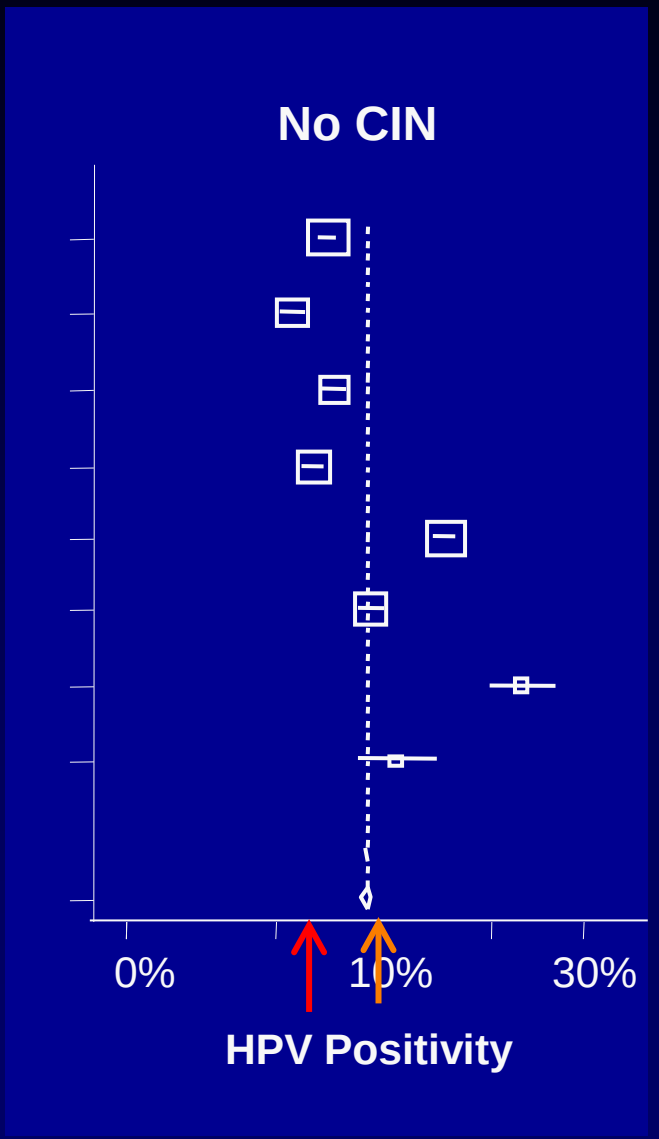


Arbyn *et al*. , Lancet Oncol 2009

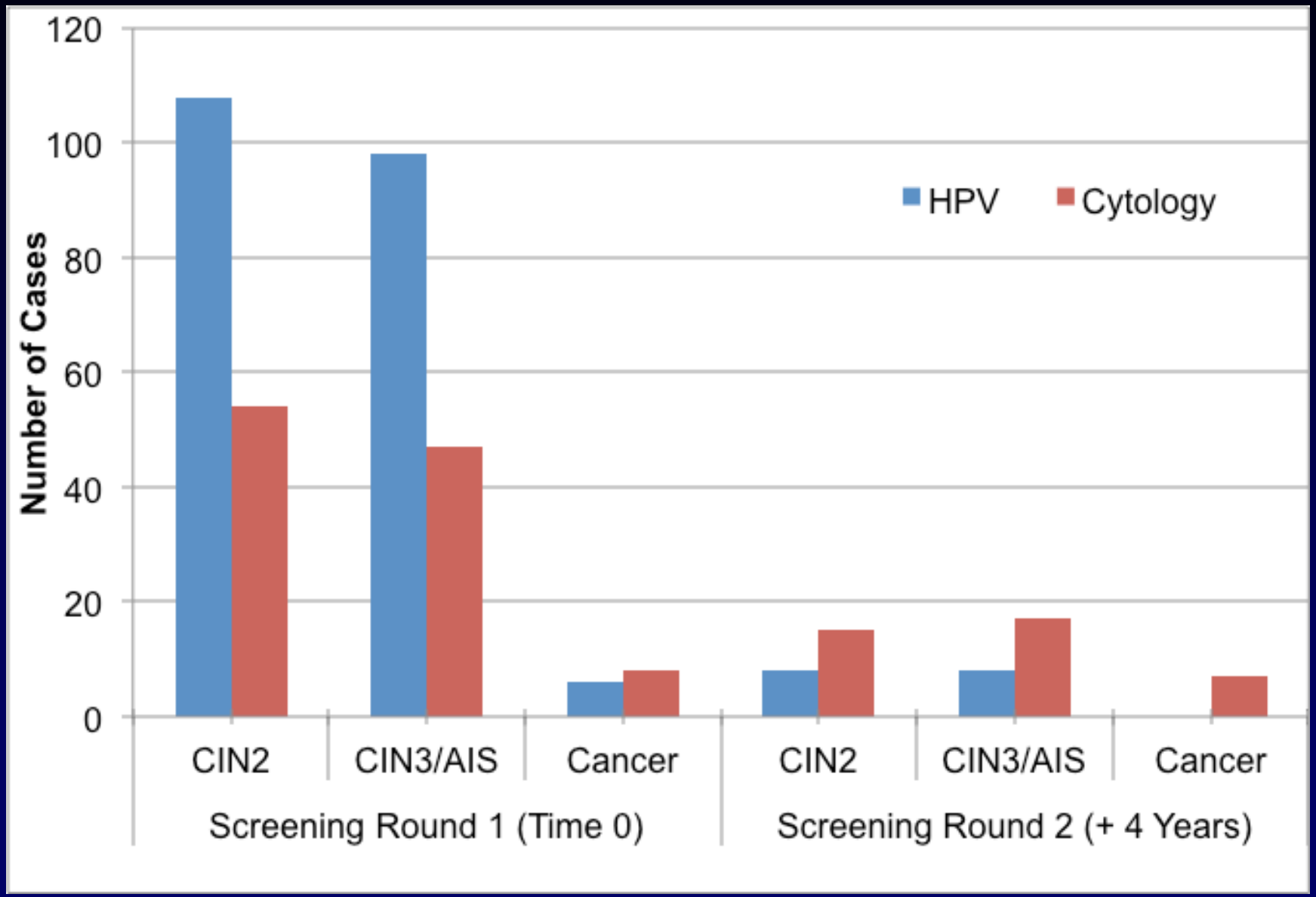
*Age >=35 years

%Cytology and HPV Positive: No CIN



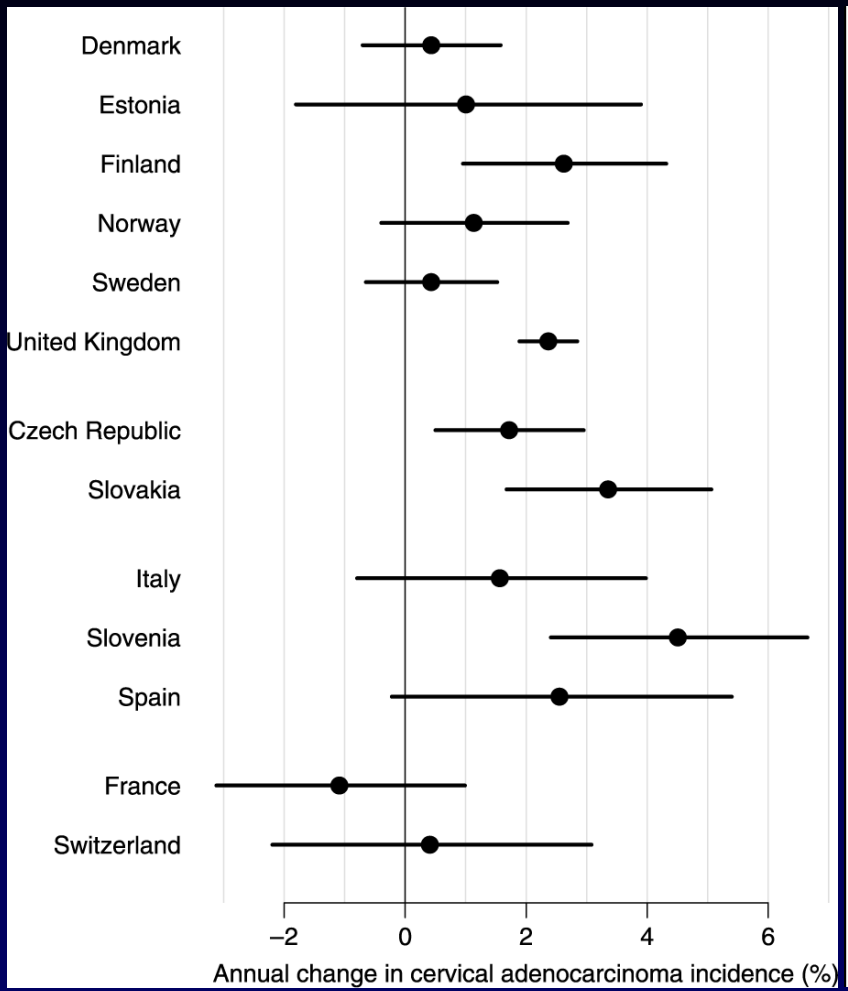


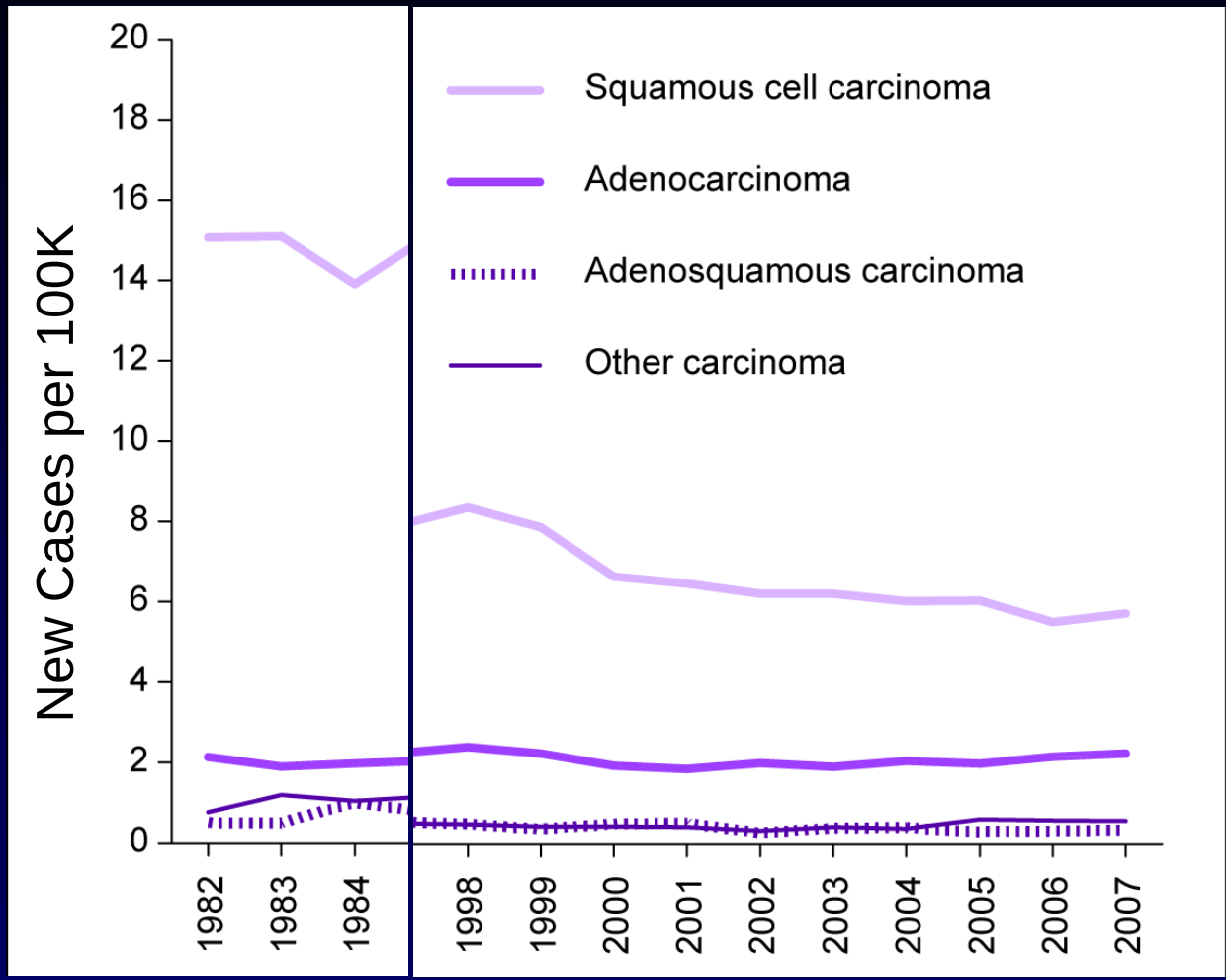
Lead-Time Detection = Reduced Cancer Risk



Ronco *et al*., Lancet Onc, 2010

Cytology Misses Glandular Disease

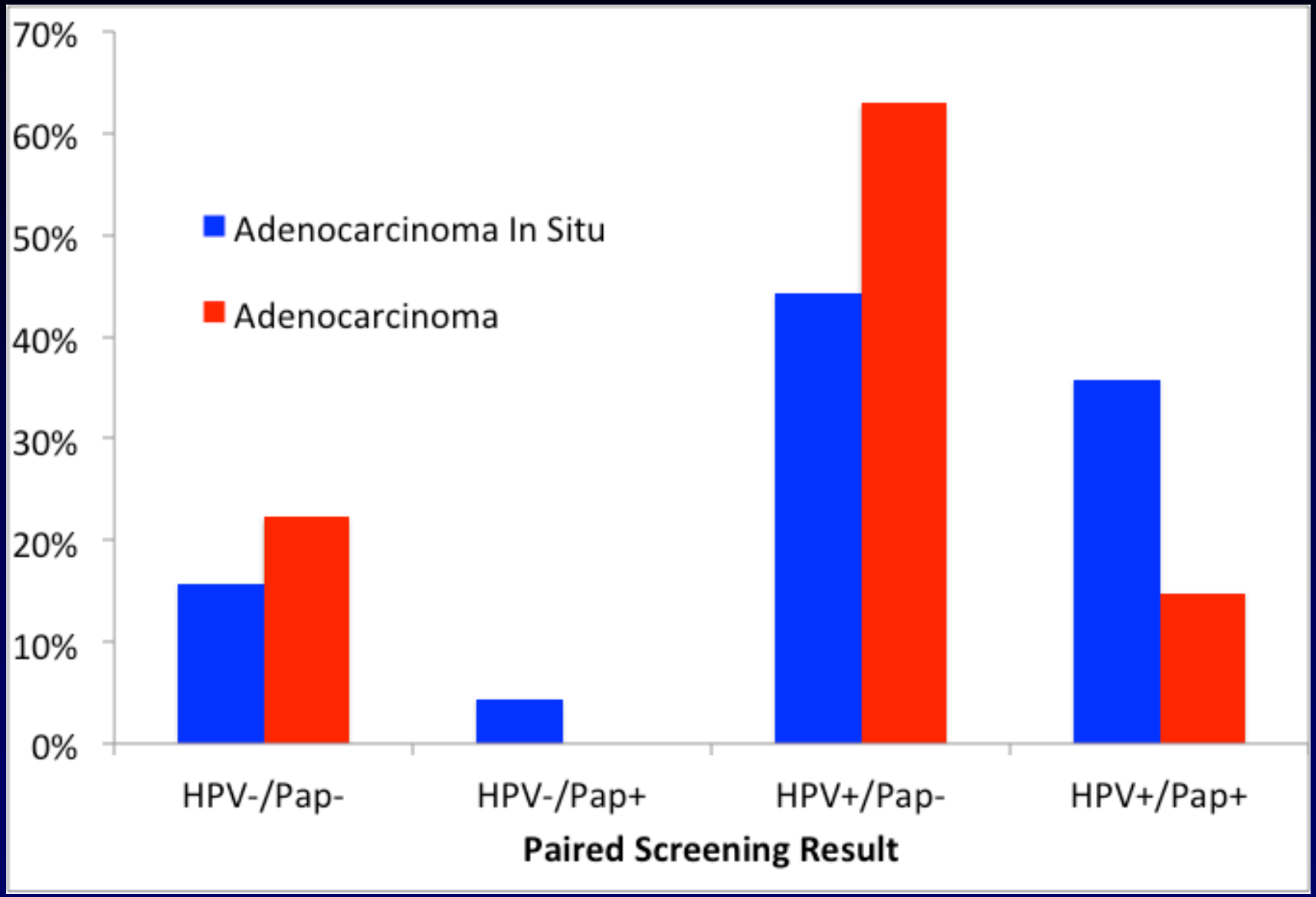




Bray *et al*., CEBP, 2005

http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737420248

HPV Testing Does Not



Katki *et al.*, Lancet Oncol, 2011

Hazard ratios (HR) of cervical cancer deaths rates

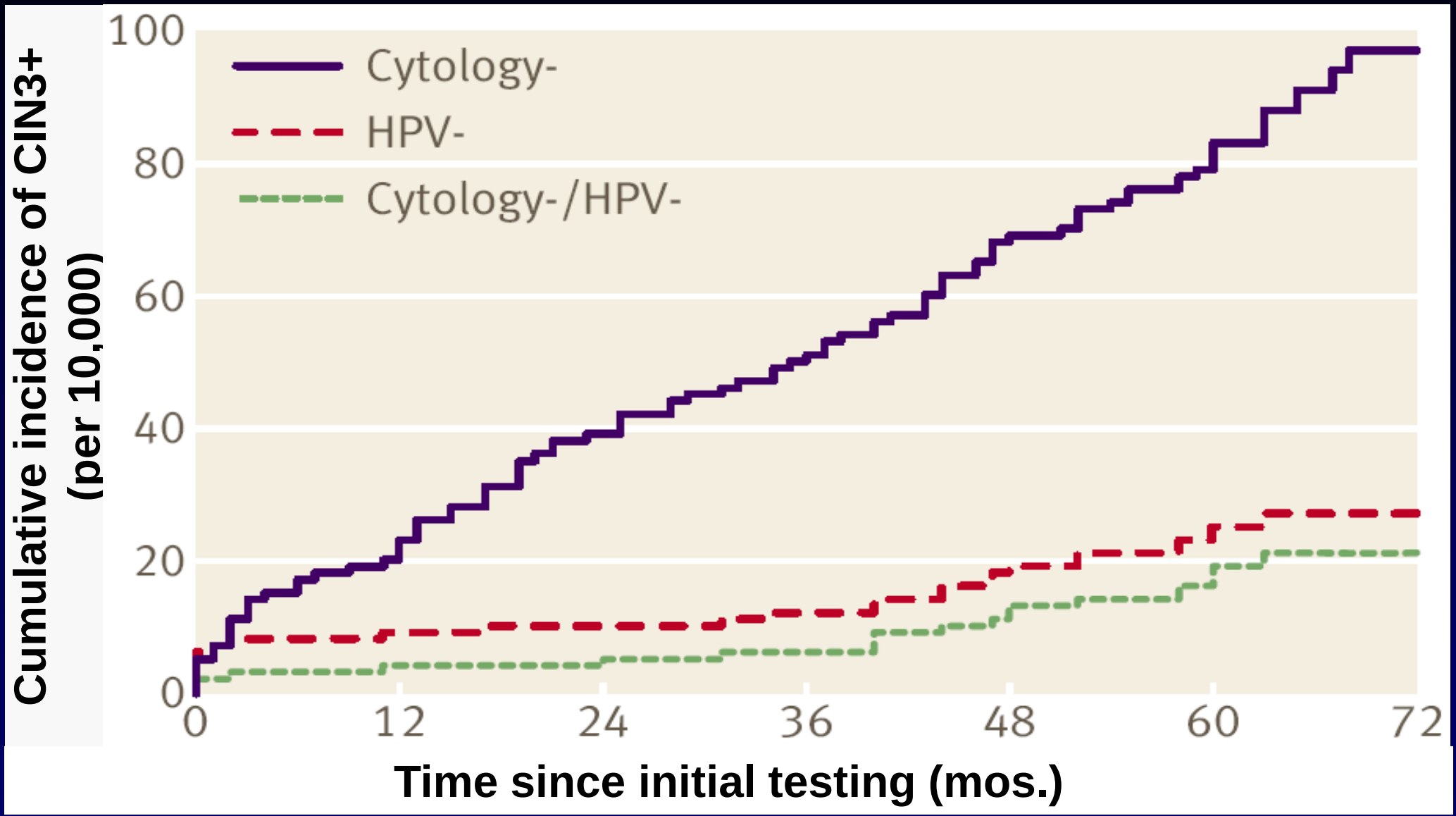
Study group	Rate/100 000	HR (95% CI)
Control	25.8	1.00
HPV	12.7	0.52 (0.33-0.83)
Cytology	21.5	0.89 (0.62-1.27)
VIA	20.9	0.86 (0.60-1.25)

CI: Confidence interval

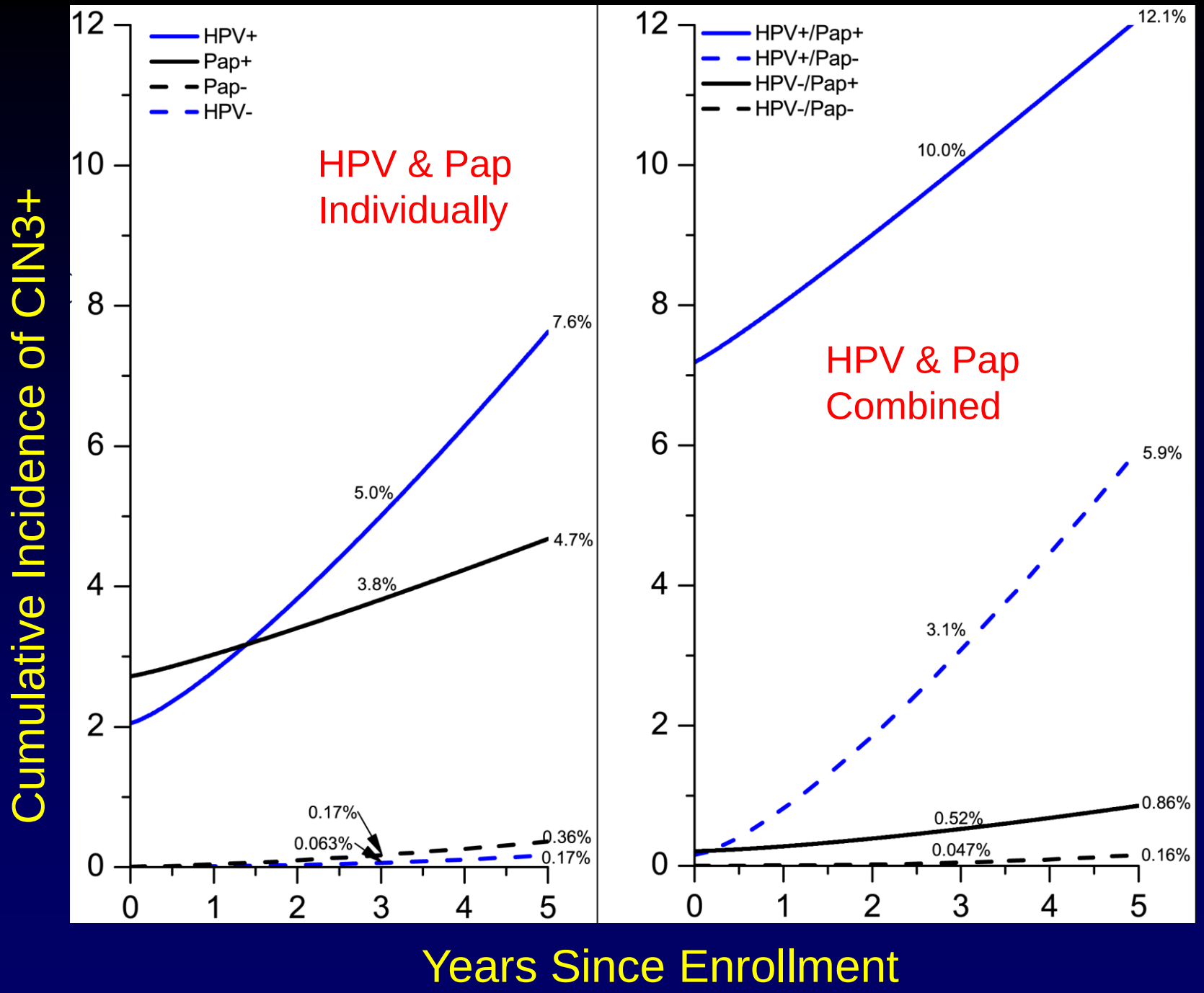
Comparative efficacy of visual inspection with acetic acid, HPV testing and conventional cytology in cervical cancer screening: a randomized intervention trial in Osmanabed District, Maharashtra State, India

Sankaranarayanan *et al*., NEJM, 2009

CIN3+ Risk Following a Negative Test



Dillner *et al*., BMJ, 2008



Cotesting @ KPNC in 330,000 Women

Katki *et al.*, Lancet Oncol, 2011

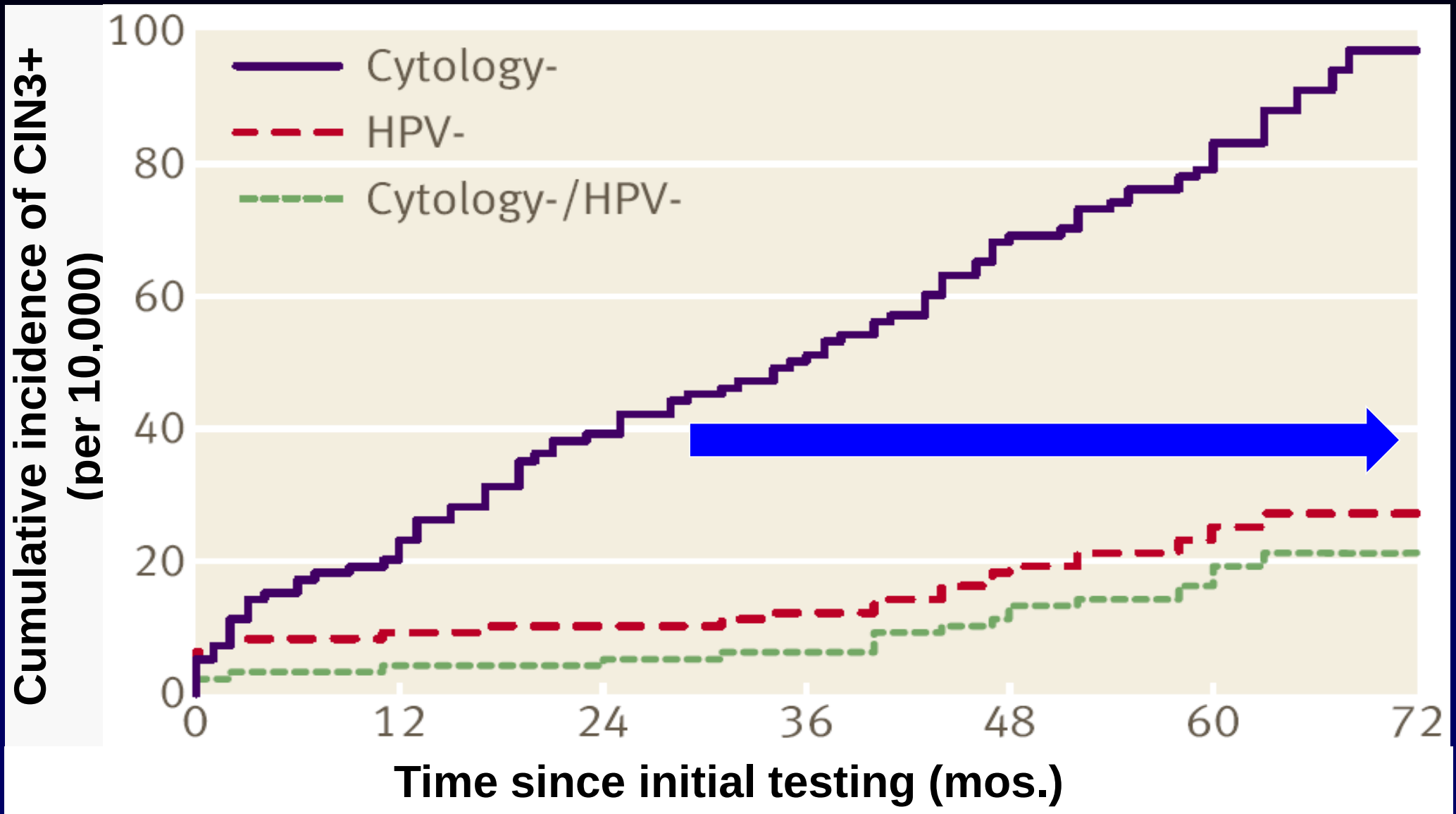
Cervical cancer incidence rates among screen negative women by study group (2000-2007)

Group	Cancer cases	Number of women	Age Standardized Incidence rate (per 100,000)
HPV	8	24,380	3.7
Cytology	22	23,762	15.5
VIA	25	23,032	16.0

Comparative efficacy of visual inspection with acetic acid, HPV testing and conventional cytology in cervical cancer screening: a randomized intervention trial in Osmanabed District, Maharashtra State, India

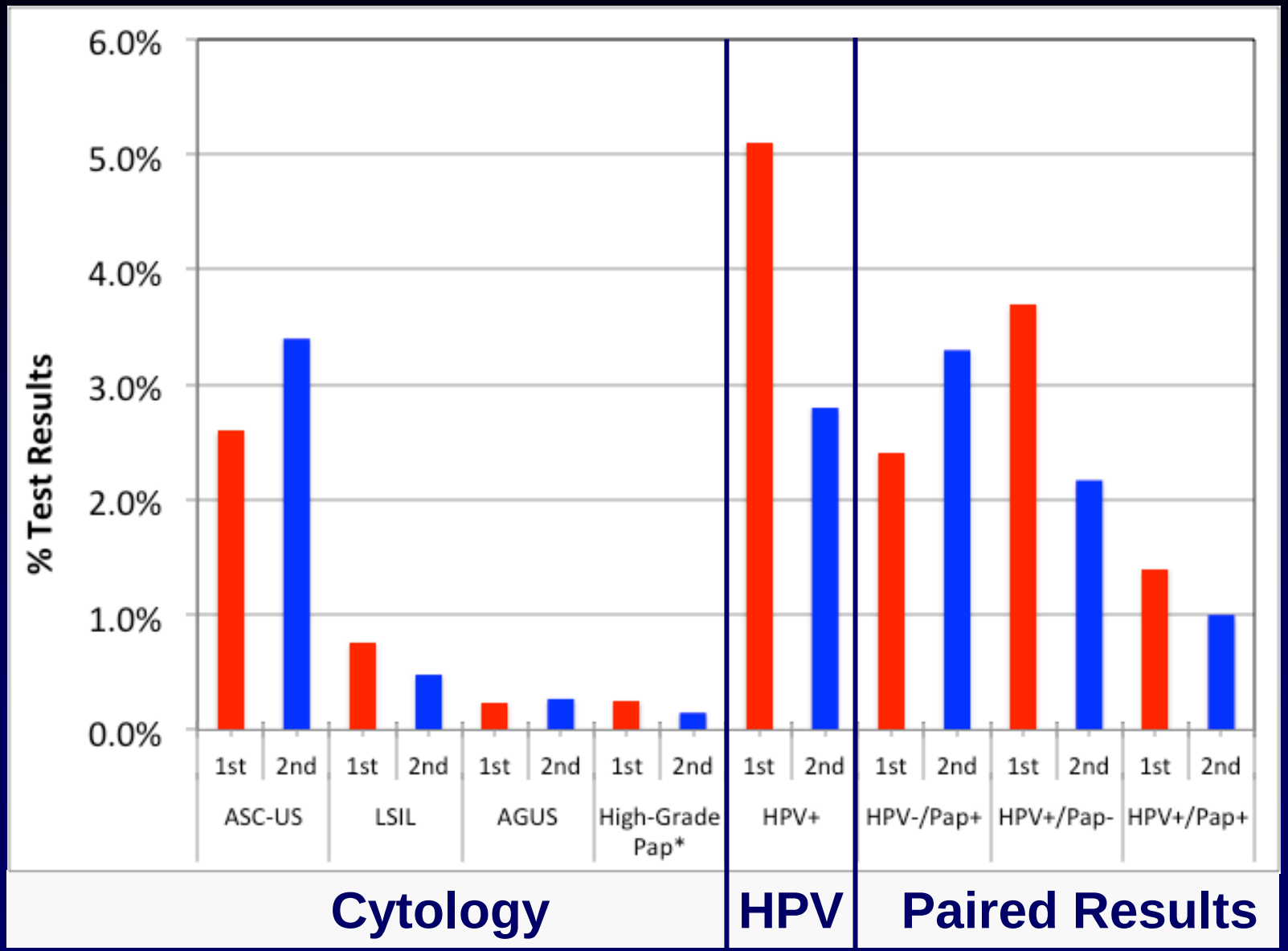
Sankaranarayanan *et al*., NEJM, 2009

CIN3+ Risk Following a Negative Test



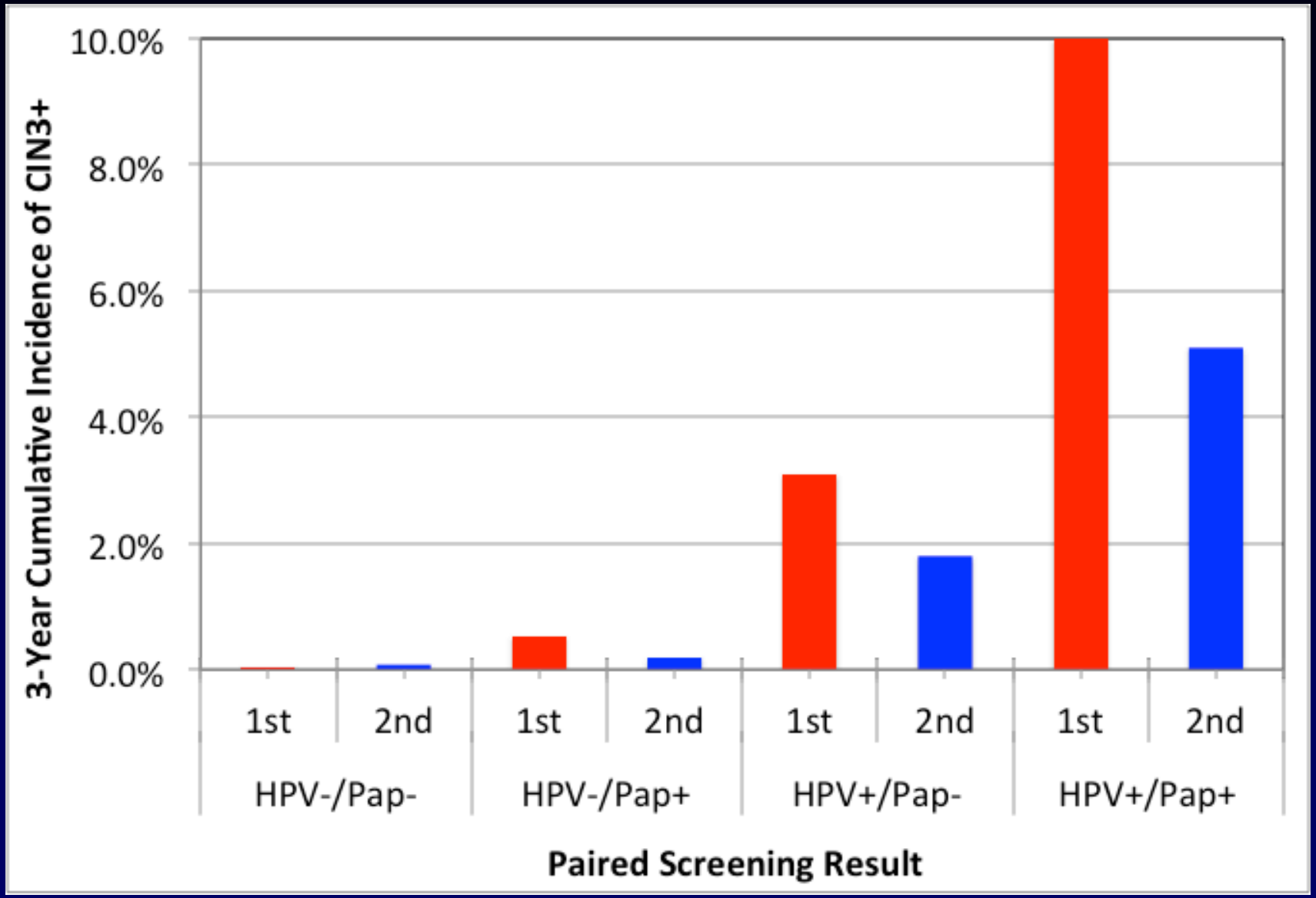
Dillner *et al*., BMJ, 2008

Screening Intervals: Impact on Diagnostic Yields



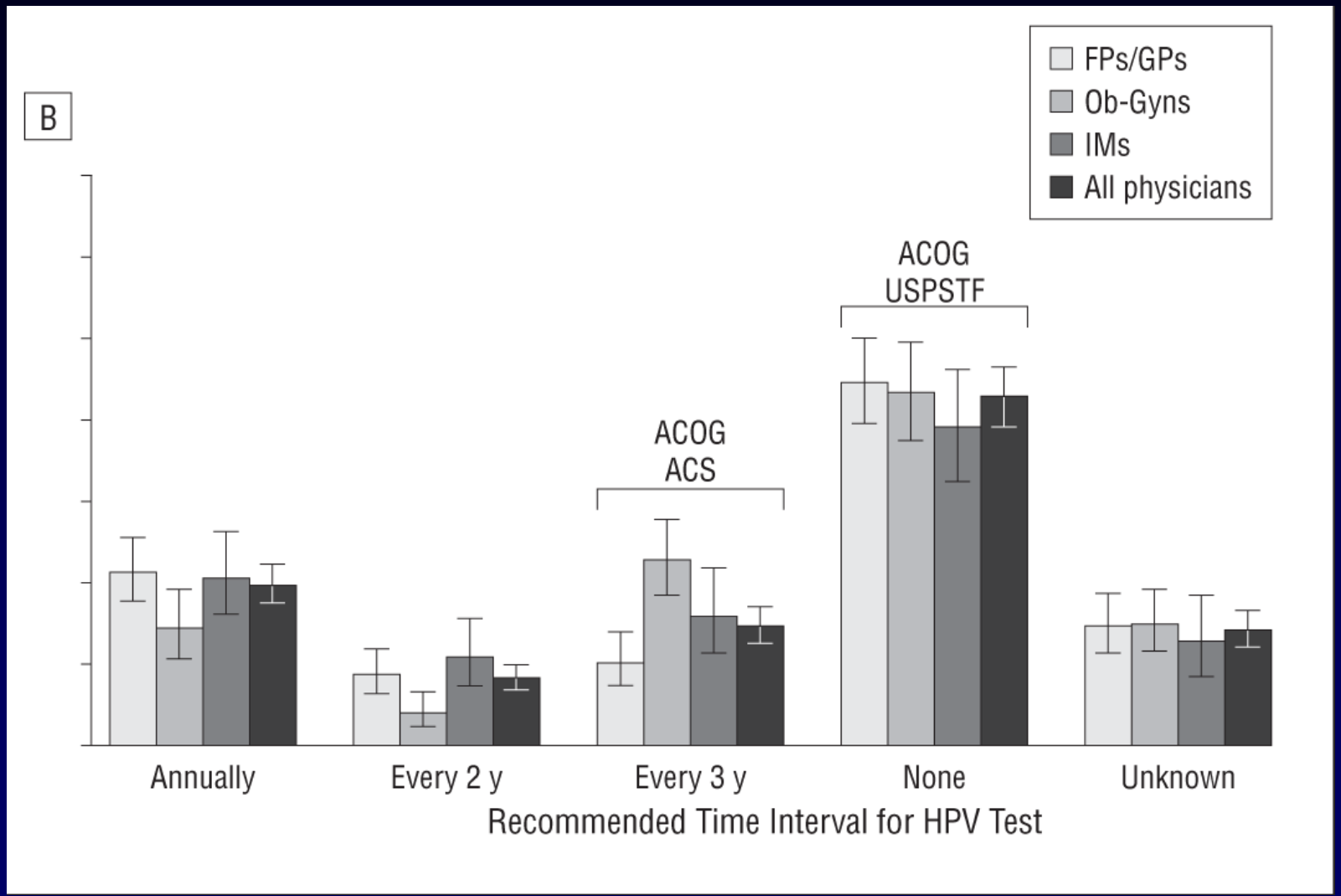
Katki *et al.*, Lancet Oncol, 2011

Screening Intervals: Impact on Screening Tests



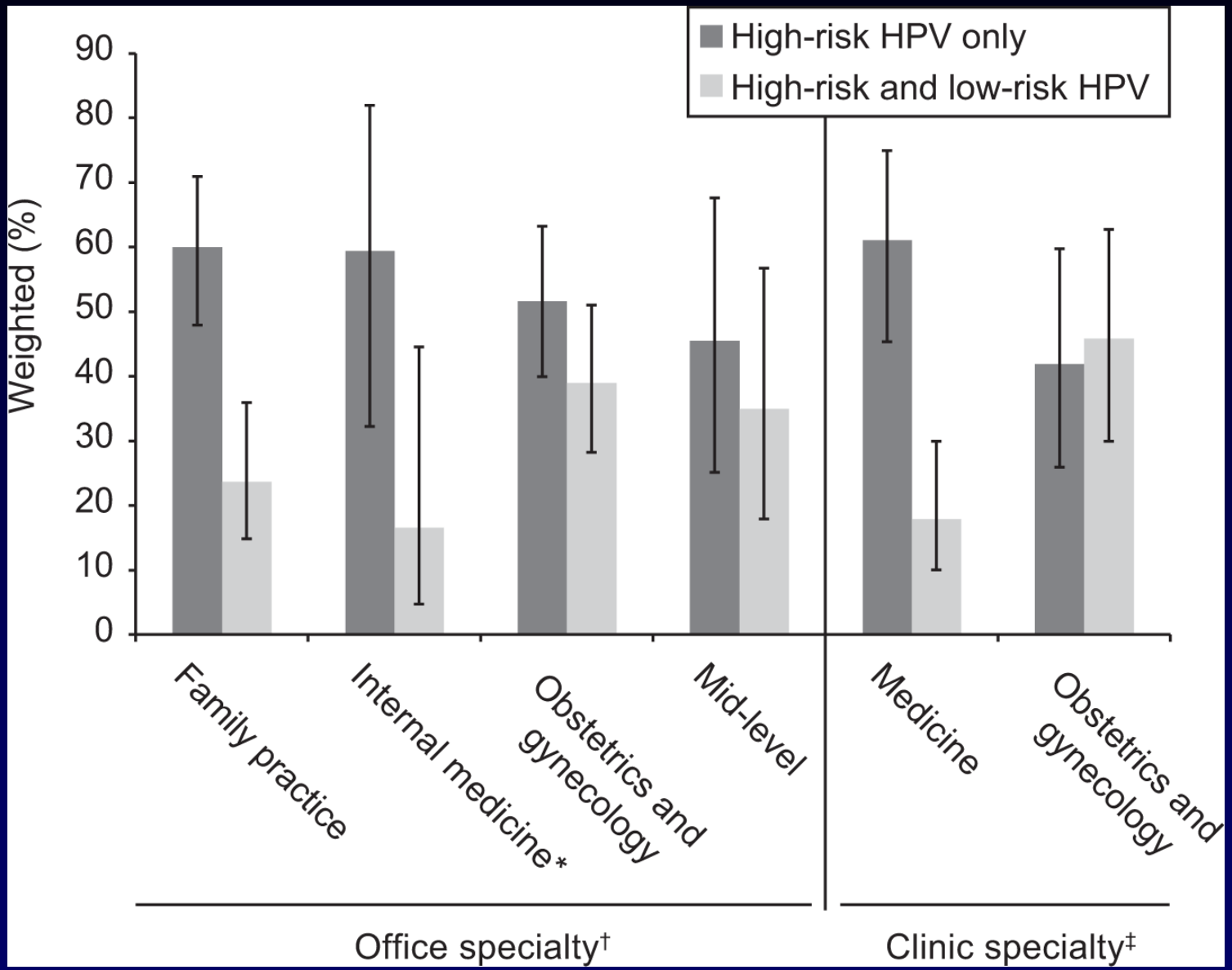
Katki *et al.*, Lancet Oncol, 2011

When Would Next HPV Test?
35 years, Pap Normal and HPV Negative?



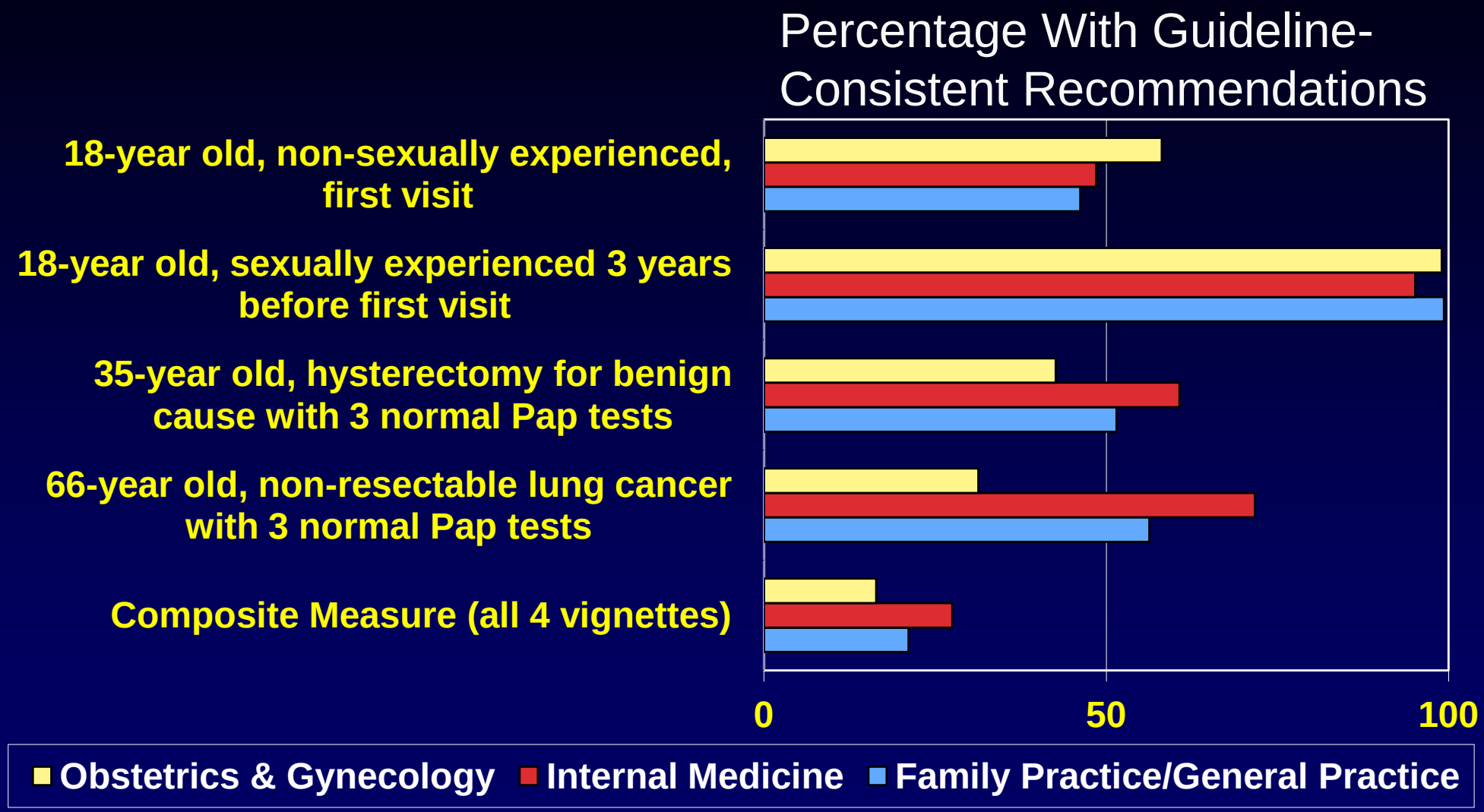
Saraiya *et al*., Arch Intern Med, 2009

Low-Risk HPV Testing



Lee *et al*., Obstet Gyn, 2011

Guideline Failures



Yabroff *et al*., AIM, 2009

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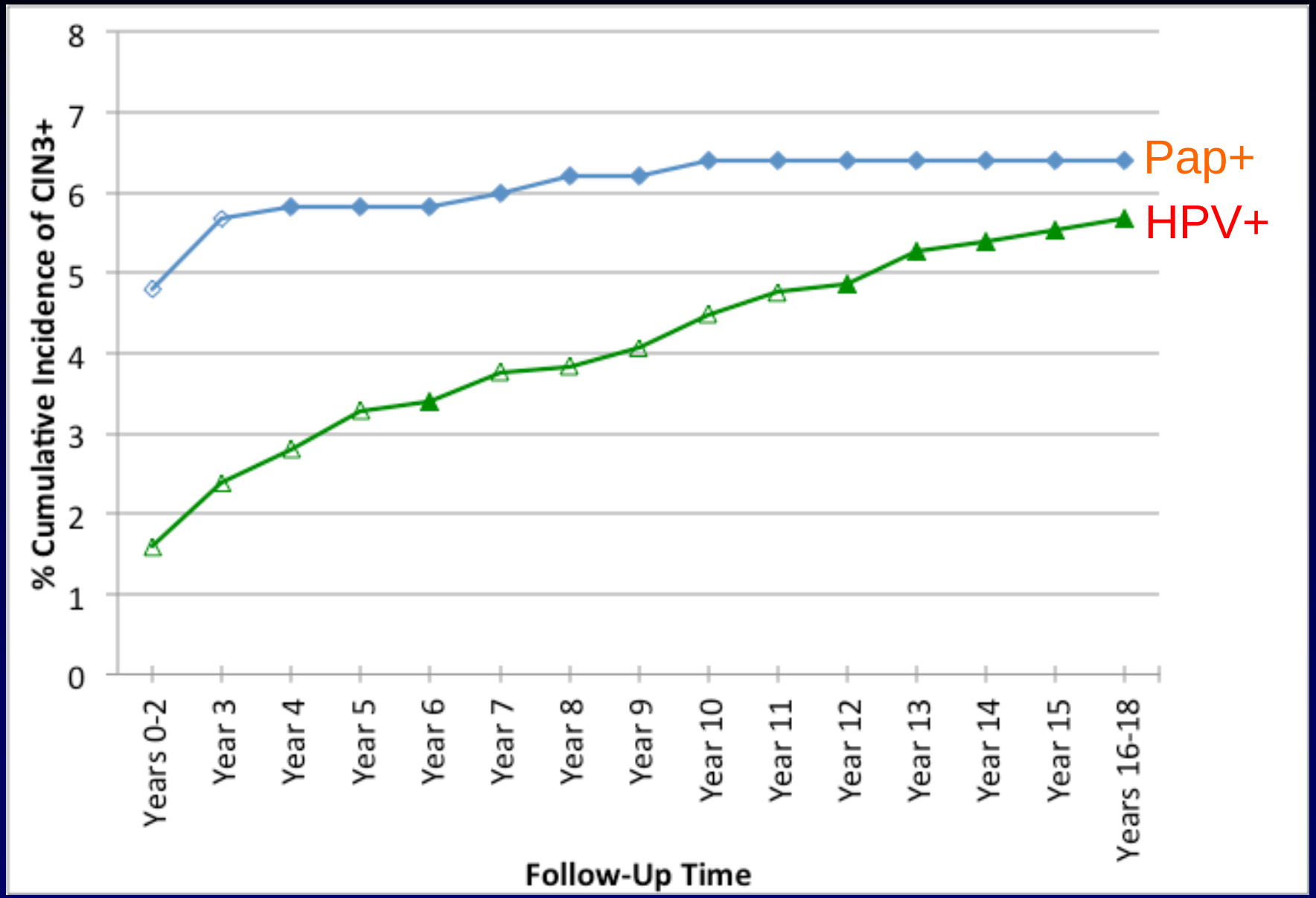
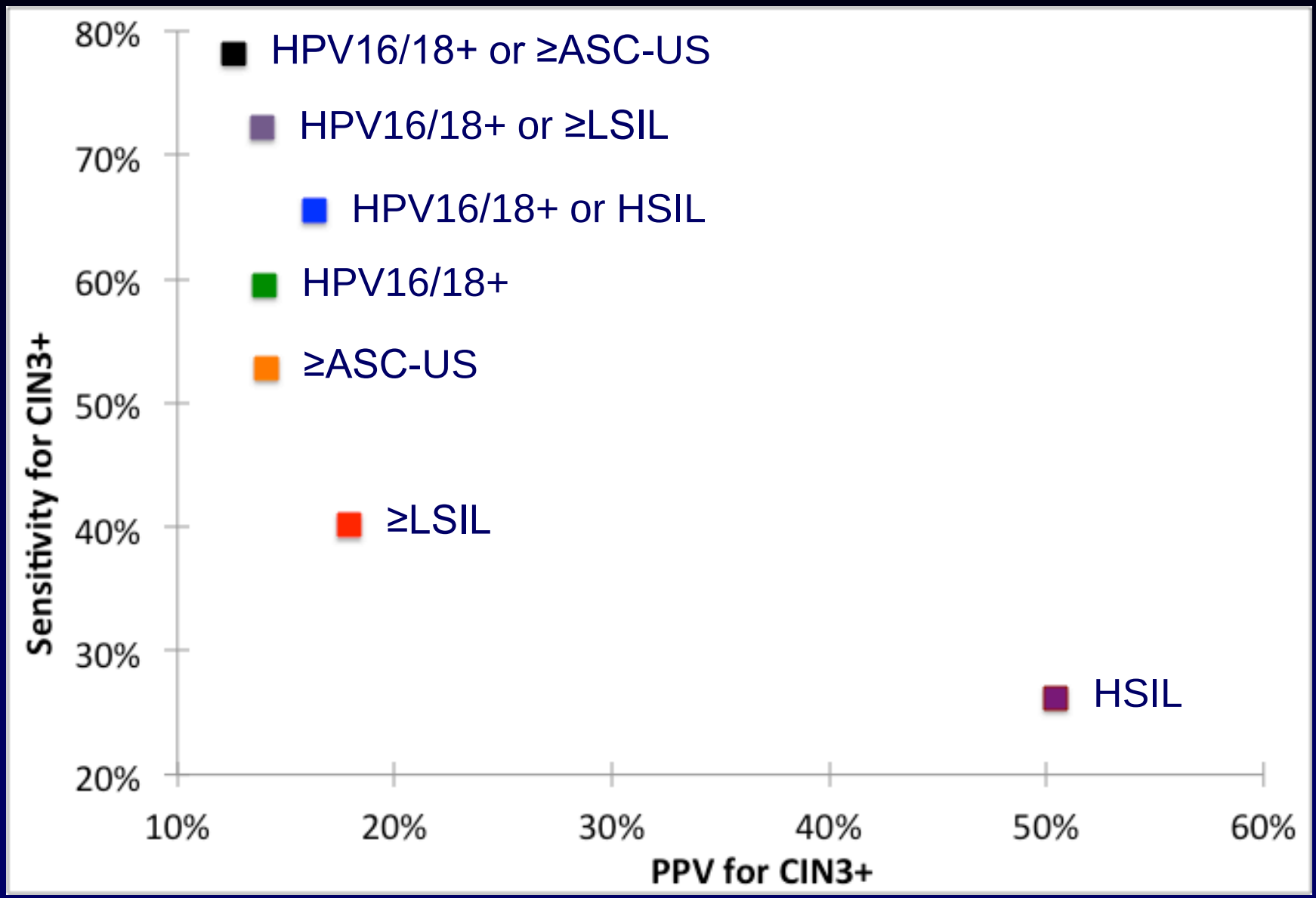
HPV Predicts CIN3+ Over 18 Years



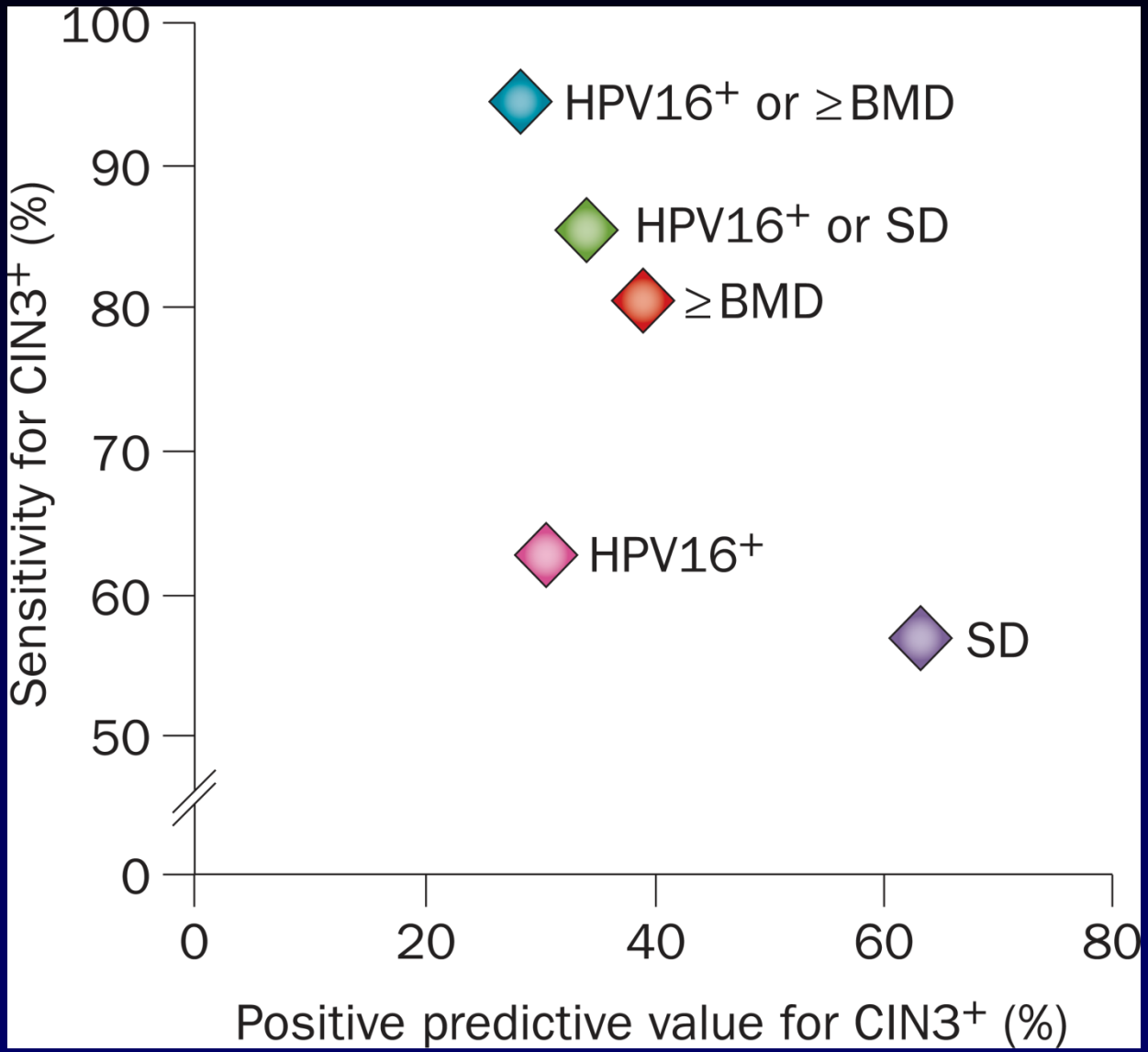
Castle *et al.*, submitted

Triage of HPV+ Women: Data from ATHENA



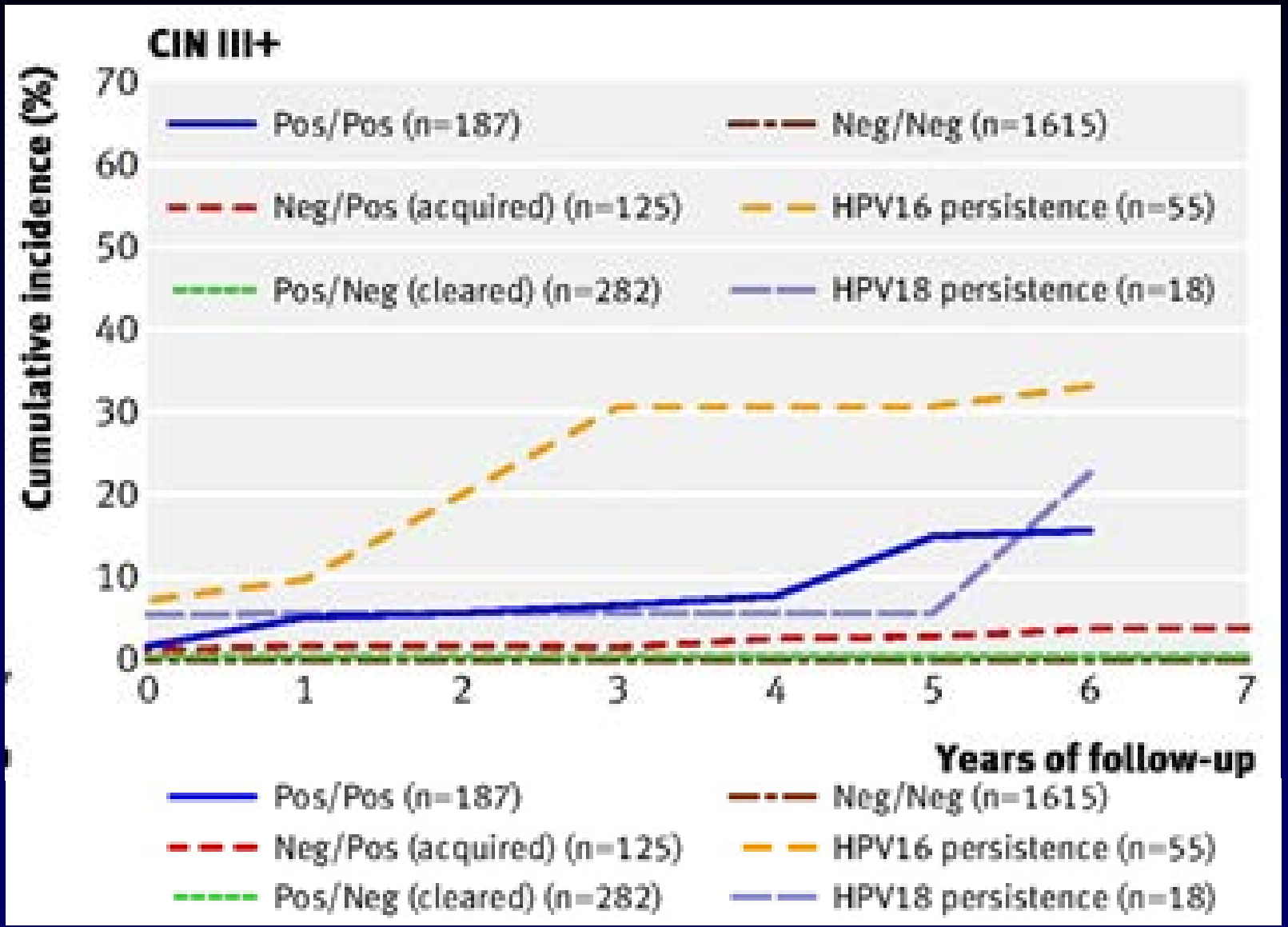
Castle *et al*., Lancet Oncol, 2011

Triage of HPV+ Women: Data from POBASCAM



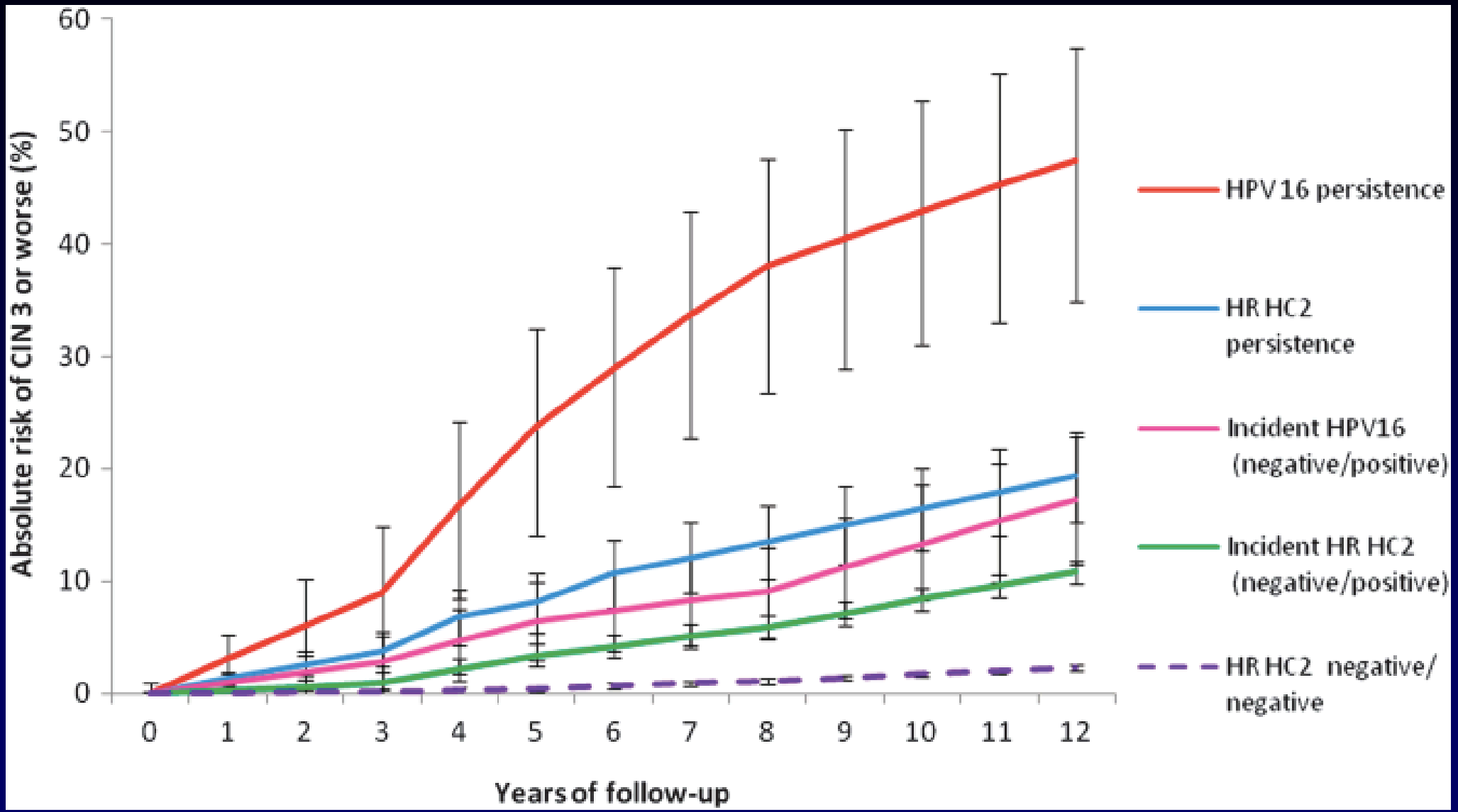
Castle, Nature Rev Clin Oncol, 2012

Short-Term HPV Persistence



Castle *et al*., BMJ, 2009

Short-Term HPV Persistence



Kjaer *et al*., JNCI, 2011

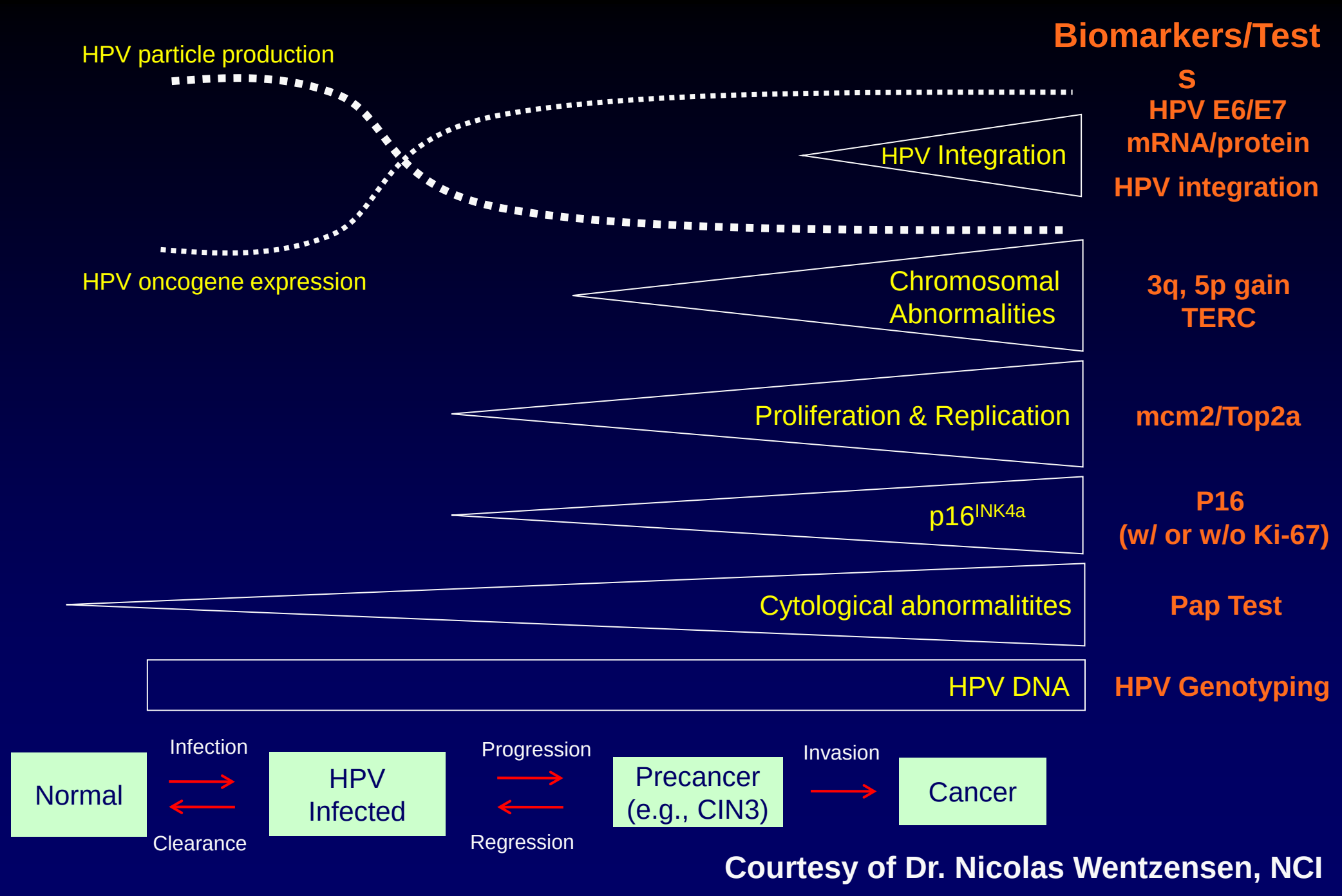
Why Not Genotype For All HPV Types?

- What would be done with knowing that a lesser oncogenic HPV genotype is present? Can you imagine giving the community physicians read out on 13 carcinogenic HPV genotypes.
- Most women (>80%) who test HPV pos/pos have a type-specific, persistent HPV infection (Castle *et al*., BMJ, 2009).
- Type-specific detection does not predict CIN2+ or CIN3+ better than pooled detection (Gage *et al*., JCM, 2011; Marks *et al*., JCM, 2012). HPV pos/pos is a very strong predictor of CIN3+ (Kjaer *et al*., JNCI, 2011)

HPV+ w/o or w/ p16INK4a Triage (vs. Cytology)

Age 35-60	Relative sensitivity for CIN3+	Relative Referral Rate
HPV testing ≥ 1pg/ml with no triage	**1.52** (1.06-2.19)	**2.38** (2.21-2.57)
HPV testing ≥ 1pg/ml and p16 1+ cells staining	**1.32** (0.88-1.95)	**1.08** (0.96-1.21)

Carozzi *et al*., Lancet Oncol, 2008


Biomarkers/Tests
HPV particle production
HPV oncogene expression
HPV Integration
HPV E6/E7 mRNA/protein
HPV integration
Chromosomal Abnormalities
3q, 5p gain
TERC
Proliferation & Replication
mcm2/Top2a
p16INK4a
P16
(w/ or w/o Ki-67)
Cytological abnormalitites
Pap Test
HPV DNA
HPV Genotyping
Normal
Infection
Clearance
HPV Infected
Progression
Regression
Precancer (e.g., CIN3)
Invasion
Cancer
Courtesy of Dr. Nicolas Wentzensen, NCI

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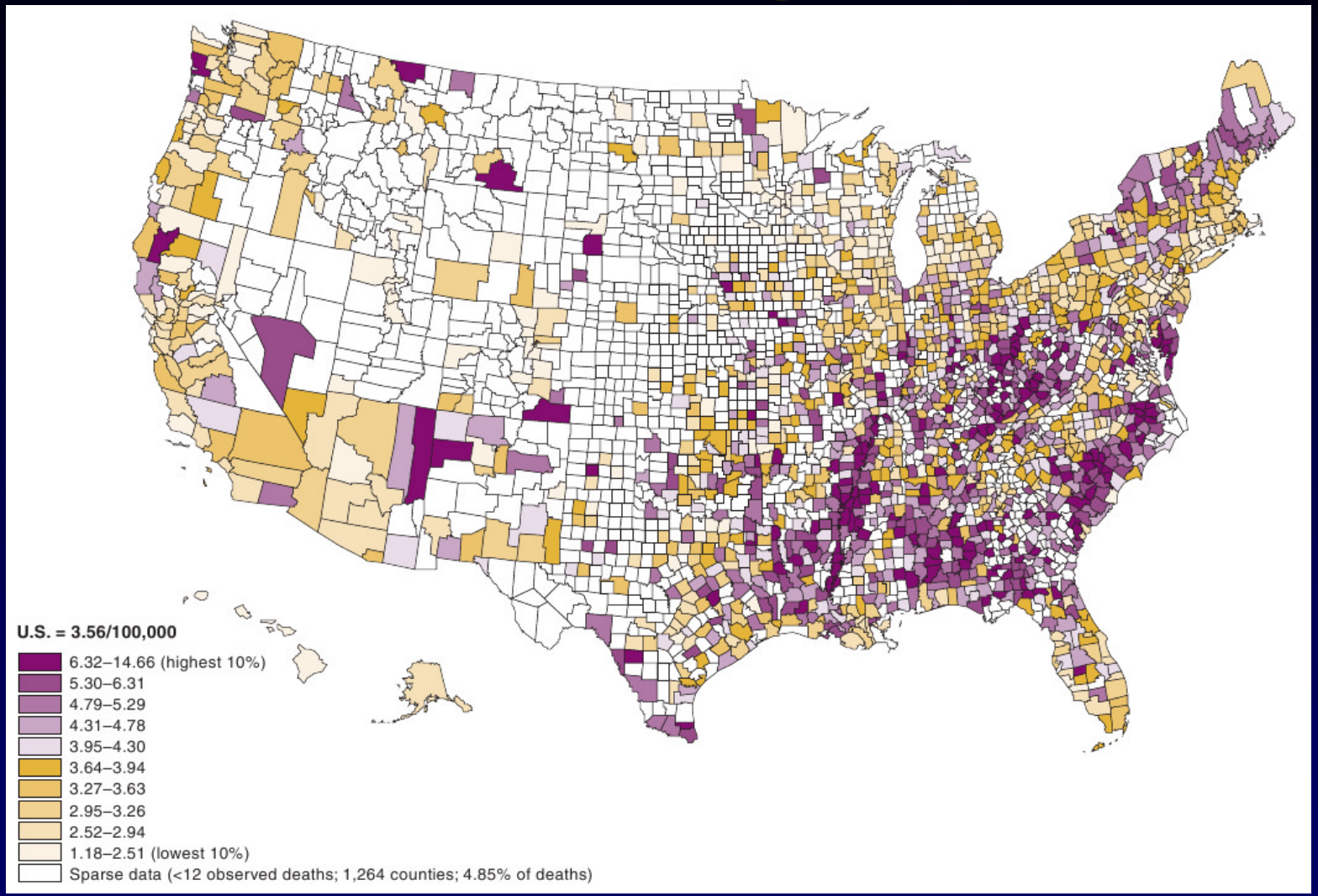
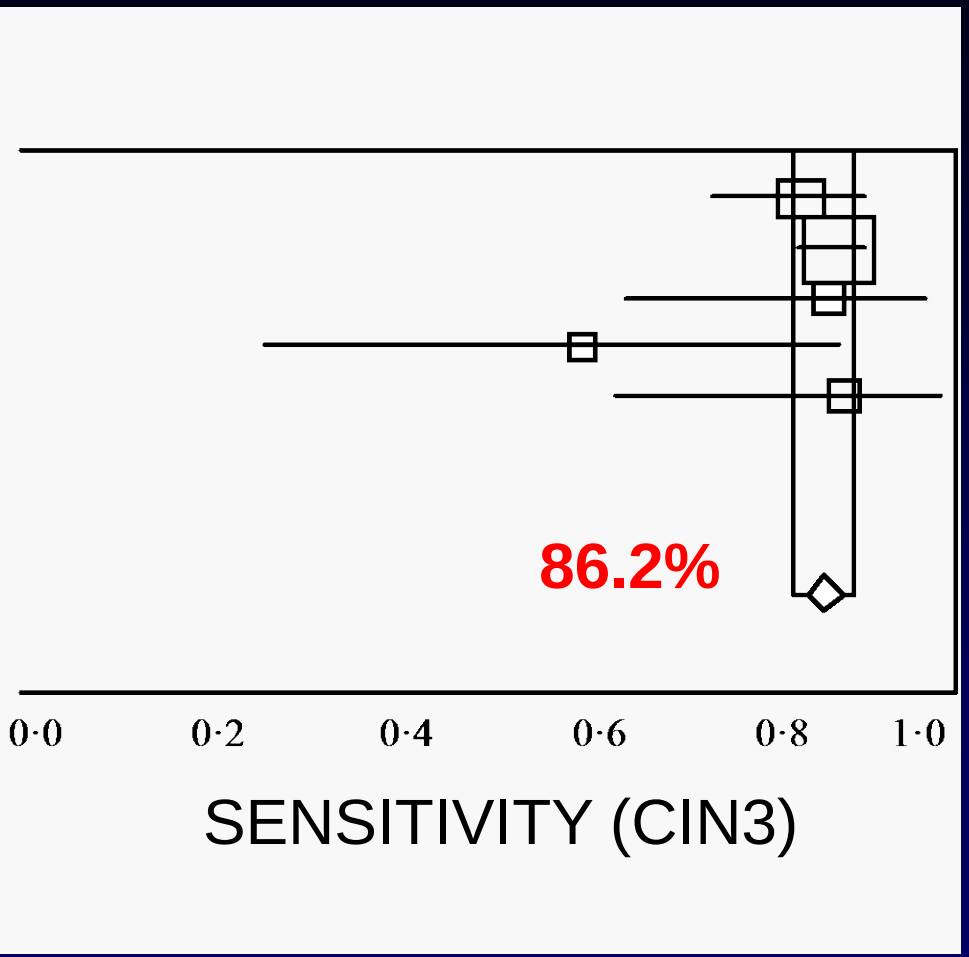
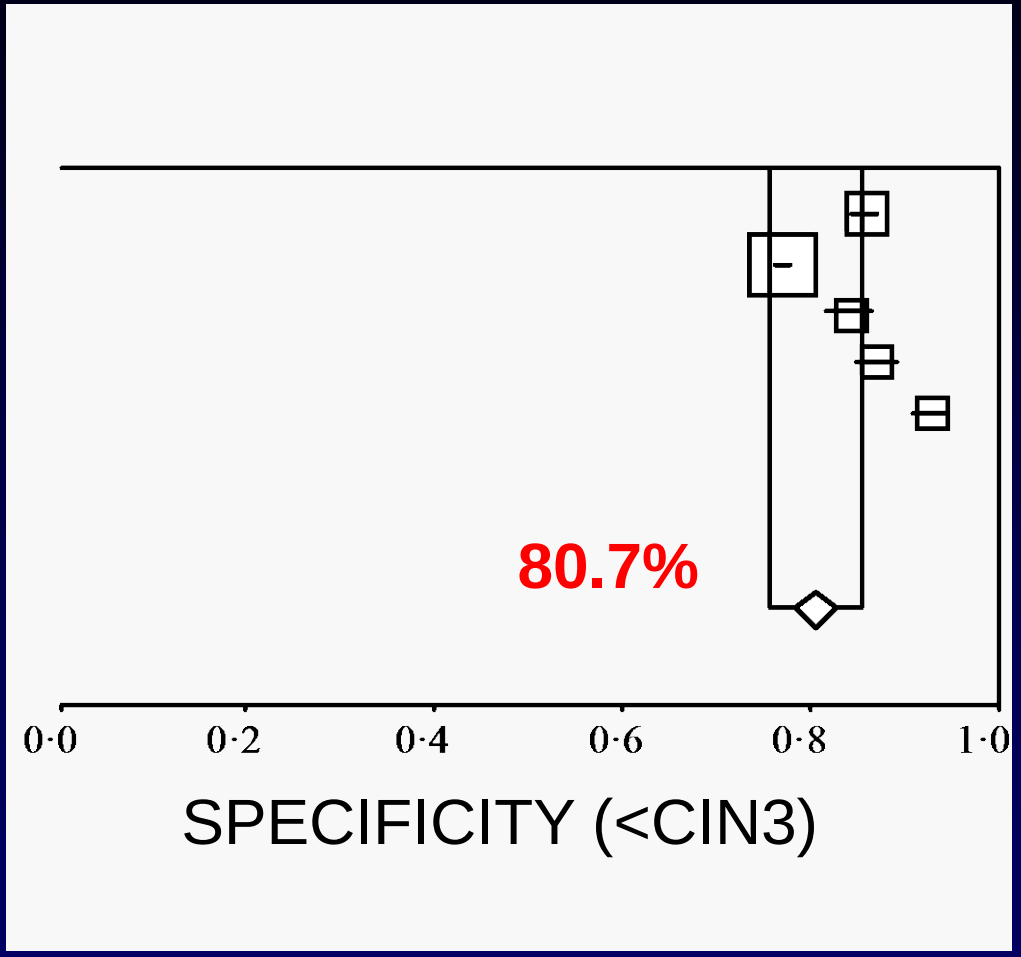
Cervical Cancer Mortality Map for The U.S.



Freeman HP, Wingrove BK. Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities. Rockville, MD: National Cancer Institute, Center to Reduce Cancer Health Disparities, May 2005. NIH Pub. No. 05–5282.

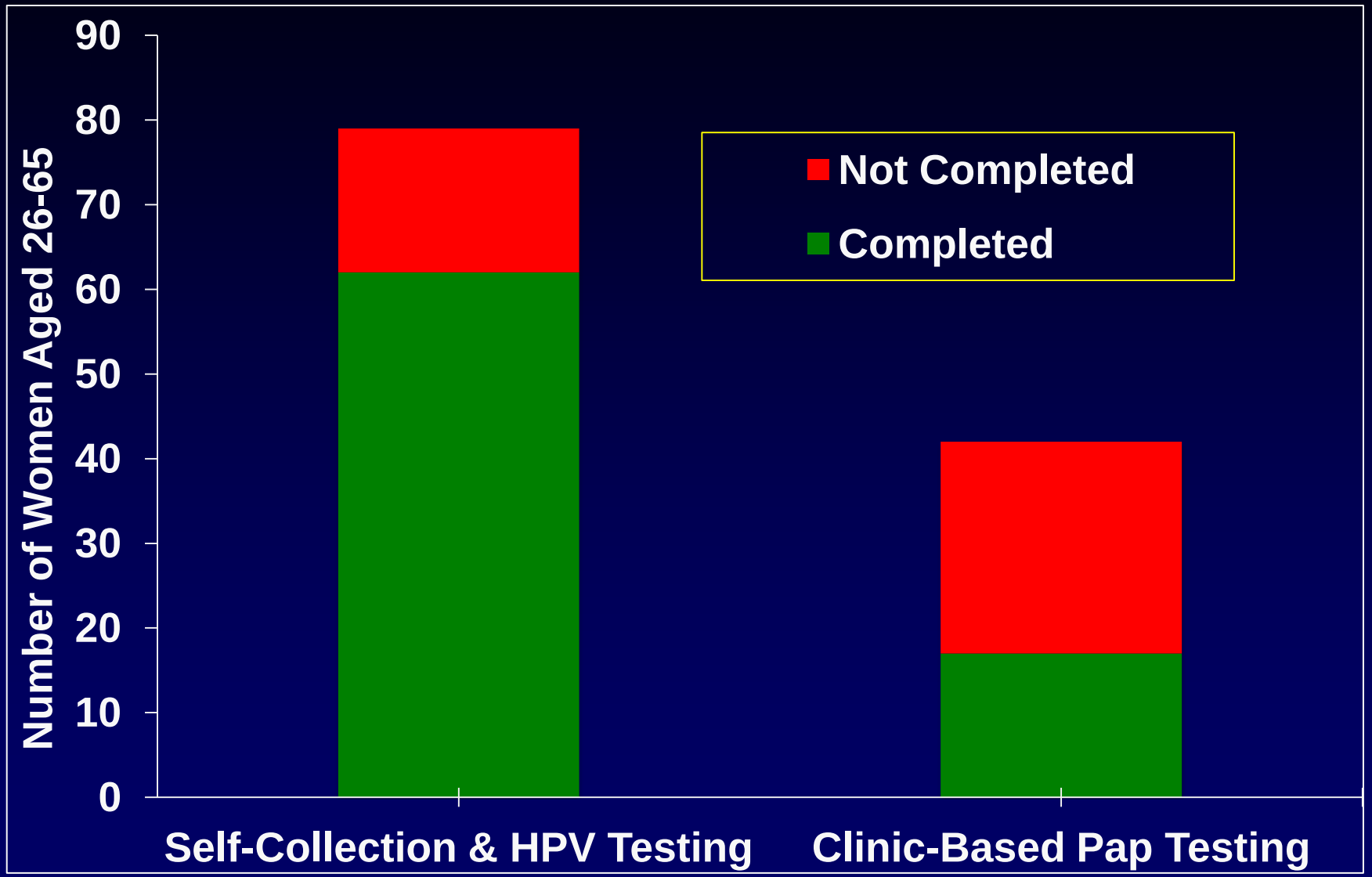
Self Collection and HPV Testing in China





Zhao *et al*., JNCI, 2012

Screening in the Mississippi Delta



Castle *et al.*, Prev Med, 2011

Final Comments

- Using HPV testing as the primary screen effective rules out disease in most women and shifts the use of Pap testing from the entire population to the 5-15% of women who have the necessary cause of cervical cancer, HPV.

- Pap testing can be used among HPV-positive women to decide which women are in immediate need of colposcopy. Other biomarkers such as HPV16/18 detection and in the future p16 immunocytochemistry can be used to complement Pap testing to increase the sensitivity of disease detection among HPV positives.

- There is no proven benefit of HPV and Pap cotesting versus HPV testing alone for screening.

- The biggest reductions in cervical cancer will be achieved by reaching underserved populations.