Scientific Background for

New Approaches in the Evaluation for High-Risk Human Papillomavirus Nucleic Acid Detection Devices

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NIH NATIONAL CANCER INSTITUTE

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Conflicts of Interest Statement

- As part of official duties at NCI, our group has received HPV testing and cytology results at reduced or no cost from companies including Qiagen, Roche, BD, and Arbor Vita.

- We conduct only etiologic research and strictly independent evaluations of test and screening strategy performance.

Purpose of This Presentation

- To give background for the scheduled discussions
  - Limited to natural history of **cervical** infections, and **screening** to prevent cervical cancer
  - Relying on well-established, referenced work (Additional references available upon request at schiffmm@mail.nih.gov)

Parts of Talk

I. Relevant aspects of HPV natural history and cervical carcinogenesis

II. Evolving principles of cervical screening

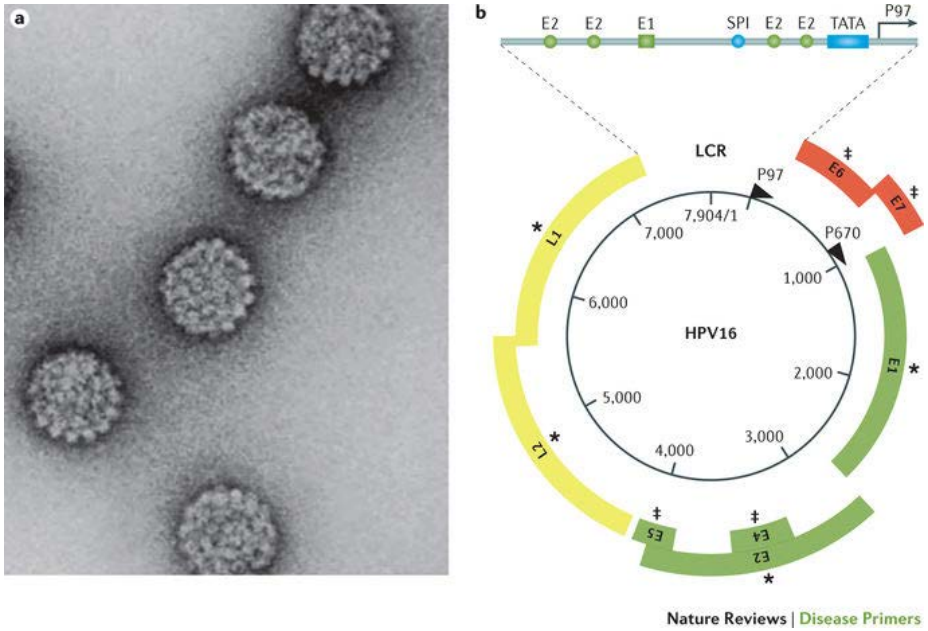
III. Background relevant to each of the Panel Questions

I. HPV Natural History and Cervical Carcinogenesis

*"**High-Risk Human Papillomavirus** Nucleic Acid Detection Devices"*

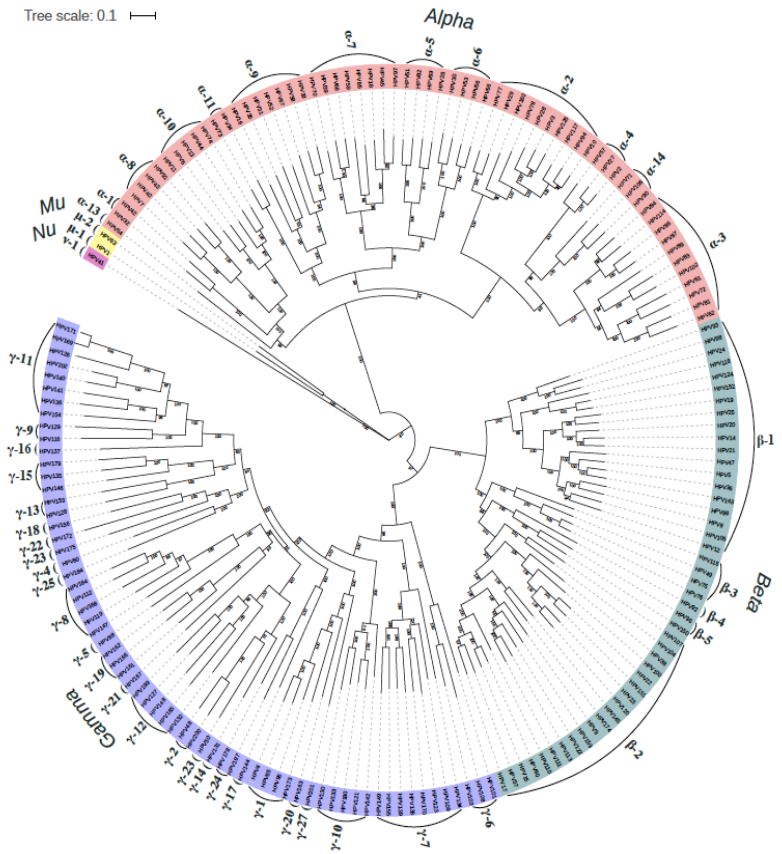
- What are high-risk human papillomaviruses?
- What is the difference between "carcinogenic" as defined by IARC and "high-risk" for inclusion in HPV tests?
- High-risk for what exactly (defining precancer, the target of screening)?

Human Papillomaviruses

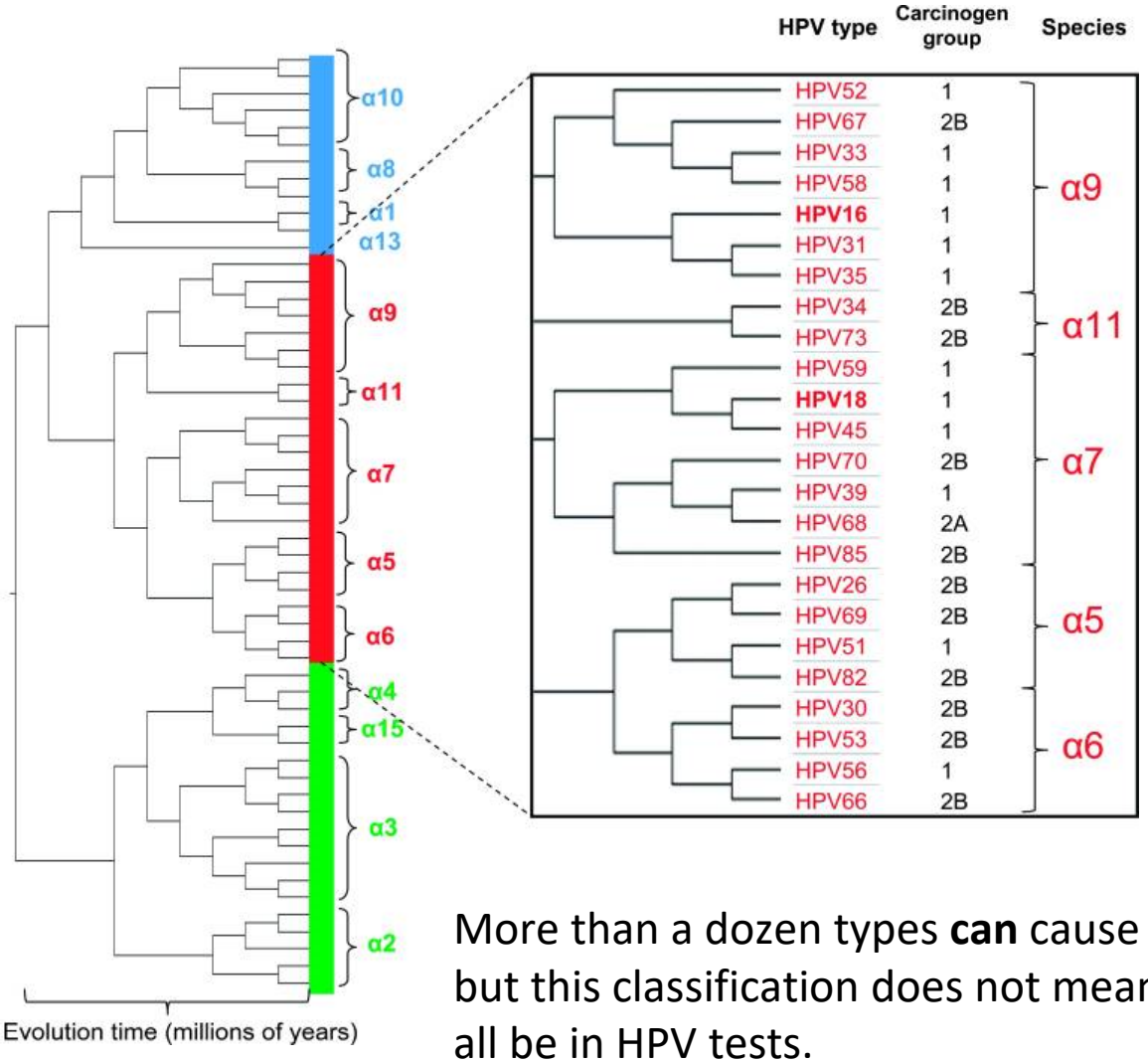


Doorbar in Schiffman et al., Nature Review Disease Primers 2016

What is HPV? Evolution and Carcinogenicity



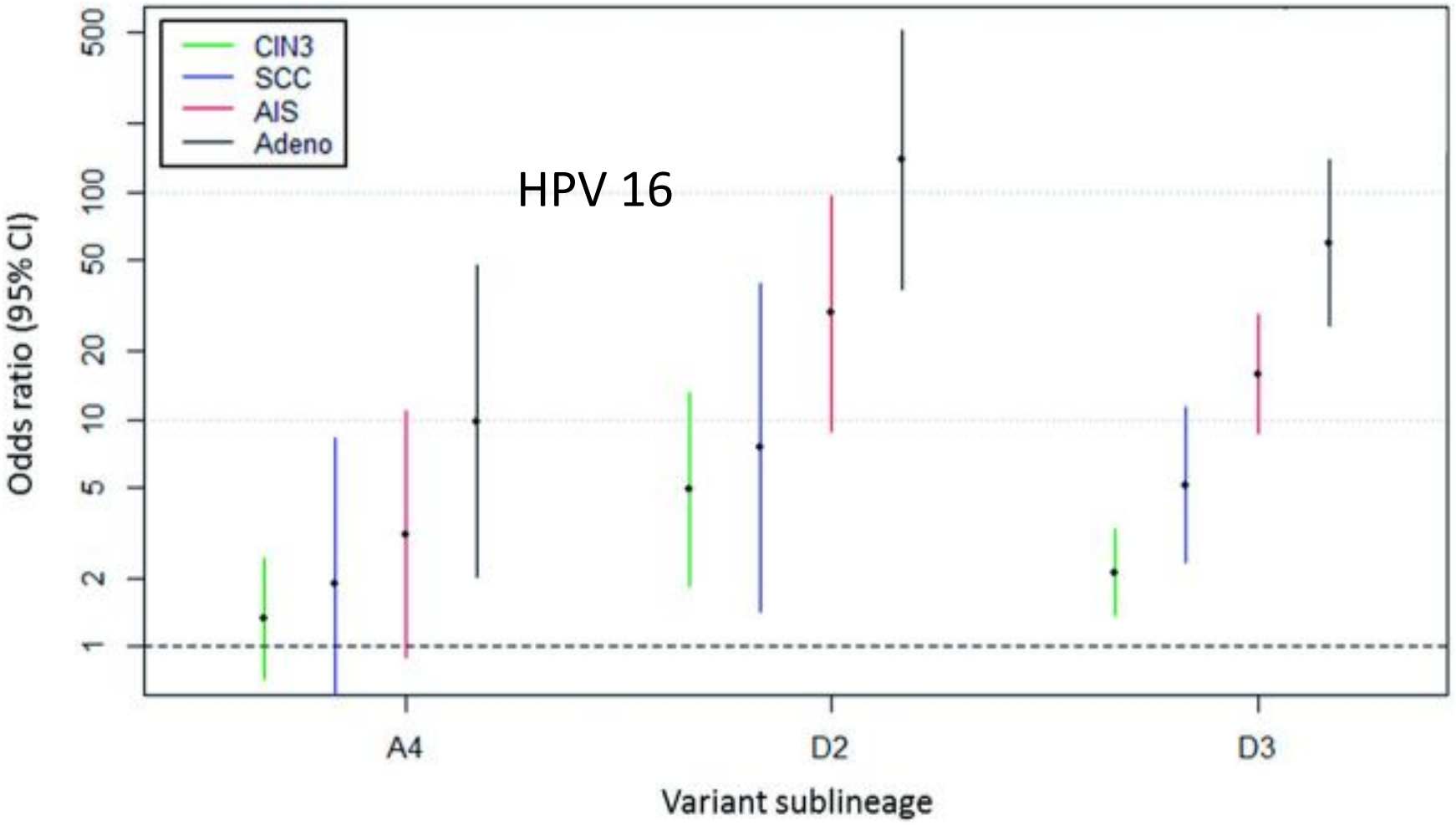
Burk in Schiffman et al., Nature Reviews Disease Primers 2016



More than a dozen types **can** cause cancer (IARC) but this classification does not mean they should all be in HPV tests.

Schiffman et al., Obstetrics & Gynecology 2010

Each HPV Type Includes Many Variants



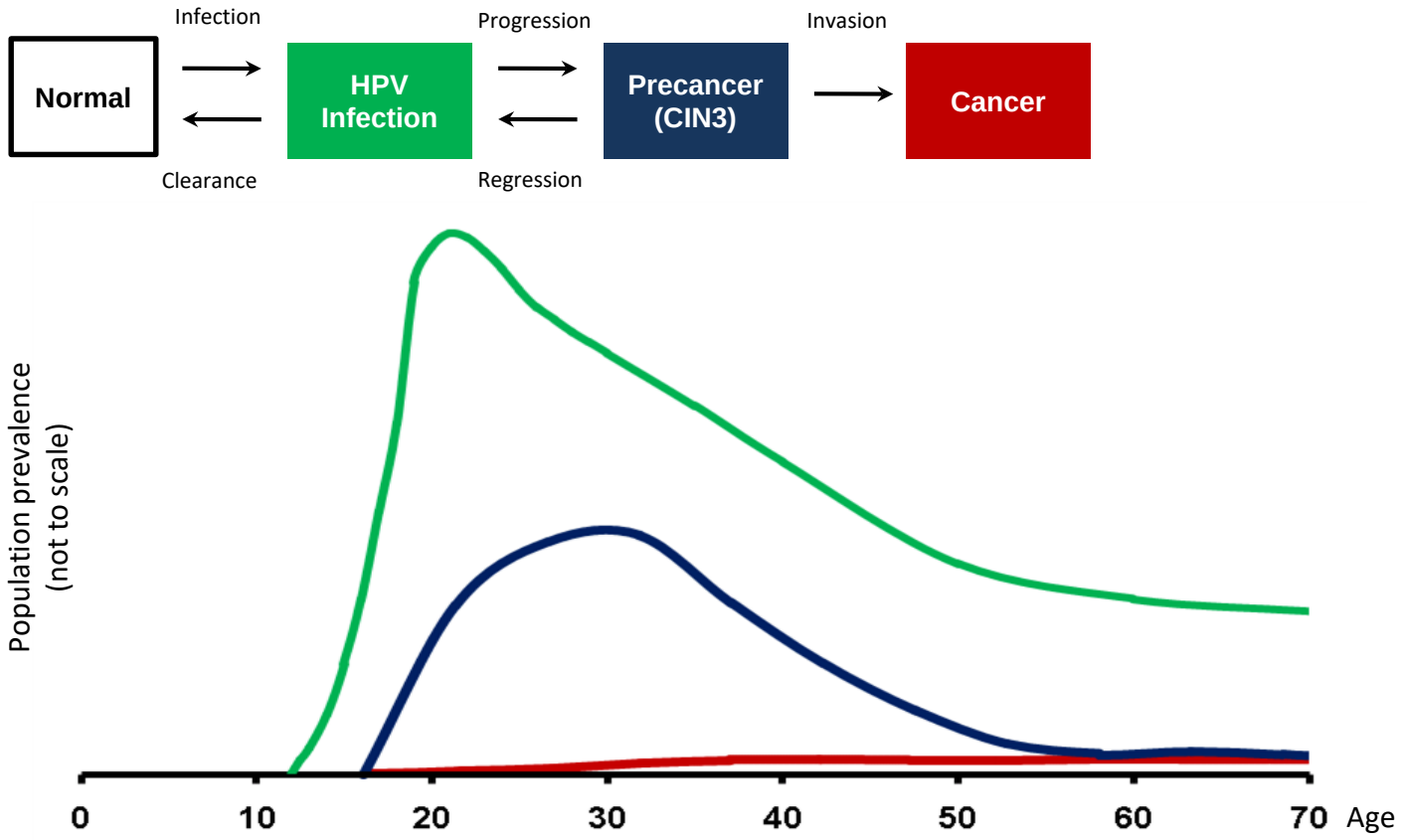
Currently, we do not make use of variant lineage associations in screening

Mirabello et al., JNCI 2016

Prevalence in cancers is best indicator of fraction caused by that type

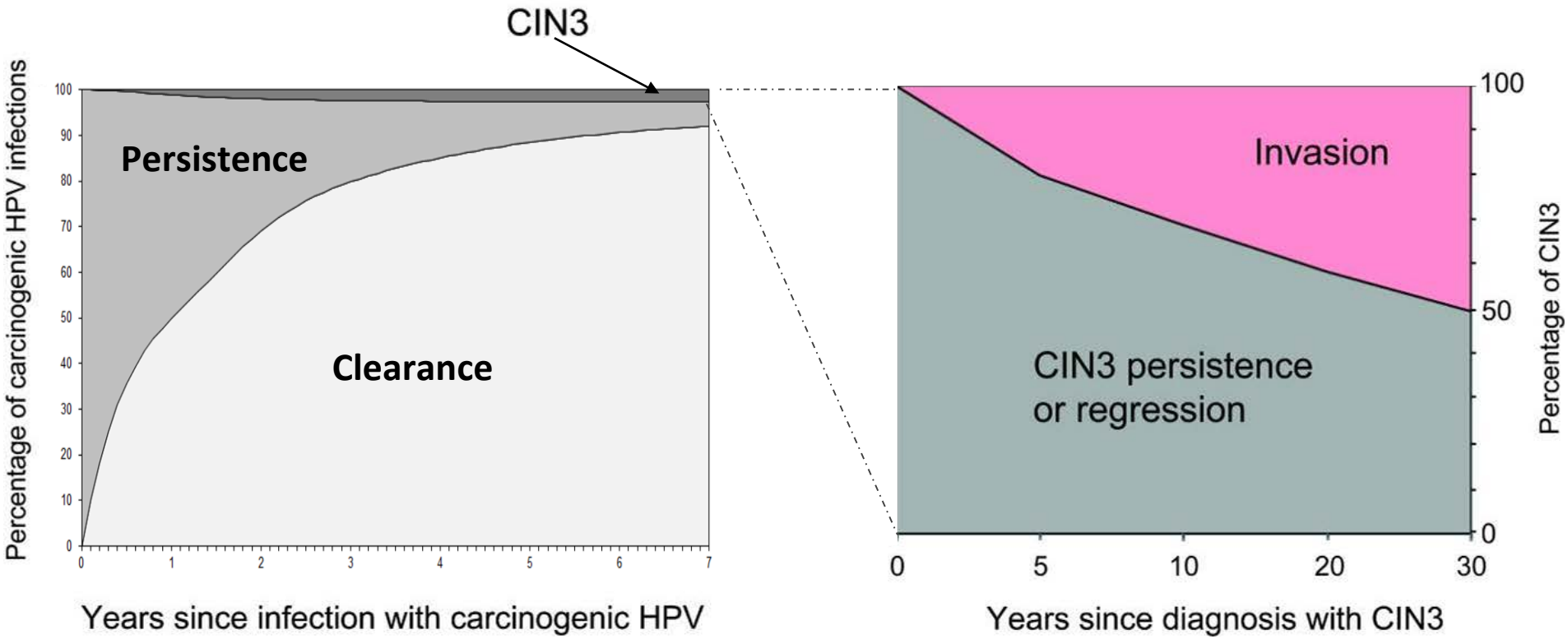
	Invasive cervical cancer			Normal		
	N tested	% pos	95% CI	N tested	% pos	95% CI
HPV16	14595	54.4	53.6–55.2	76385	2.6	2.5–2.8
HPV18	14387	15.9	15.3–16.5	76385	0.9	0.8–1.0
HPV33	13827	4.3	4.0–4.6	74141	0.5	0.4–0.5
HPV45	9843	3.7	3.3–4.1	65806	0.4	0.4–0.4
HPV31	11960	3.5	3.2–3.9	74076	0.6	0.6–0.7
HPV58	10157	3.3	2.9–3.6	72877	0.9	0.8–1.0
HPV52	9509	2.5	2.2–2.8	69030	0.9	0.8–1.0
HPV35	9507	1.7	1.5–2.0	74084	0.4	0.3–0.4
HPV59	6972	1.0	0.8–1.3	64901	0.3	0.2–0.3
HPV51	7339	0.7	0.5–0.9	67139	0.6	0.6–0.7
HPV56	7427	0.7	0.5–0.9	68121	0.5	0.5–0.6
HPV39	7078	0.6	0.5–0.9	64521	0.4	0.3–0.4
HPV68	6723	0.5	0.3–0.7	63210	0.3	0.2–0.3
HPV73	5837	0.5	0.3–0.7	44063	0.1	0.1–0.1
HPV66	6664	0.3	0.2–0.5	59774	0.4	0.3–0.4
HPV70	5159	0.2	0.1–0.4	35014	0.3	0.3–0.3
HPV82	5352	0.1	0.1–0.3	42536	0.1	0.0–0.1
HPV6	9911	0.5	0.4–0.7	58370	0.3	0.2–0.3

Schiffman, Clifford, Buonaguro
Infectious Agents and Cancer 2009



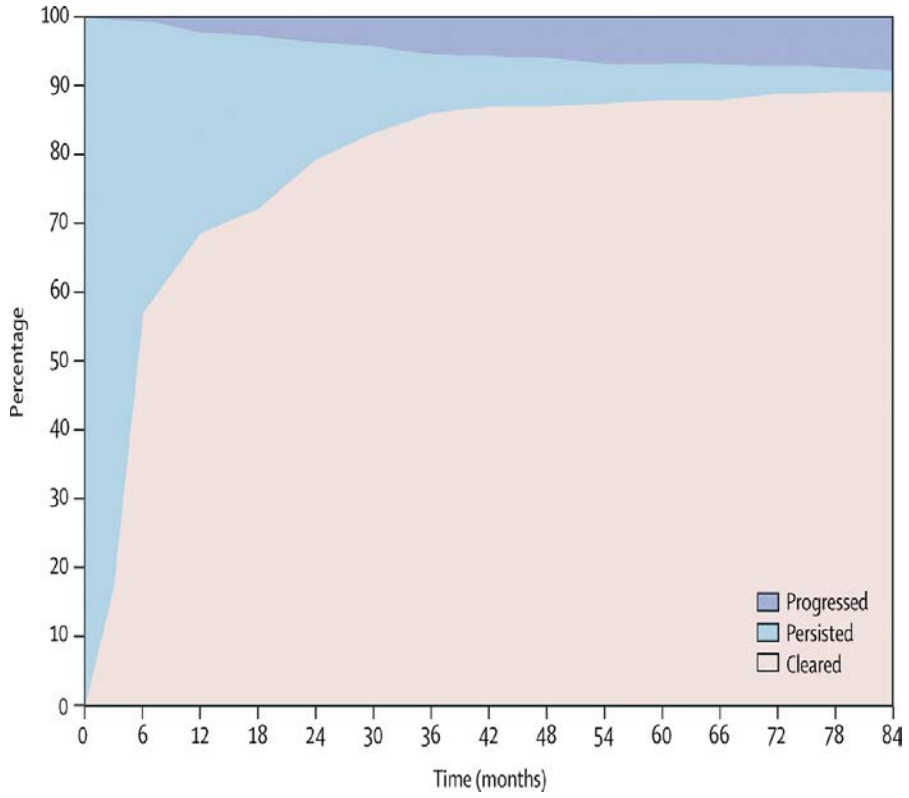
Schiffman et al., Cancer Epidemiology Biomarkers Prevention 2013

HPV and Cervical Carcinogenesis



Demarco et al. (in preparation) and McCredie et al., Lancet Oncology 2008

Most HPV infections “clear”…
those that persist cause CIN3+ over time
… HPV type and history predict current and future risks

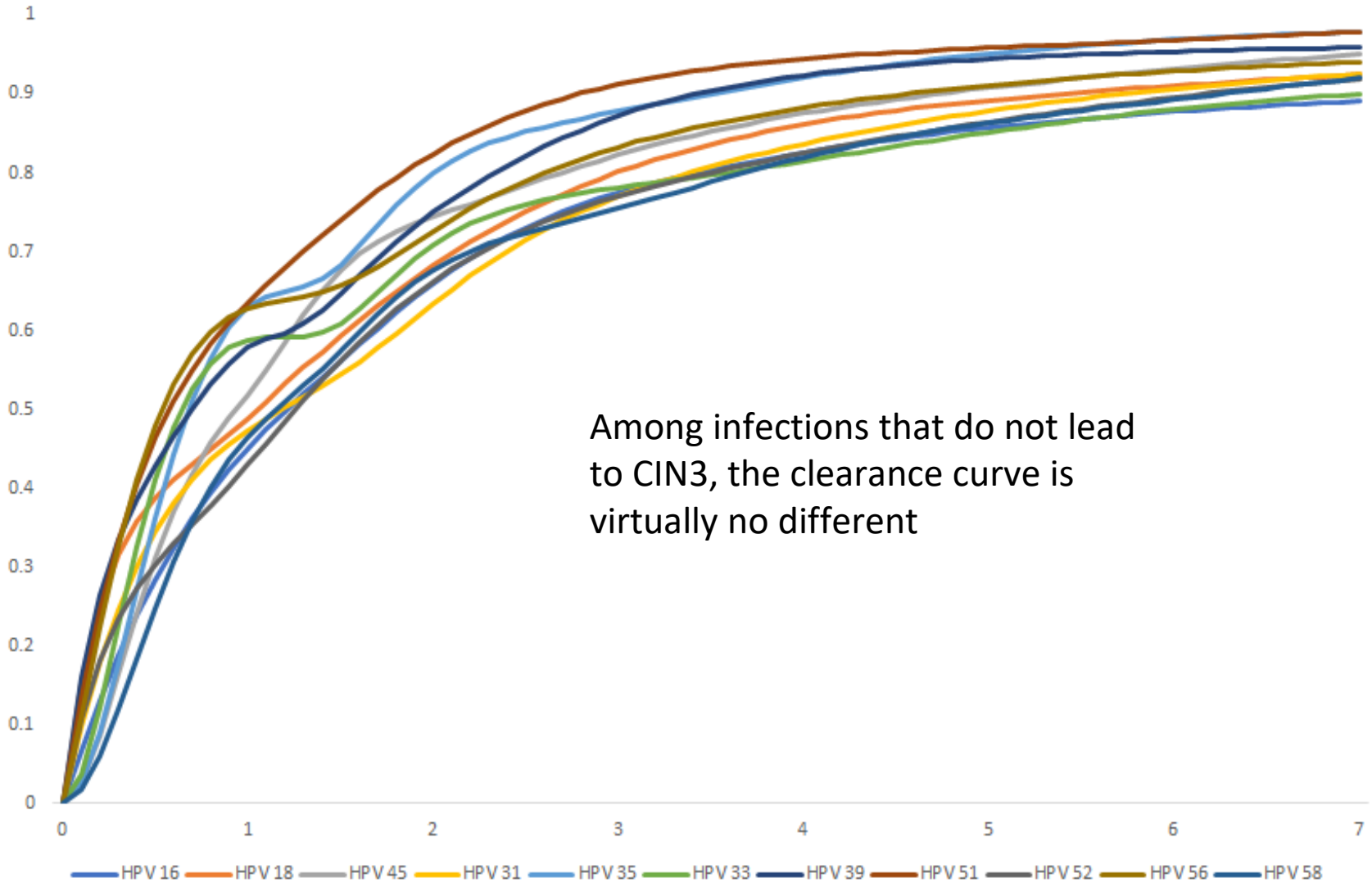


Schiffman et al., Lancet 2007

Natural history of HPV **differs by type**

- Risk of progression to CIN3 different by type
- Progression risk varies slightly by viral load, at least for HPV16 and (perhaps) related types
- Adenocarcinoma natural history (HPV18, HPV45 and subset of HPV16) is somewhat different than squamous

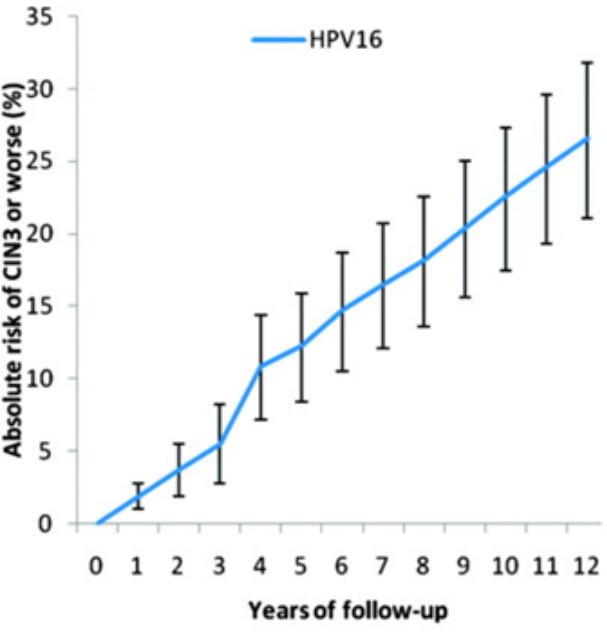
Type-specific risk of clearance

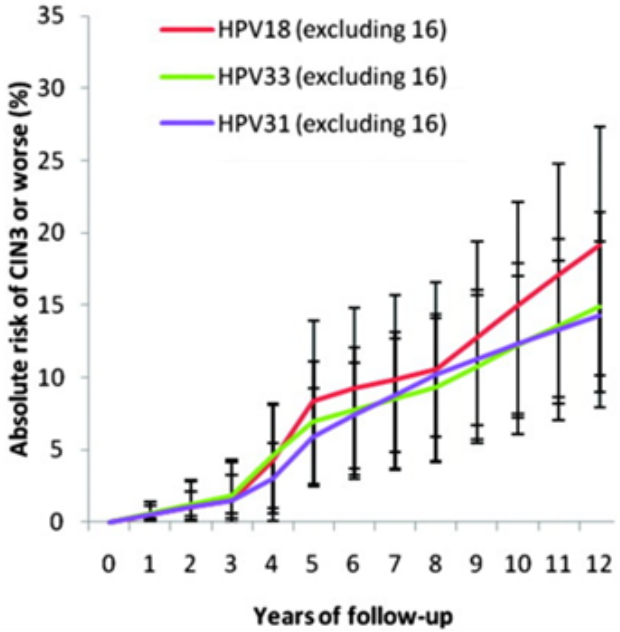


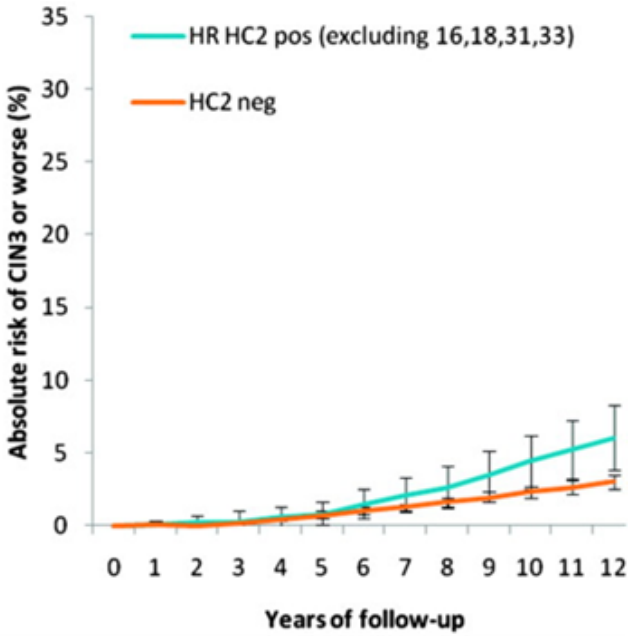
Among infections that do not lead to CIN3, the clearance curve is virtually no different

Demarco et al. (in preparation)

Type-specific absolute risk of CIN3+







Kjaer et al., Journal of the National Cancer Institute 2010

Risk of Progression to CIN3 Differs by Persistence of Infection

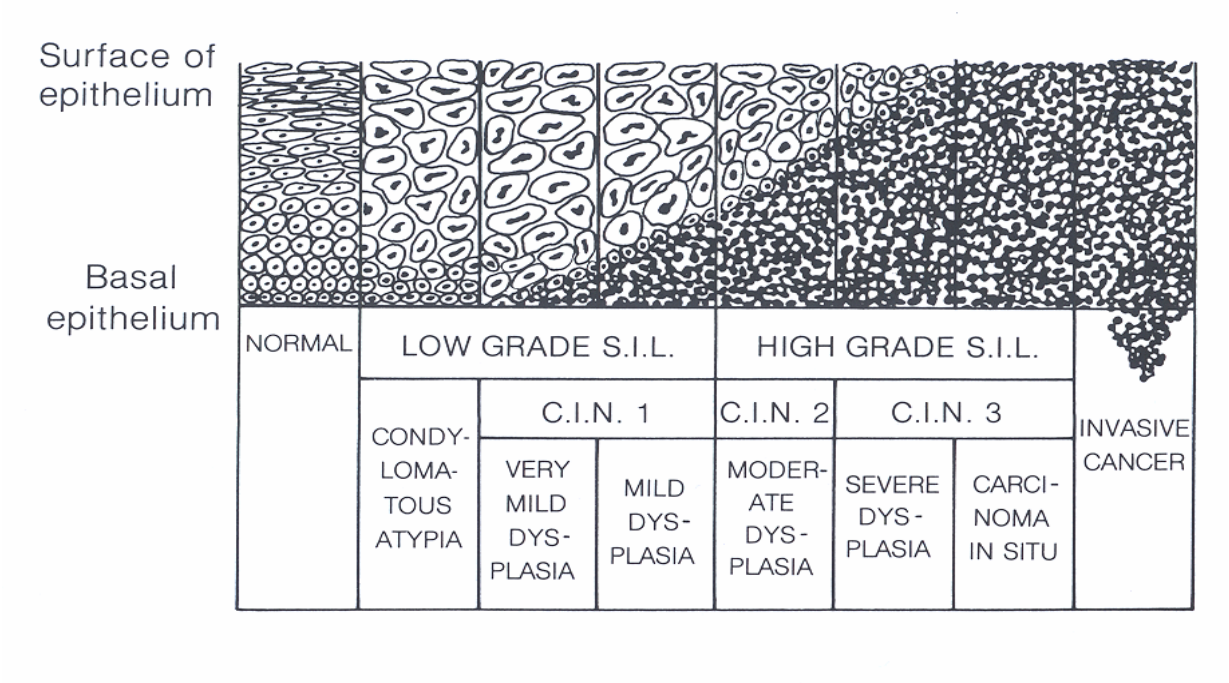
	Incident		Prevalent	
	Freq	Risk	Freq	Risk
HPV 16	668	9.3	605	25.9
HPV 18	259	6.4	188	14.6

Demarco et al. (in preparation)

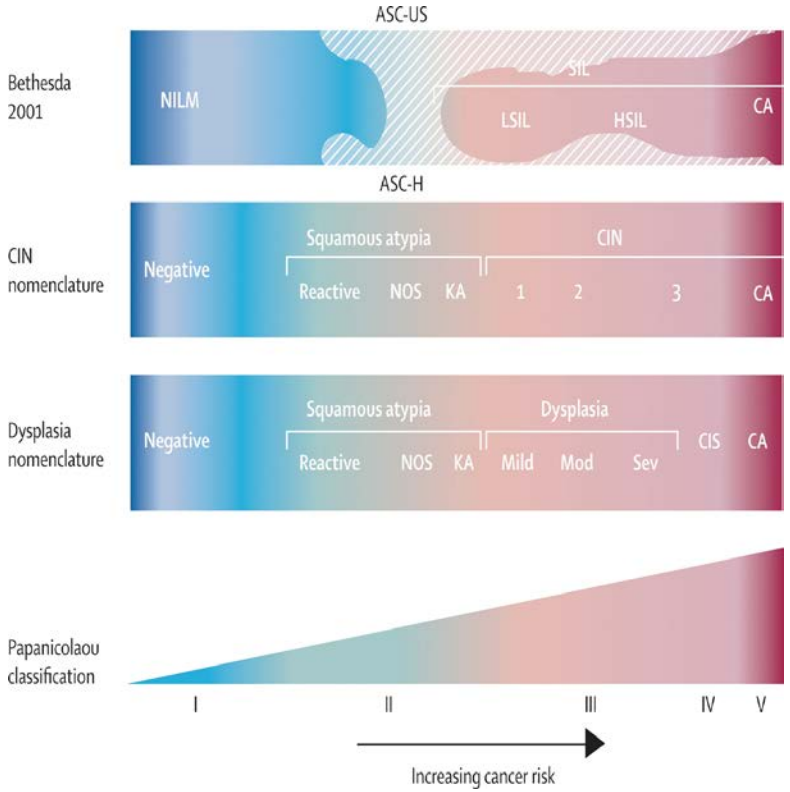
High-Risk HPV: High Risk for What?

Heterogeneity of “Precancer” as surrogate for cancer risk

The Apparent Continuum of Cervical Cancer Precursors



Many People Still Prefer Cytology/Histopathology Terms



Schiffman et al., Lancet 2007

The CIN Three-Part Scale is Obsolete

Obstet Gynecol. 1990 Jan;75(1):131-3.

A modified terminology for cervical intraepithelial neoplasia.

Richart RM.

Recent data are consistent with the concept that human papillomavirus (HPV) is etiologically important in the causation of cervical squamous cell cancer. There appear to be certain important events in the process of HPV infection and neoplasia. It is suggested that the terminology of the HPV-related precursor lesions be modified and that two terms, rather than three, would best satisfy the requirements of both science and clinical care. The "early" lesions should be referred to as "low-grade cervical intraepithelial neoplasia (CIN) with HPV-related changes" and the lesions that have the features of cancer precursors as "high-grade CIN."

CIN2 Is a Highly Unreliable Diagnosis, Signifying Uncertain Precancer

			Community Diagnosis					
			Neg	**CIN1**	**CIN2**	**CIN3/AIS**	**Cancer**	**Total**
Consensus Biopsy Diagnosis	**Neg**	**n**	**653**	88	6	1	0	748
		%row	**86.5%**	19.5%	4.1%	1.1%	0.0%	
	CIN1	**n**	90	**279**	23	2	0	394
		%row	11.9%	**61.9%**	15.6%	2.2%	0.0%	
	CIN2	**n**	10	77	**70**	20	0	177
		%row	1.3%	17.1%	**47.6%**	21.7%	0.0%	
	CIN3/AIS	**n**	2	7	48	**69**	1	127
		%row	0.3%	1.6%	32.7%	**75.0%**	16.7%	
	Cancer	**n**	0	0	0	0	**5**	5
		%row	0.0%	0.0%	0.0%	0.0%	**83.3%**	1,451
	Total		755	451	147	92	6	

Stoler et al., JAMA 2001

HPV Types Differ Between CIN2 and CIN3

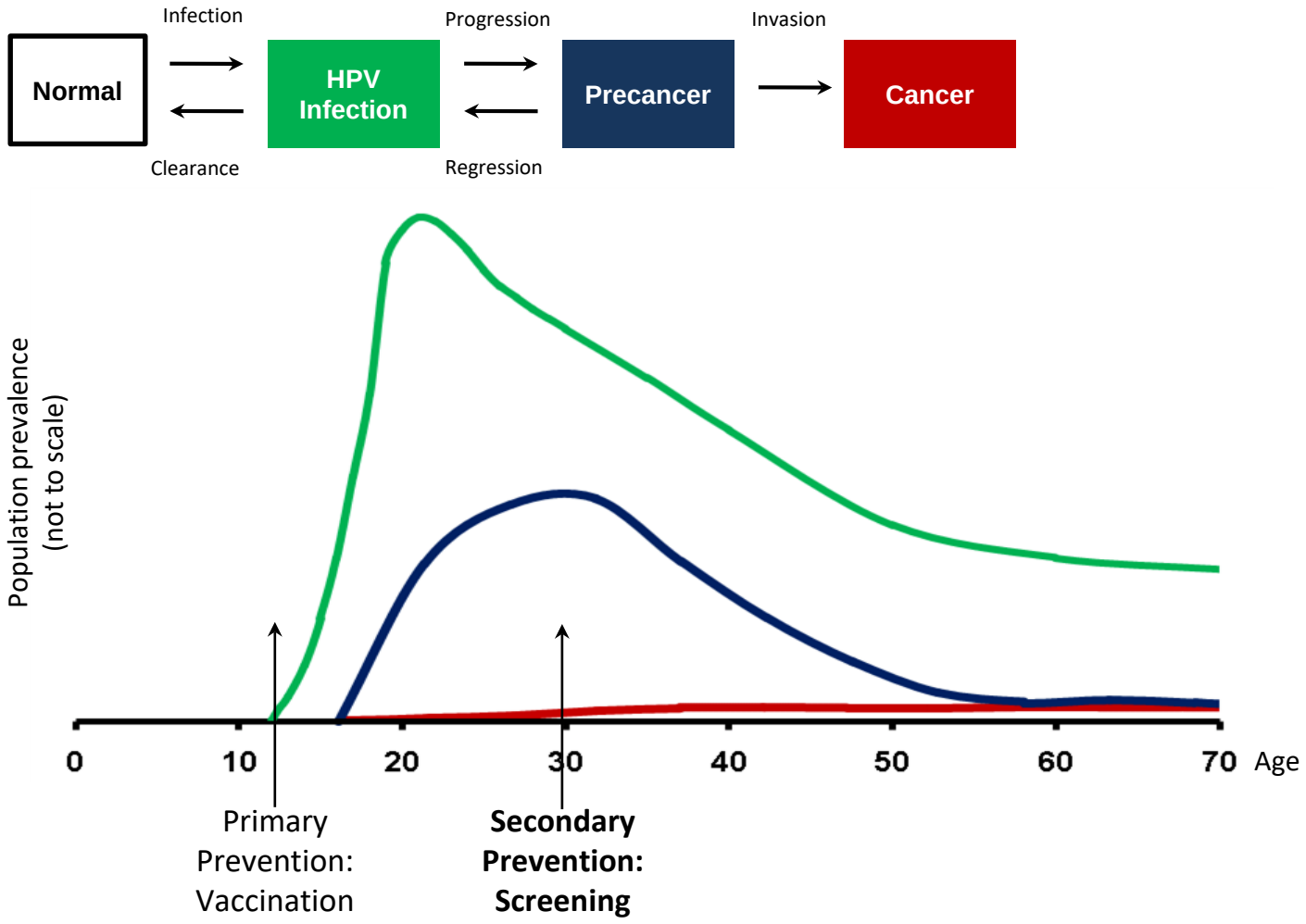
CIN2			CIN3			Cancer		
HPV type	N	%	HPV type	N	%	HPV type	N	%
16	905	36.3%	16	1038	52.9%	16	37	61.7%
52	345	13.9%	31	237	9.5%	18	10	16.7%
31	324	13.0%	52	183	7.3%	31	4	6.7%
58	176	7.1%	58	118	4.7%	45	3	5.0%
35	143	5.7%	18	93	3.7%	52	2	3.3%
51	136	5.5%	33	70	2.8%	33	1	1.7%
39	111	4.5%	35	59	2.4%	39	1	1.7%
18	97	3.9%	51	52	2.1%	51	1	1.7%
56	62	2.5%	45	37	1.5%	68	1	1.7%
45	57	2.3%	39	36	1.4%		0	0.0%
33	53	2.1%	56	19	0.8%		0	0.0%
59	44	1.8%	68	15	0.6%		0	0.0%
68	37	1.5%	59	7	0.3%		0	0.0%
Total	2490			1964		total	60	

Demarco et al. (in preparation)

CIN3/AIS Histopathology Currently Strongest Surrogate of Cervical Cancer Risk

- True precancer (a lesion that would likely invade if untreated) is an unknown subset of CIN2/CIN3/AIS
- Biomarkers of cancer risk exist; none ideal
  - p16 is most used (LAST)
  - Restriction to carcinogenic types is useful
  - HPV and host methylation are promising
  - E6/E7 overexpression has high PPV
  - Integration is especially important for HPV18/45

II. Cervical Screening



Schiffman et al., Cancer Epidemiology Biomarkers Prevention 2013

Important historical precedents and newest developments in guidelines and evidence

- Risk-based guidelines now emphasize PPV, NPV, risk stratification
- Less emphasis on sensitivity, specificity for "disease"
- Replacement of morphologic subjective terms (cytology, colposcopic impression, even histopathology like CIN2) with HPV status

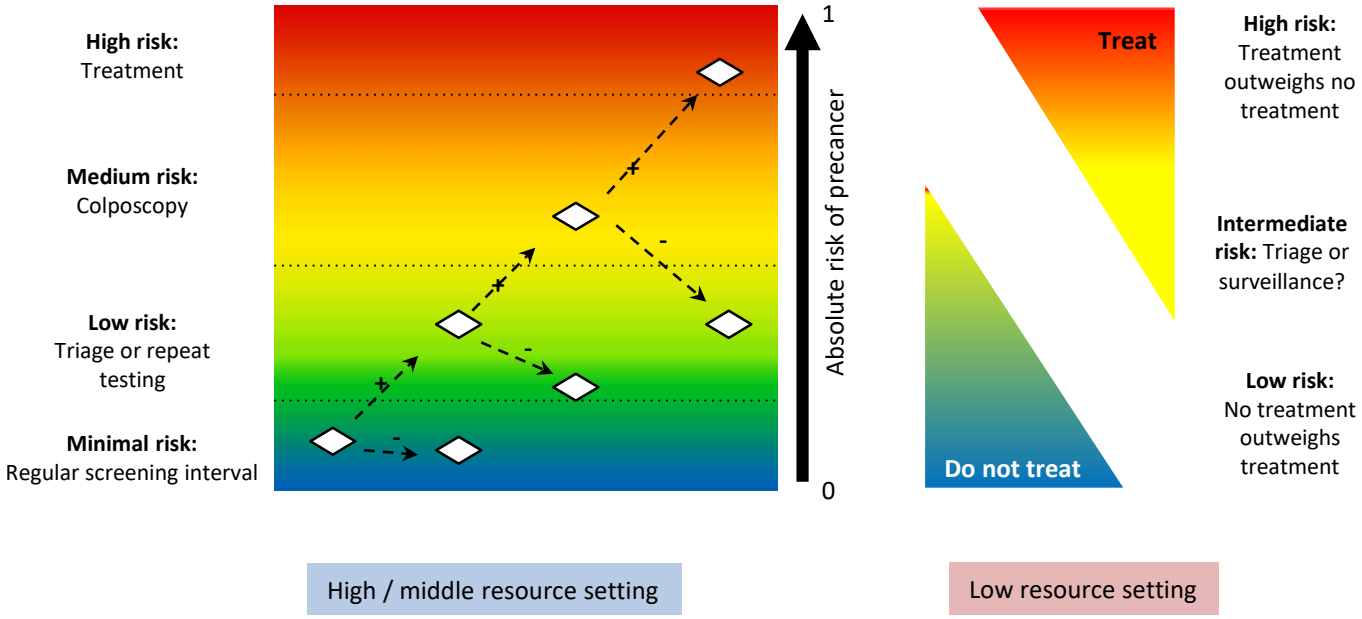
Critical 2 by 2 Table and Its Extensions

HPV Test Result	Precancer	Controls	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b + c + d = N

HPV superseding cytology

- Evidence of increased sensitivity and NPV
- If triaged, stronger risk stratification, cytology alone cannot achieve it, most of cytologic abnormals are uncertain
- With passing of cytology alone, ASC-US triage becoming obsolete as indication
- Unclear whether cotesting is cost-effective
- Many pending developments in triage tests, continued risk-based revisions to guidelines
- Important to consider triage of any HPV testing but difficult to anticipate all the options

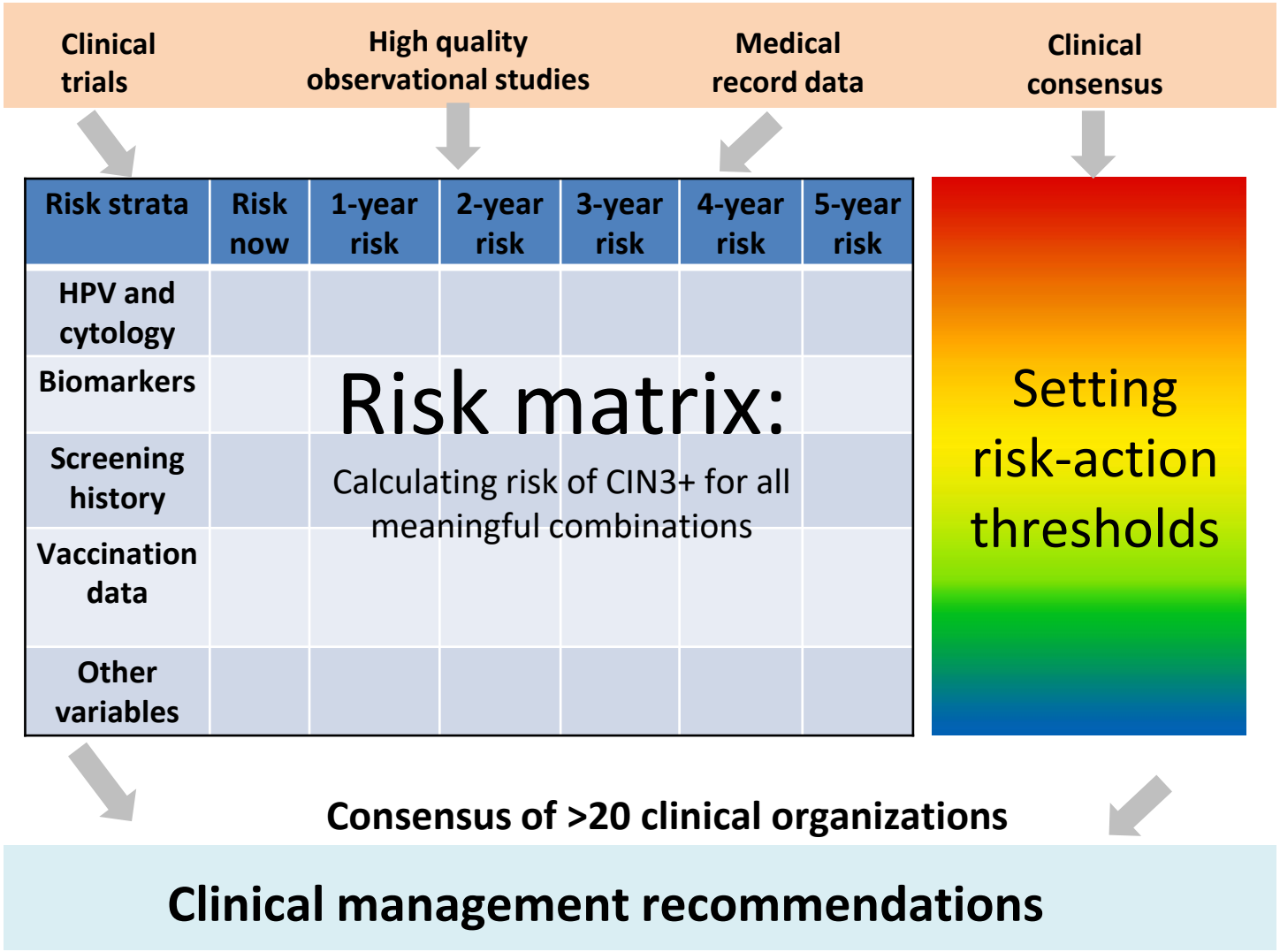
Risk-based approach to screening and management



High / middle resource setting

Low resource setting

Wentzensen et al., Journal of Clinical Virology 2016



Schiffman et al., Journal of Lower Genital Tract Disease 2017

III. Details Specific to Discussion Questions

Topics for Panel Discussion

1. **Clinical Study Design: Benefits and Risks**
    a. Supplementing from referral populations
    b. Using archived specimens
    c. Capping the vaccinated population

2. **Colposcopy Referral Protocol in Clinical Studies**

3. **Indications for use**
    a. Consolidating the indications for use to encompass one general screening population
    b. Removing reference to specific triage tests and clinical actions

4. **Data Analyses to Support Indications for Use**
    a. Composite molecular comparator
    b. Relative device performance

5. **Clinical Endpoint Comparator**
    a. Mixed histological/molecular comparator

Critical 2 by 2 Table and Its Extensions

HPV Test Result	Precancer	Controls	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b + c + d = N

Panel Questions

Panel Question 1

Would the panel recommend one or a combination of the following three proposals to increase the number of women positive for CIN3+ and/or HR HPV in clinical studies:

1. **Supplementing from referral clinics**

1. **Utilizing archived specimens**

1. **Capping the vaccinated population**

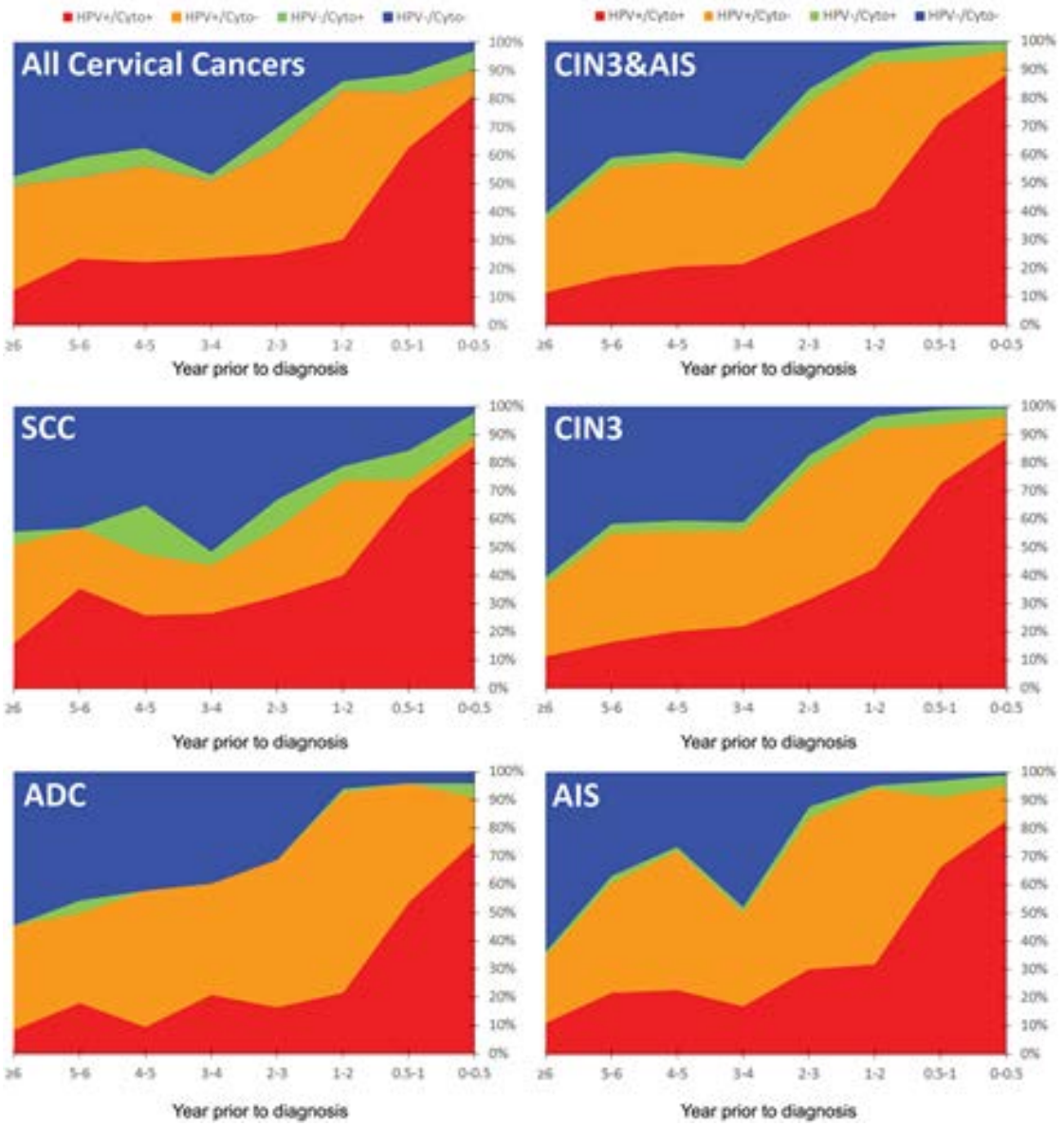
Critical 2 by 2 Table and Its Extensions

HPV Test Result	Precancer	Controls	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b + c + d = N

Obtaining sufficient cases

- 0.5% precancer in screening population
- If only prevalent risk is important, could use case-control or case-cohort
- Length of NPV (reassurance) limits use of case-cohort approach (HPV positivity of cases)
- Archived specimens (proof of comparability?)
- Vaccination population capping (feasible, herd protection)

HPV positivity by time before diagnosis



Schiffman et al., Journal of the National Cancer Institute 2017

Panel Questions

Panel Question 2

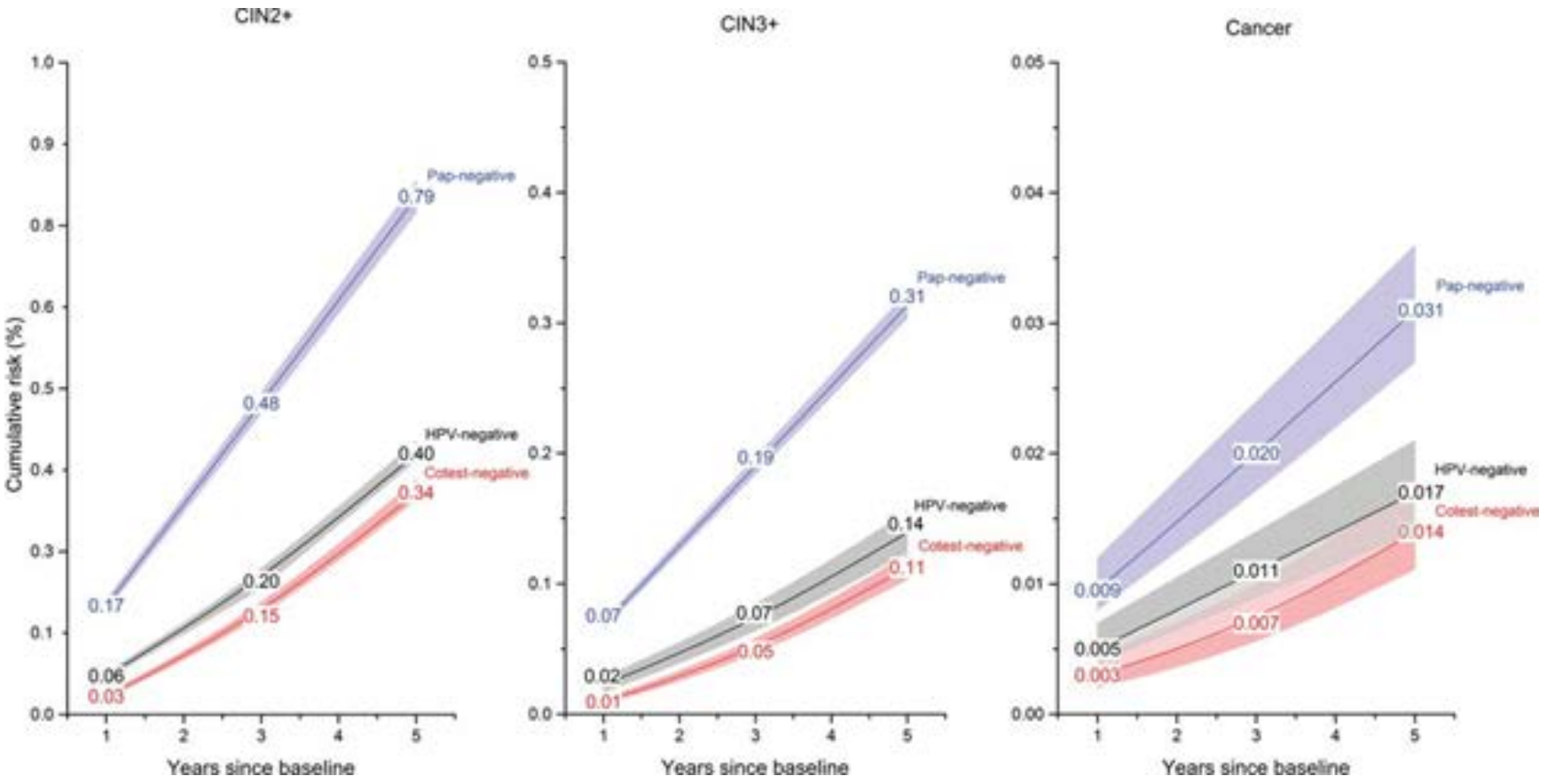
Regarding the NILM/HR HPV double negative and ASC-US/HR HPV double negative populations in clinical studies supporting HPV device approval:

Do the benefits of colposcopy referral for the assessment of verification bias outweigh the risks associated with the procedure and potential overtreatment?

Please discuss for each of the two populations separately.

Critical 2 by 2 Table and Its Extensions

HPV Test Result	Precancer	Controls	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b + c + d = N



Gage et al., Journal of the National Cancer Institute 2014

Colposcopic Biopsy and Verification Bias

- Attempt to correct very slight verification bias can result in amplified misclassification bias
  - Example of possibly flawed labeling
- HPV negative ASC-US has low risk (0.24% 3-year risk of CIN3+)
- HPV negative NILM has extremely low risk (0.07% 3-year risk of CIN3+)

Panel Questions

Panel Question 3

Regarding the indications for use (IFU), do the benefits outweigh the risks for:

A. **Consolidating the indications to encompass one general screening population**

B. **Removing references to specific triage tests and clinical actions?**

Please discuss any potential risk mitigation measures if a new IFU statement is adopted.

Critical 2 by 2 Table and Its Extensions

HPV Test Result	Precancer	Controls	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b + c + d = N

Impact of Preceding Negative HPV test

HPV result	Cyto result	3-year risk of CIN3+	
		Enrollment	After HPV-negative
Positive	HSIL+	52.06	33.35
Positive	LSIL	6.25	3.40
Positive	ASC-US	6.53	3.39
Negative	ASC-US	0.24	0.20
Negative	NILM	0.07	0.05

Panel Questions

Panel Question 4

Please discuss whether the following types of data evaluations are acceptable for the assessment of safety and effectiveness for new HR HPV devices:

A. **Adoption of a molecular composite comparator method**
B. **Evaluation of relative performance against a clinical endpoint comparator**

Please discuss the benefits and risks to these approaches, as well as minimum acceptable performance criteria.

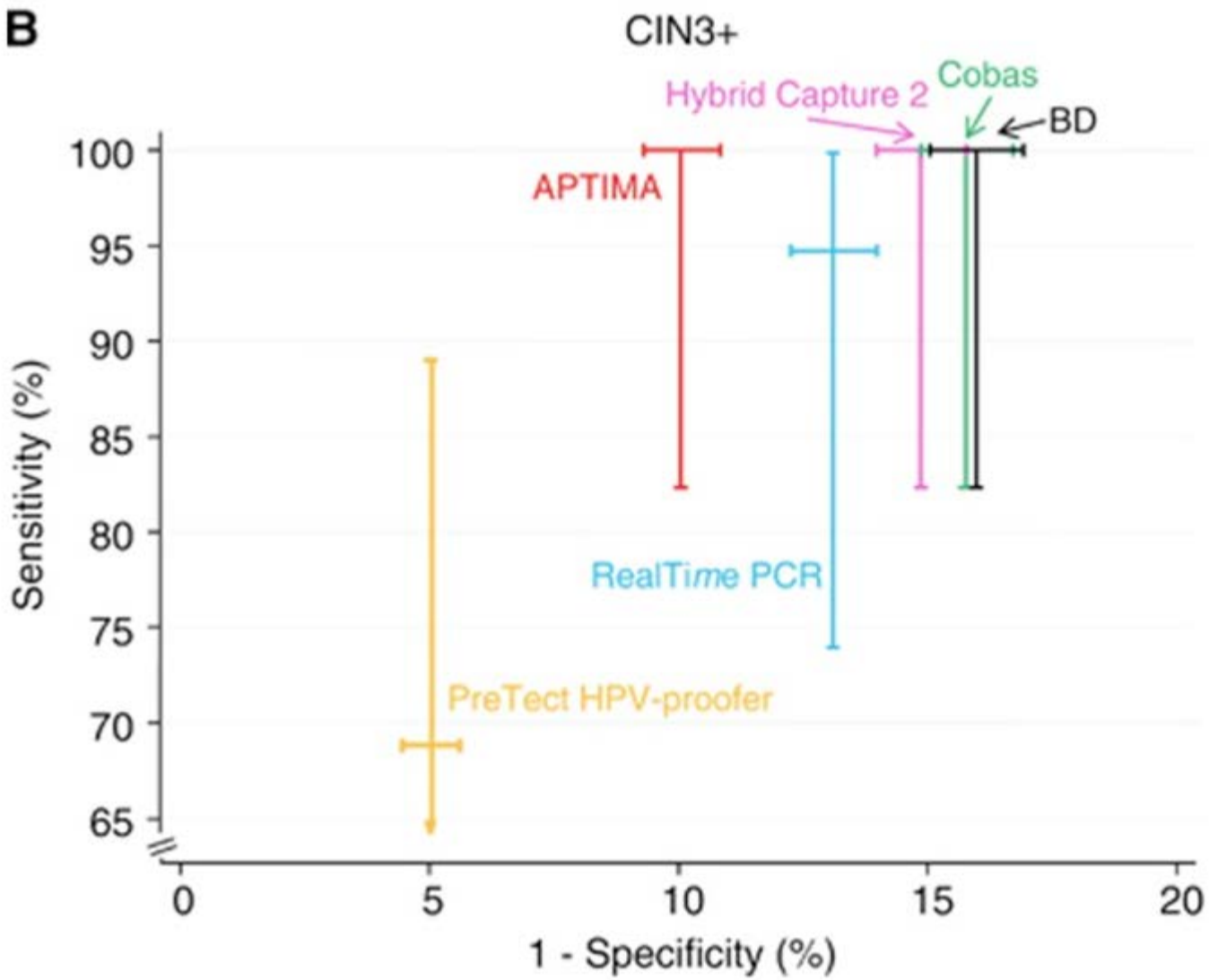
Panel Questions

Panel Question 5

If the panel recommends assessing HR HPV device performance against a clinical endpoint comparator:

A. **Is utilizing a mixed histological/molecular comparator acceptable?**

B. **If so, how should the combination of HPV result and histological diagnosis factor in when assigning "comparator positive" and "comparator negative" results?**



HPV tests are not all the same

Cuzick et al., British Journal of Cancer 2013

Critical 2 by 2 Table and Its Extensions

HPV Test Result	Precancer	Controls	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b + c + d = N

Need prospective data to judge intermediate-term predictive values

Data suggest

- Consider CIN3 that has HPV types that are proven carcinogenic (n=13) as current optimal screening “target”
- Supplement cases using carefully selected referral clinics in same catchment area as screening clinics?
  - Attention to sensitivity and NPV time course

Thank you for the opportunity to assist in this important update

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