Epidemiologic evidence of HPV latency

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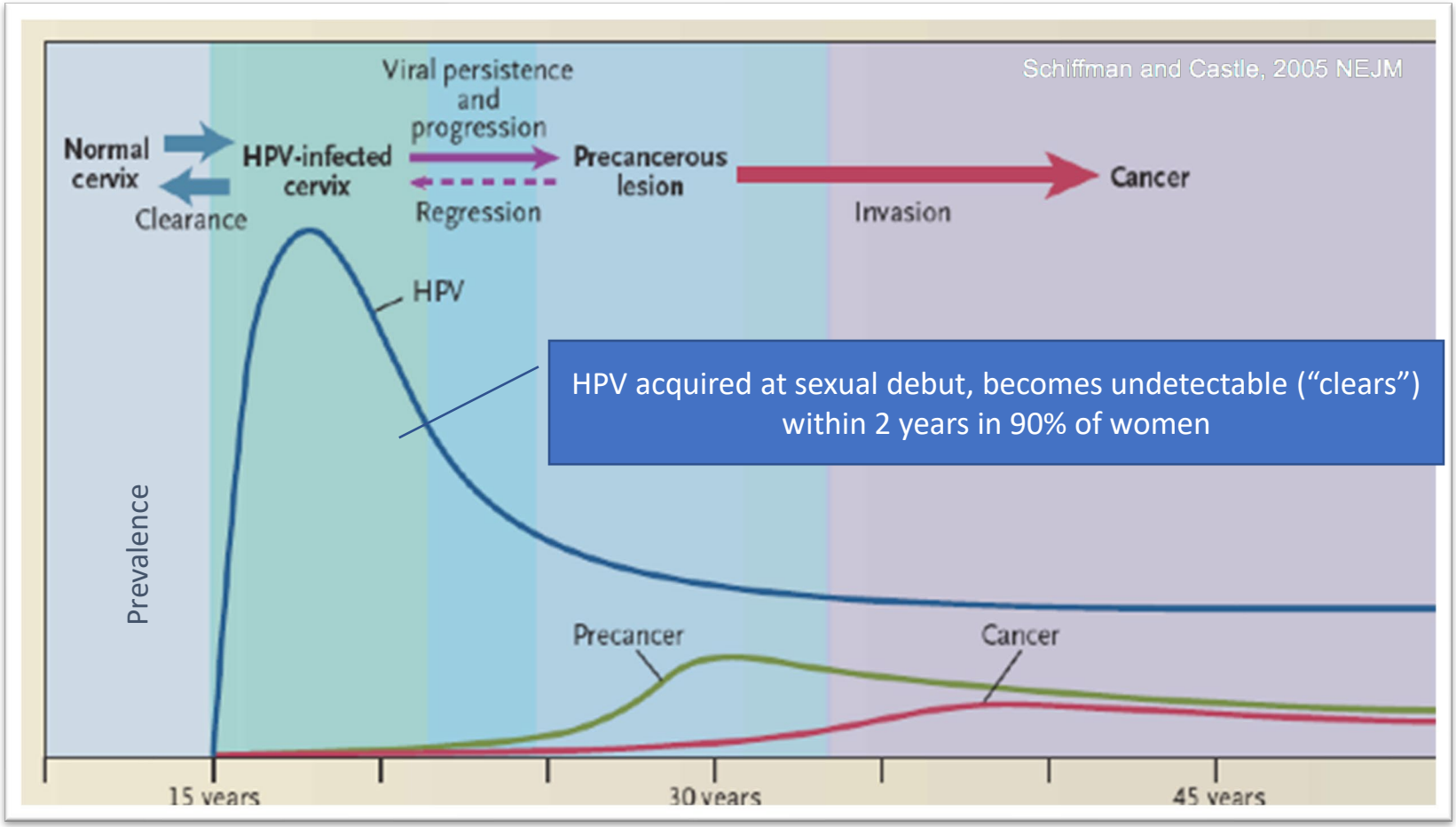
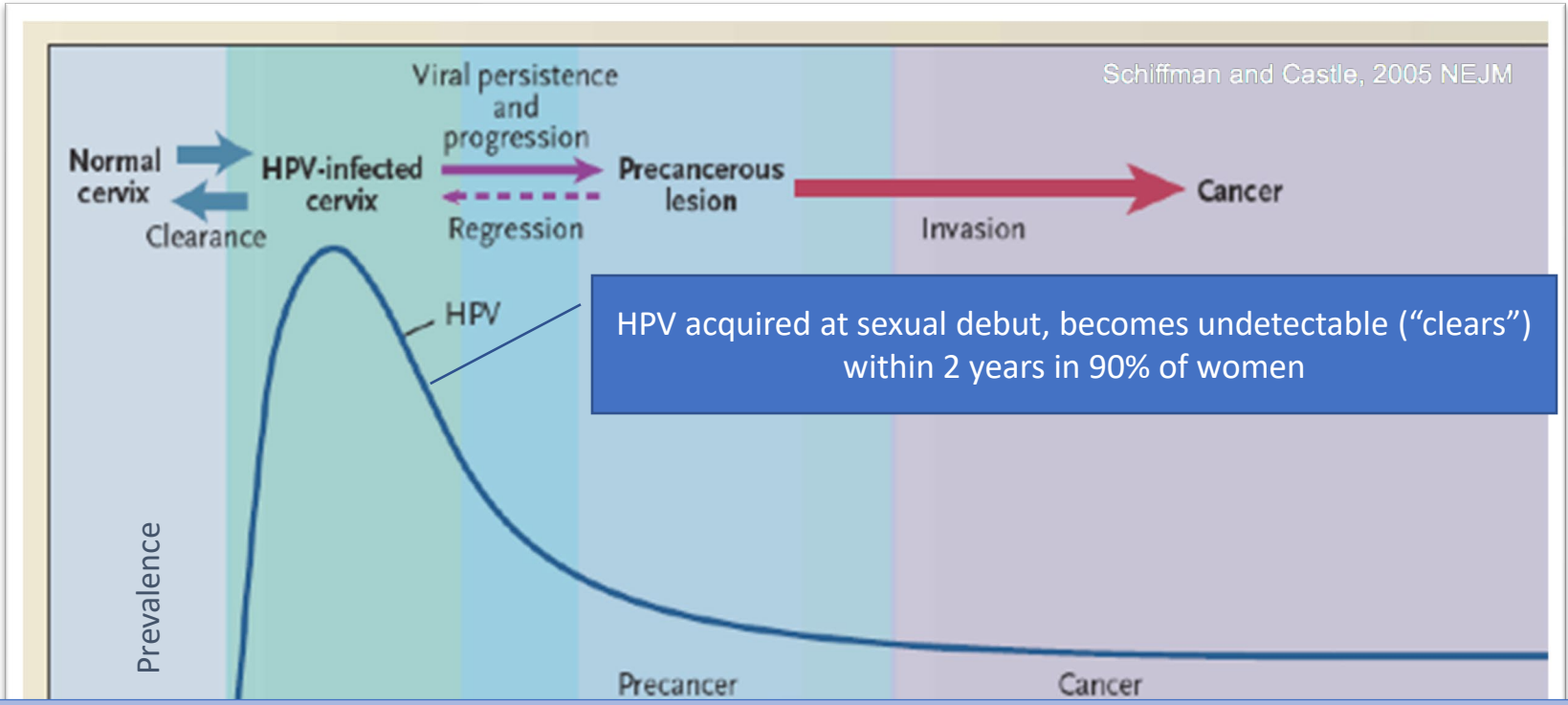
No conflicts to declare

The opinions expressed my own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States Government.

The KNOWNS


Schiffman and Castle, 2005 NEJM
Normal cervix
Clearance
HPV-infected cervix
Viral persistence and progression
Regression
Precancerous lesion
Invasion
Cancer
HPV
Prevalence
HPV acquired at sexual debut, becomes undetectable ("clears") within 2 years in 90% of women
Precancer
Cancer
15 years
30 years
45 years

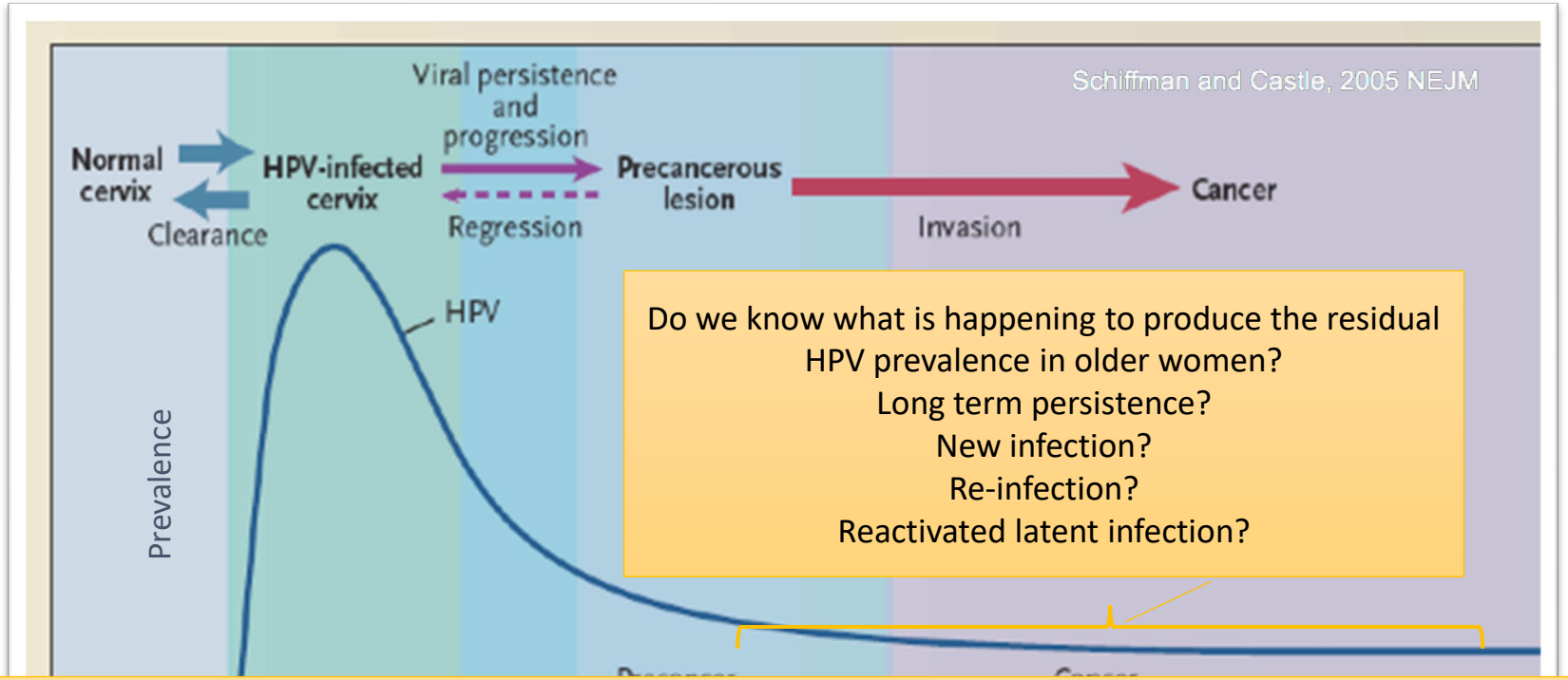
The KNOWNS



NO DEBATE:

- Individuals with persistent high-risk (HR) HPV detection are at highest risk for progression to precancer and cancer.
- Women testing negative for cervical HR-HPV are at low **near term** risk of precancer and cancer.
- Women and men with new sexual partners are at a higher risk for new HPV detection no matter their age.

The UNKNOWNS?



ISSUES REQUIRING CLARITY:

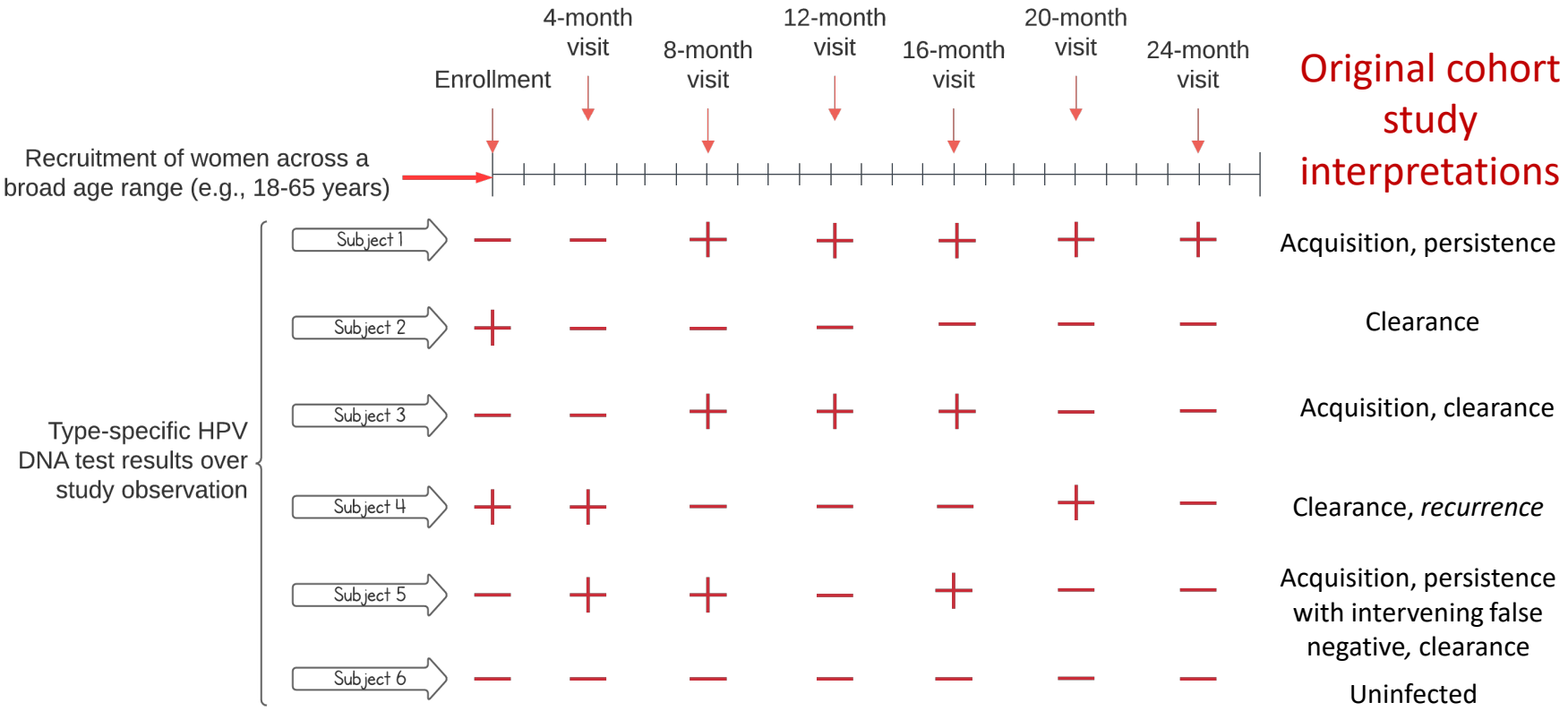
- When HPV 'clears' (tests negative) what does that infer about infection? Eradication or immune control?
  - Is immune control representing latent infection or low viral copy number?
- What proportion of newly detected HPV is acquisition, re-infection, reactivated latent infection, deposition from a recent sex act, or autoinoculation?
- Is the risk of precancer/cancer the same given different pathways to new HPV detection

Challenges in HPV natural history studies

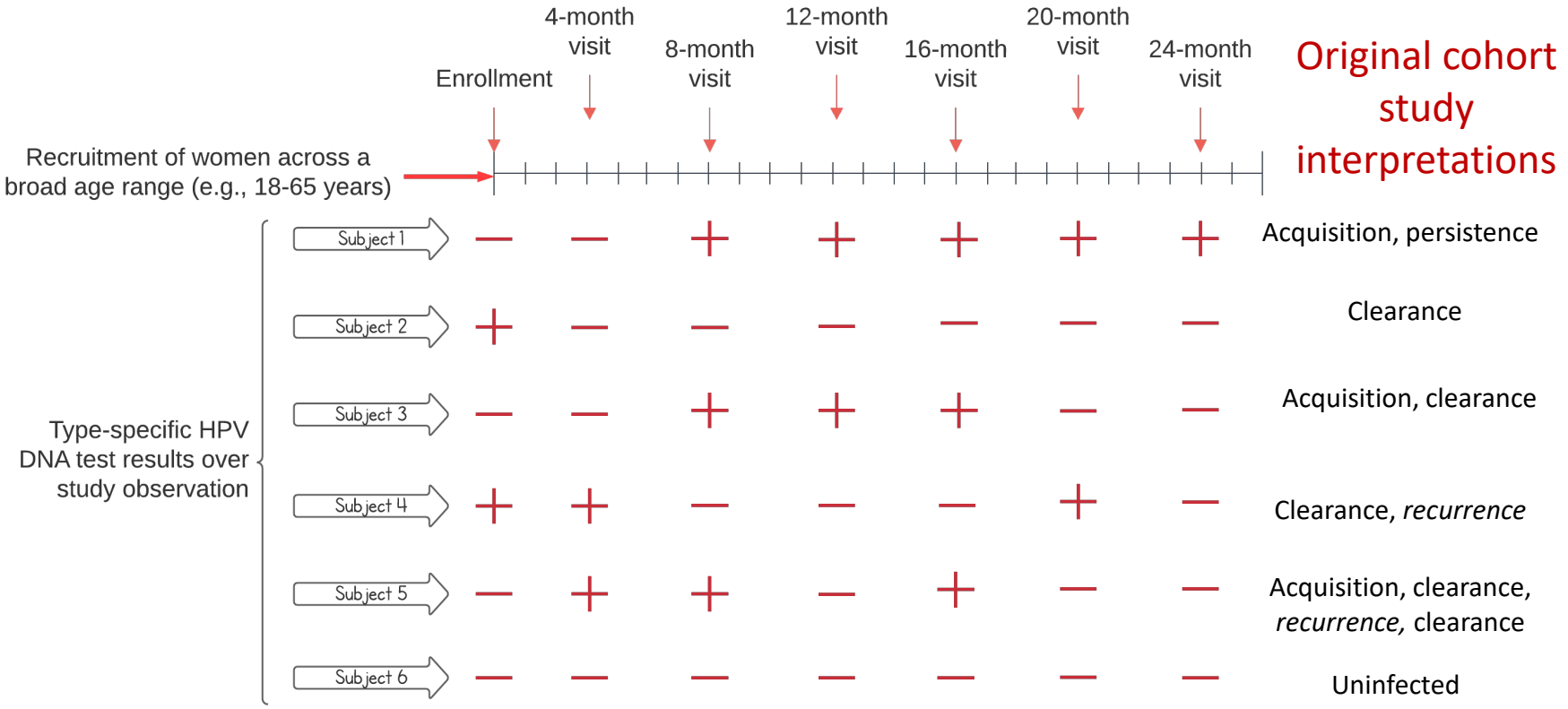
Easier to measure and classify HPV patterns as an exposure leading to a disease endpoint

More difficult to make inference for understanding **within-woman** natural history **over a lifespan**

In HPV natural history studies, we measure *HPV DNA detection*, NOT *HPV infection*



Inherent epidemiological biases with all study designs



Unknown test history before enrollment

Unknown test status between study visits

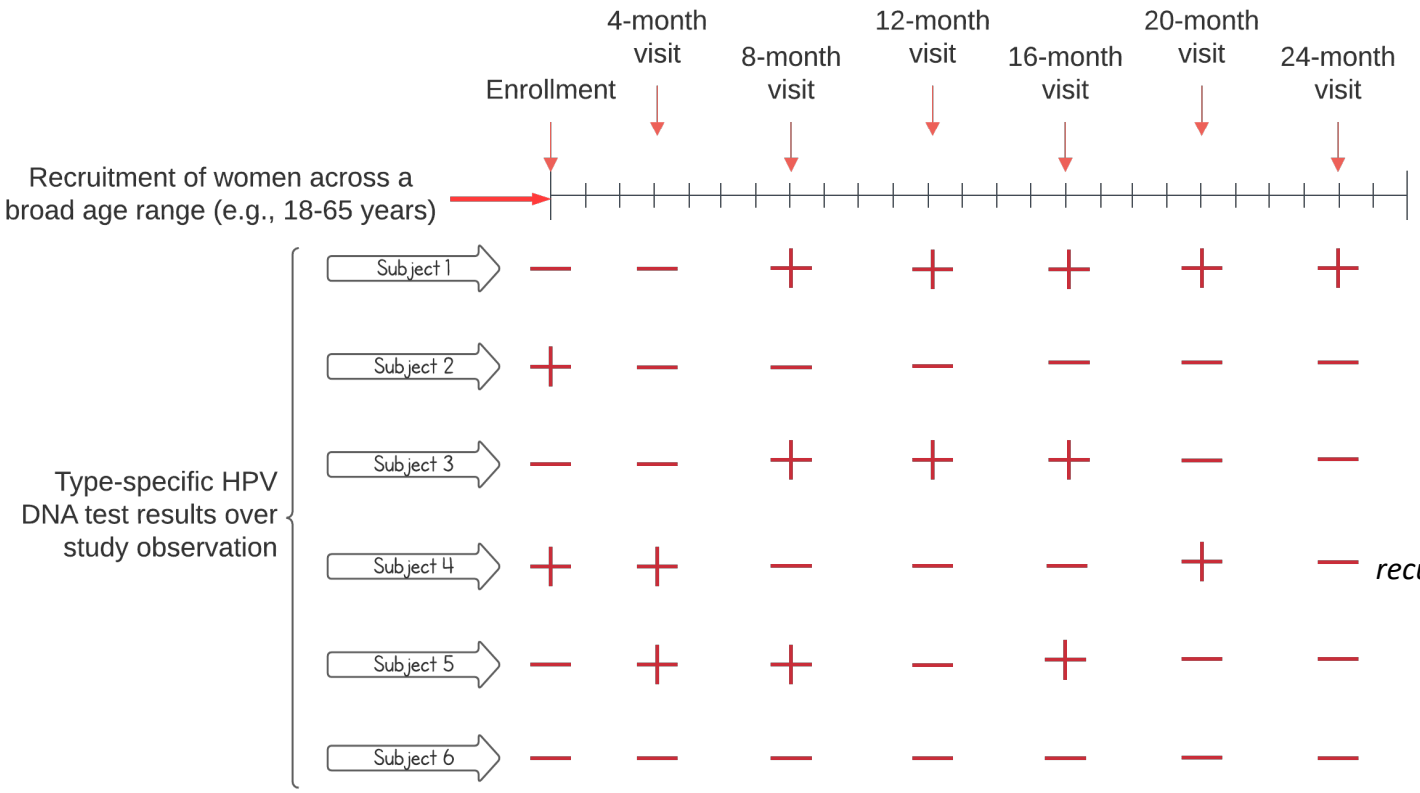
Unknown test status after study ends

Left truncation bias

Interval sampling bias

Right truncation bias

Multiple non-mutually exclusive and plausible interpretations of complex HPV detection patterns



Plausible alternative interpretations

Acquisition/recurrence, persistence

Clearance/immune control

Acquisition/recurrence, clearance/immune control

Clearance/immune control, *recurrence,* clearance/immune control

Acquisition/recurrence, clearance/immune control, *recurrence,* clearance/immune control

Uninfected/well-controlled

Unknown test history before enrollment

Unknown test status between study visits

Unknown test status after study ends

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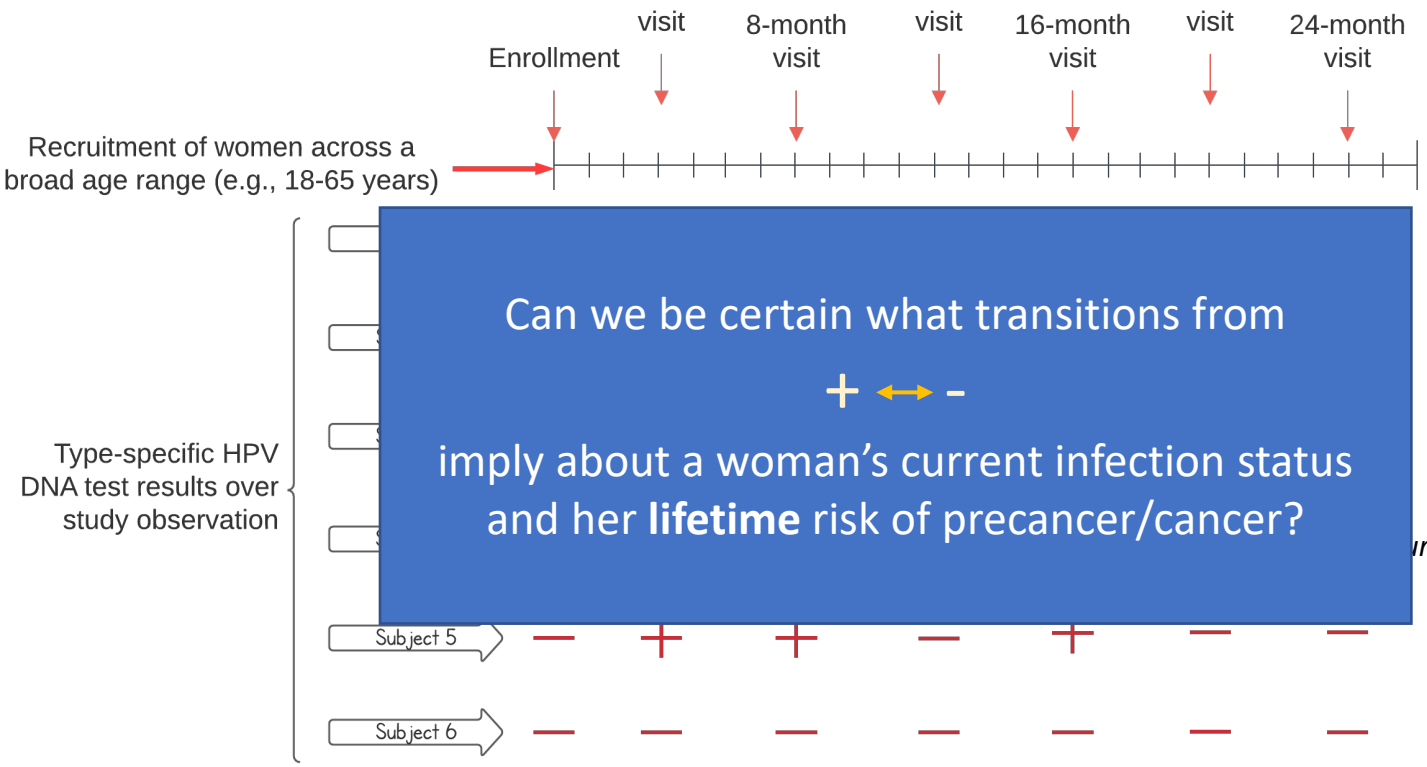
Interval sampling bias

Right truncation bias

Limitations in inferring disease risk due to the observational study biases



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Uninfected

Unknown test history before enrollment

Unknown test status between study visits

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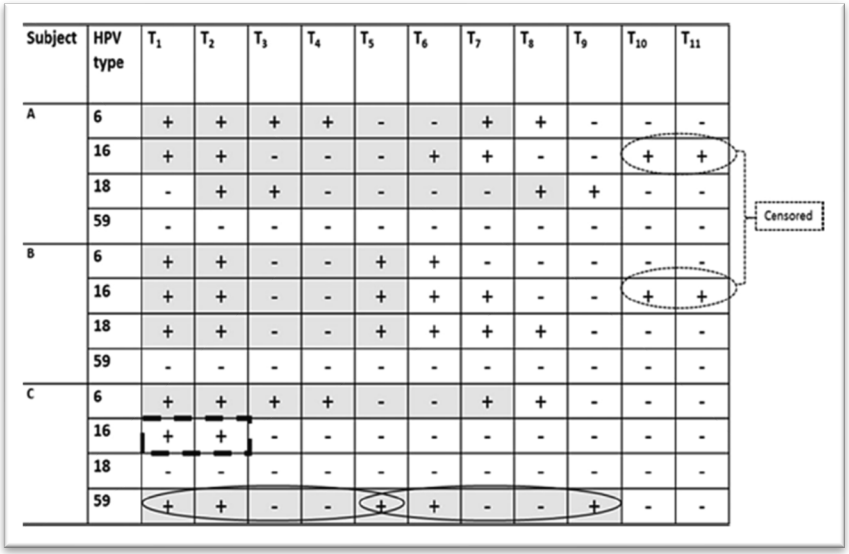
What DO we know?

Recurrent detection in sexually active adolescents (mean age 15.4 years at enrollment)

- 181/766 (23.6%) of type-specific detections 'cleared' and were re-detected during study period (mean follow-up 5.8 years (95% CI 3.9-9.2)
  - Mean duration of detectability = 463 days
  - Mean duration of non-detection = 290 days

- Re-enrollment of HPV16 positive women: 11/27 (40.7%) women with HPV16 detection had HPV16 redetection
  - Median time from last detection in original study to redetection was 7.1 years (IQR 5.6-11.2)



- Samples collected every 3 months

- Suggests that HPV *infection* duration is much longer than previously thought

Shew et al. (2015) J Med Virol

Ermel et al. (2018) Papillomavirus Research

Re-detection of HPV is common

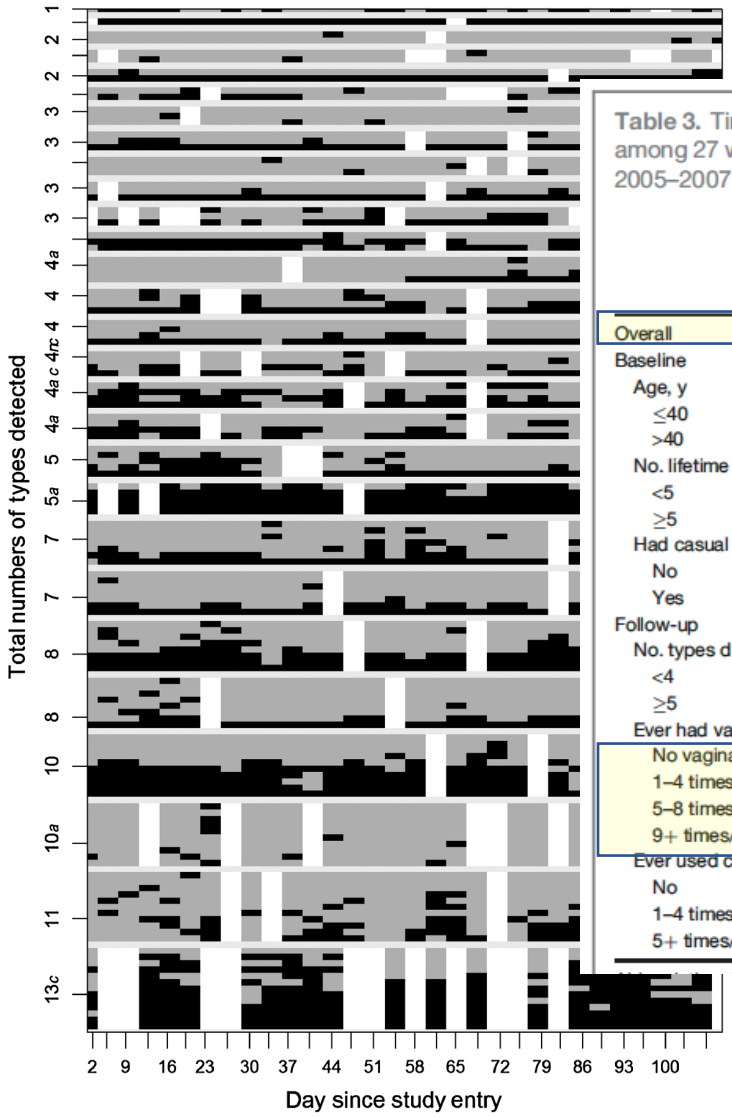


Table 3. Time to recurrent detection of HPV DNA (all types) by selected baseline and follow-up covariates among 27 women[a] (319 events) over 16 weeks in the Baltimore–Washington Metropolitan Area, Maryland, 2005–2007

			No. recurrences		Time to a recurrent detection (days)[b]	
	No. subjects	No. events	Median	Min.–max.	Median	95% CI[c]
Overall	27	319	10	2–43	11	(10–11)
Baseline						
Age, y						
≤40	17	173	9	2–24	11	(7–14)
>40	10	146	12.5	3–43	11	(10–12.6)
No. lifetime partners[d]						
<5	7	62	9	2–13	14	(11–21)
≥5	19	233	10	3–43	11	(7–11)
Had casual sex partners, last 12 mo						
No	24	265	9	2–43	11	(11–14)
Yes	3	54	14	12–28	7	(7–11)
Follow-up						
No. types detected						
<4	16	107	6	2–14	11	(10–18)
≥5	11	212	15	10–43	11	(7–11)
Ever had vaginal intercourse during follow-up[d]						
No vaginal sex	5	54	11	6–14	11	(7–14)
1–4 times/16 wks	7	72	6	3–28	11	(11–17)
5–8 times/16 wks	5	43	9	6–10	7	(4–17)
9+ times/16 wks	9	146	12	2–43	11	(7–14)
Ever used condom[d]						
No	17	220	11	4–43	11	(10–14)
1–4 times/16 wks	7	83	9	3–28	11	(7–15.6)
5+ times/16 wks	2	12	6	2–10	11	(7–94)

Sampling every 3-4 days for 16 weeks

Liu et al, 2014

Re-detection of HPV is common

Pattern	Times the pattern was observed	Pattern	Times the pattern was observed	Pattern	Times the pattern was observed
000000000000110	2	00000000000001	79	000000000010001	1
000000000000111	5	000000000000010	18	00000000001001	4
0000000000011	9	0000000000001	30	0000000000101	2
00000000000110	17	00000000000010	55	00000000001010	1
000000000001100	2	000000000000100	23	00000000001011	4
00000000000111	6	000000000001	25	000000000010110	1
000000000001110	3	0000000000010	23	00000000001101	1
000000000011	10	00000000000100	51	000000000100010	1
0000000000110	6	000000000001000	20	0000000001001	1
00000000001100	10	0000000000010000	1	00000000010010	1
000000000011000	3	00000000001	9	000000000100100	1
0000000000111	5	000000000010	11	00000000010100	4
00000000001110	5	0000000000100	32	000000000101000	1
000000000011100	2	00000000001000	94	00000000011001	1
00000000001111	8	000000000010000	20	00000000011011	2
000000000011110	2	0000000001	3	000000001000001	1
000000000011111	1	00000000010	10	000000001000010	1
00000000011	2	000000000100	8	000000001001	1
000000000110	3	0000000001000	20	00000000100100	1
0000000001100	4	00000000010000	42	00000000100101	1
00000000011000	6	000000000100000	14	00000000100110	1
000000000110000	3	000000001	3	00000000101	1
000000000111	3	0000000010	3	0000000010100	1
0000000001110	1	00000000100	11	00000000101000	1
00000000011100	2	000000001000	12	000000001010000	2
000000000111000	2	0000000010000	13	00000000101011	1
0000000001111	1	00000000100000	38	000000001011001	1
00000000011110	1	000000001000000	14	000000001110101	1
00000000011111	4	00000001	14	0000000100011	1
000000000111111	1	000000010	8	00000001000110	1
0000000011	5	0000000100	5	0000000100100	1
0000000011000	4	00000001000	6	00000001001000	1

Sampling every 4-6 months for median of 6.5 years

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Cumulative incidence of redetection higher than first detection, not different by age

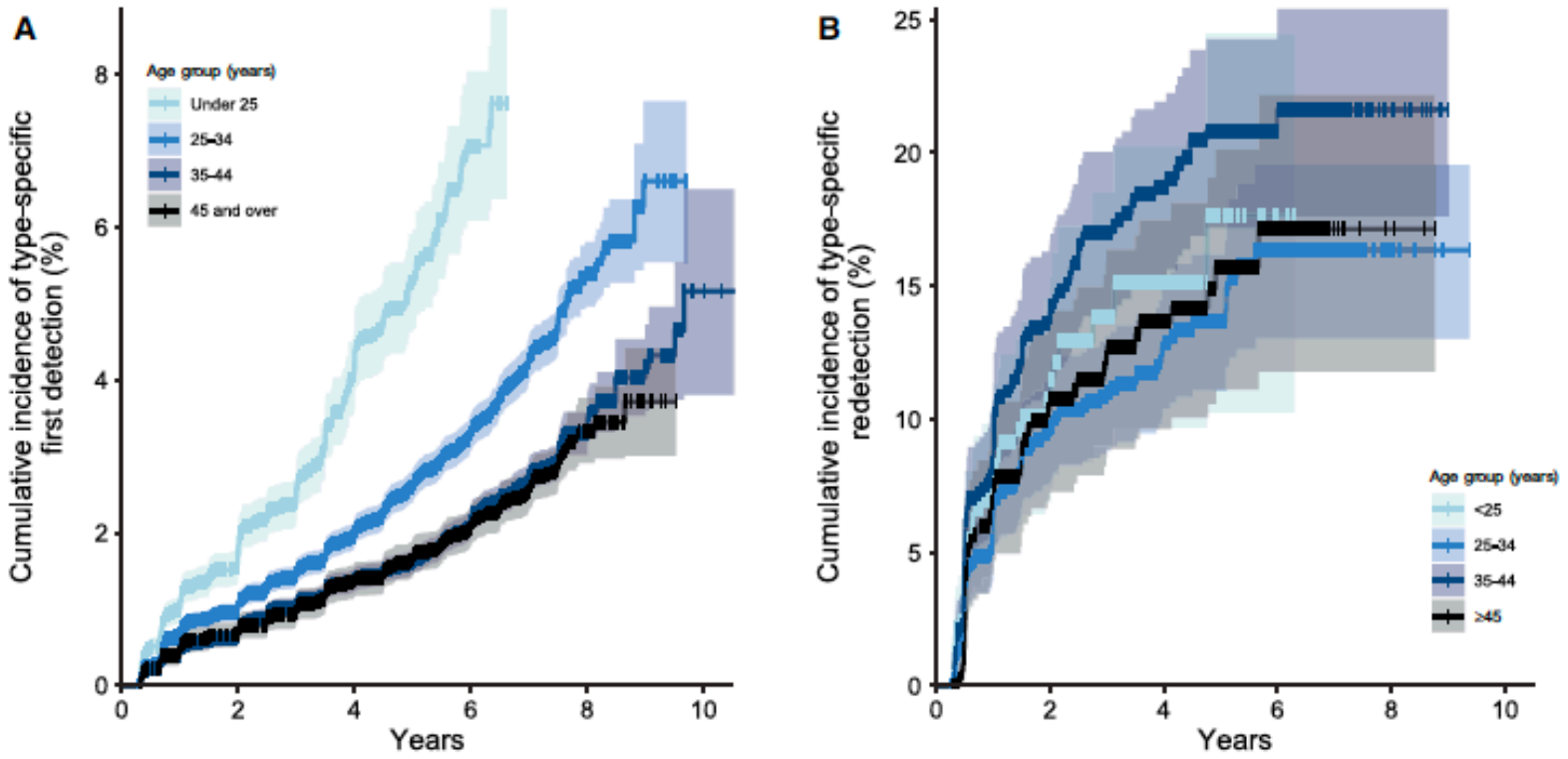

Figure 2. Cumulative incidence of human papillomavirus (HPV) genotype-specific first detection (*A*) and redetection (*B*) by age at time of detection, pooled across all HPV genotypes. Time to detection is modeled from the baseline study visit for first HPV detection, and from the first negative visit following the prior detection of that genotype for redetection. Age is modeled as a time-varying exposure. Notches represent censored observations, and shaded regions represent 95% confidence intervals.

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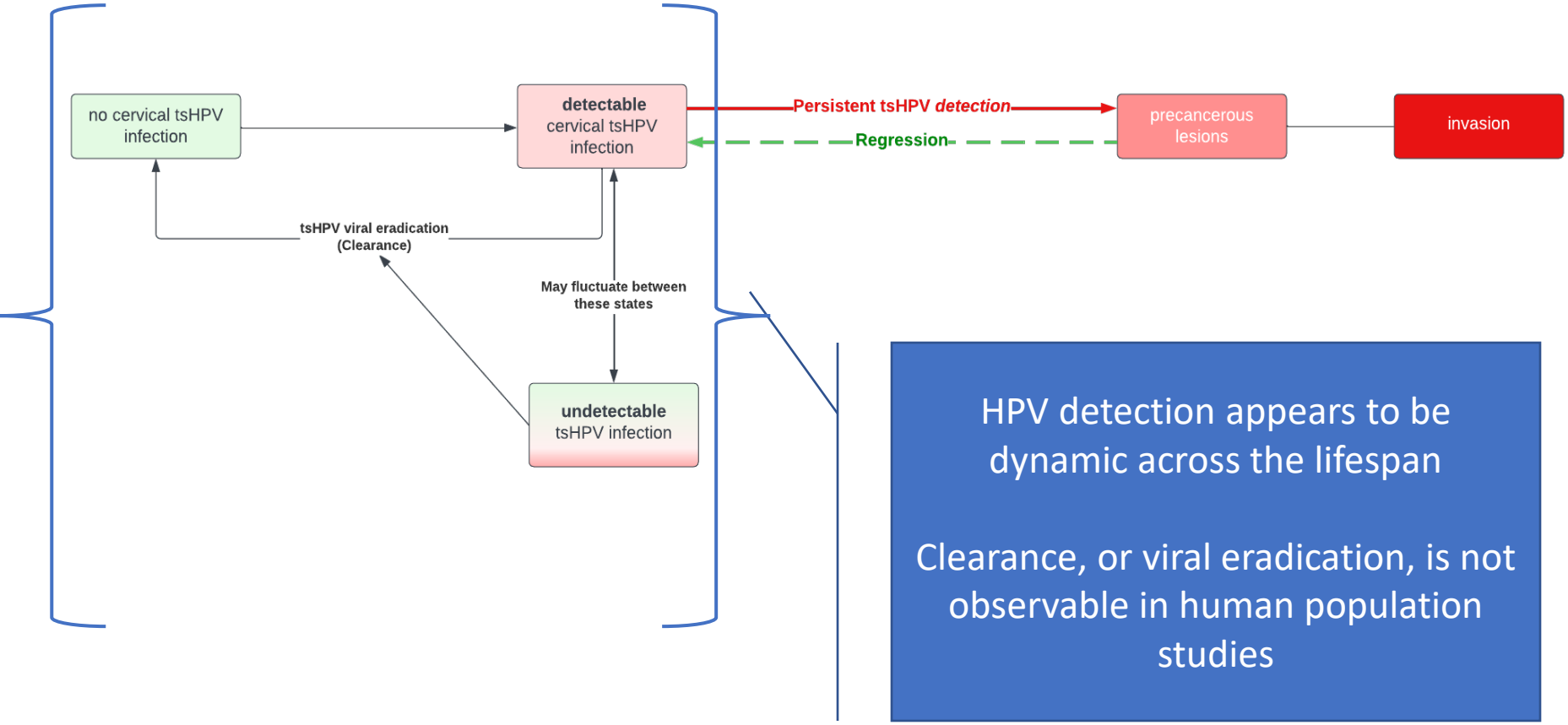
Modified HPV natural history schema



HPV detection appears to be dynamic across the lifespan

Clearance, or viral eradication, is not observable in human population studies

Naturally acquired antibodies and risk of redetection and “new” detection

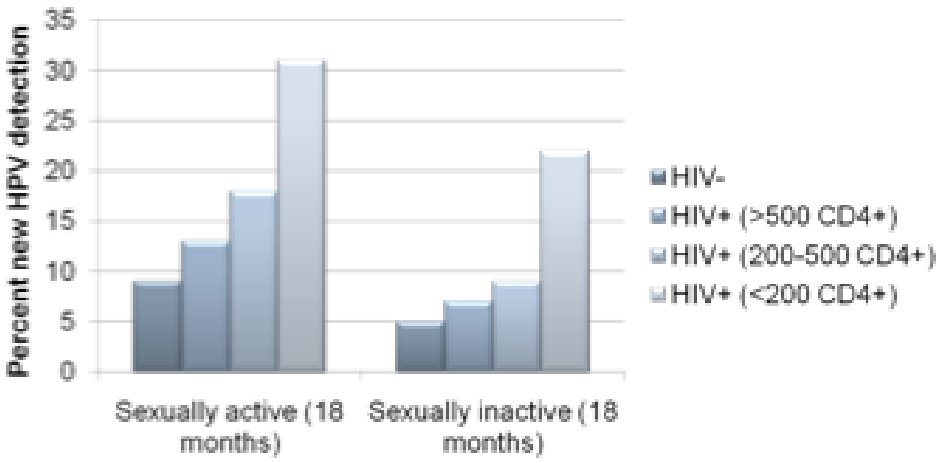
Outcome	Antibody level (n)	Events	Time at risk (women- months)	Incidence (/1000 women- months)	HR (95% CI) Crude	HR (95% CI) Age-adjusted
HPV16 DNA redetection						
After *two* HPV16 DNA negative tests, consecutively[a]	<Upper tertile (123)	9	4764.60	1.89	1	1
	≥Upper tertile (73)	13	2924.80	4.44	**2.40 (1.03–5.62)**	**2.45 (1.04–5.74)**
After *three* HPV16 DNA negative tests, consecutively[b]	<Upper tertile (110)	3	4015.23	0.75	1	1
	≥Upper tertile (66)	9	2424.44	4.44	**5.07 (1.37–18.72)**	**5.10 (1.37–19.00)**
Newly detected HPV infection[c]						
HPV16	<Upper tertile (984)	87	70 151.40	1.24	1	1
	≥Upper tertile (451)	45	28 681.25	1.57	1.28 (0.89–1.84)	1.36 (0.95–1.96)
HPV16 related genotypes (31, 35, 52, 67, 33, 58)	<Upper tertile (984)	123	69 003.72	1.78	1	1
	≥Upper tertile (451)	62	28 645.53	2.16	1.24 (0.91–1.69)	1.35 (0.99–1.84)
HR-HPV genotypes not related to HPV16	<Upper tertile (984)	286	61 656.38	4.64	1	1
	≥Upper tertile (451)	139	24 821.88	5.60	1.23 (1.00–1.50)	**1.32 (1.08–1.62)**

Outcome	Antibody level (n)	Events	Time at risk (women- months)	Incidence (/1000 women- months)	HR (95% CI) Crude	HR (95% CI) Age-adjusted
HPV16 DNA redetection						
After *two* HPV16 DNA negative tests, consecutively[a]	<1:640 (91)	8	3749.08	2.13	1	1
	≥1:640 (12)	1	548.49	1.82	0.98 (0.12–7.86)	1.04 (0.13–8.39)
	<1:160 (82)	8	3287.43	2.43	1	1
	≥1:160 (21)	1	1010.13	0.99	0.47 (0.06–3.74)	0.49 (0.06–3.95)
	<1:40 (70)	4	2866.81	1.39	1	1
	≥1:40 (33)	5	1430.76	3.49	2.60 (0.70–9.70)	2.78 (0.74–10.43)
Newly detected HPV infection[c]						
HPV16	<1:640 (320)	49	22 259.87	2.20	1	1
	≥1:640 (9)	0	642.63	0.00	NA	NA
	<1:160 (303)	43	21 100.03	2.20	1	1
	≥1:160 (26)	6	1802.47	2.04	1.64 (0.70–3.86)	1.59 (0.67–3.73)
	<1:40 (256)	38	17 803.12	2.13	1	1
	≥1:40 (73)	11	5099.37	2.16	1.04 (0.53–2.04)	1.02 (0.52–2.00)

Trevisan A, Candeias JMG, Thomann P, Villa LL, Franco EL, Trottier H. Naturally developed HPV16 antibodies and risk of newly detected cervical HPV infection outcomes. J Med Virol. 2024 Apr;96(4):e29608. doi: 10.1002/jmv.29608. PMID: 38623750.

Immune surveillance likely important in maintaining HPV in a mostly undetectable state

HPV incident detection strongly associated with immune status



- HPV new detection increases proportionately with increasing immune suppression
- *The excess risk in sexually active vs inactive women gives us a sense of the proportion of acquisition vs. reactivation*

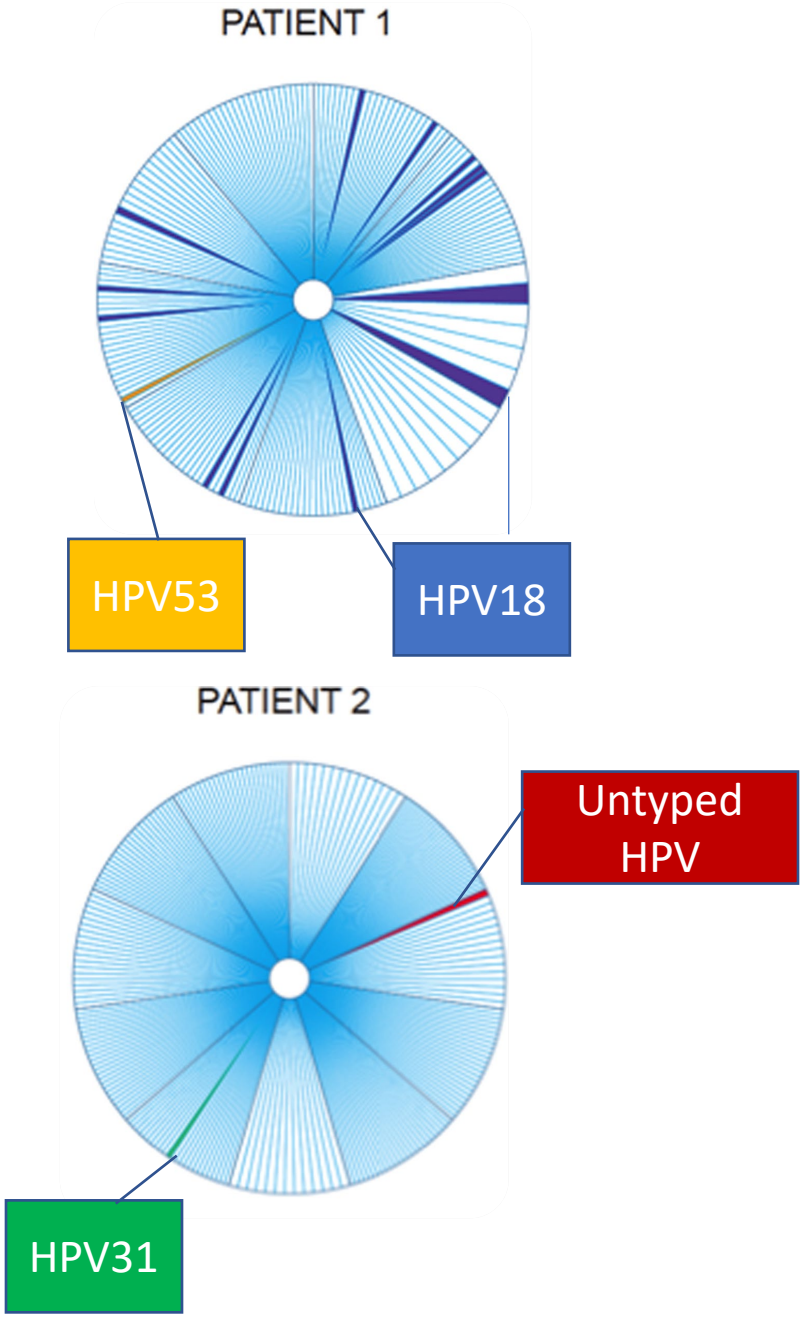
- Data support inference that a large proportion of new HPV DNA detection in adult women represents loss of immune control of persistent infection, even in sexually active women
- Similar results for anal HPV in sexually inactive gay and bisexual men (GBM)
  - Poynten IM, et al. CEBP 2022

Strickler JNCI (2005)

Is clearance feasible?

- Nearly impossible to confirm viral clearance or latency
- Extensive tissue testing of hysterectomized cervix shows focal HPV detection in women who test negative for HPV on exfoliated swab

- Molecular evidence that HPV DNA can remain in cervical tissue without being detectable in screening
- Focal detection supports possibility of predilection of latent infection in a limited number of *stem-like?* basal cells

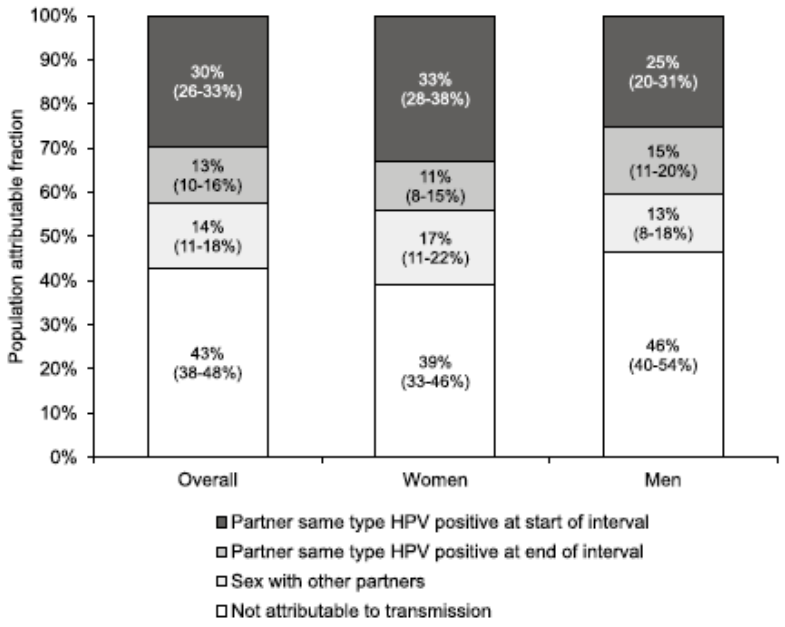


Hammer et al (2019) Papillomavirus Res

What proportion of HPV is newly detected vs redetected?

Partner transmission: The HITCH Cohort

- 544 type-specific incident detections in 849 participants
- Estimate that 43% (38-48%) of all newly detected HPV were NOT attributable to recent sexual transmission
  - Those new detections were associated with higher numbers of lifetime sex partners
- Careful collection of partner sexual behaviors over 6 months in new partnerships strengthens the inference from the older women studies



Malagón T, et al. CID 2021

Does risk of neoplasia differ from a first detection vs. recurrent detection?

Table 4. Cross-sectional Prevalence of Cytological Results by Genotype-Specific HPV Positivity, Pooled Over All High-risk HPV Genotypes and Visits Over all Women

High-risk HPV Status at Visit, Genotype Specific[a]	ASCUS+ Prevalence			LSIL Prevalence			HSIL Prevalence		
	n/Visits[b]	%	(95% CI)	n/Visits[b]	(%)	(95% CI)	n/Visits[b]	(%)	(95% CI)
Negative	7842/308 004	2.5	(2.3 to 2.8)	3095/308 004	1.0	(.9 to .1)	928/308 004	0.3	(.2 to .4)
Positive, first detection	399/2264	17.6	(15.4 to 19.6)	202/2264	8.9	(7.5 to 10.2)	65/2264	2.9	(1.9 to 3.7)
Positive, redetections	40/250	16.0	(10.4 to 21.1)	18/250	7.2	(3.1 to 10.6)	8/250	3.2	(1.3 to 4.9)
Difference, first detection – redetections		1.6	(–3.1 to 6.7)		1.7	(–1.6 to 5.5)		–0.3	(–2.2 to 1.6)

- The Ludwig-McGill study suggests no difference in low or high grade disease prevalence from a first detection vs. re-detection

- Cumulative 5-year risk of CIN3+ is similar following an HPV detection at any age (Katki, J Low Gen Tract Dis, 2013)
  - *Given that most prevalent detection appears to be attributed to redetection – suggests that risk is not higher or lower for near term disease if HPV is recently acquired or not.*

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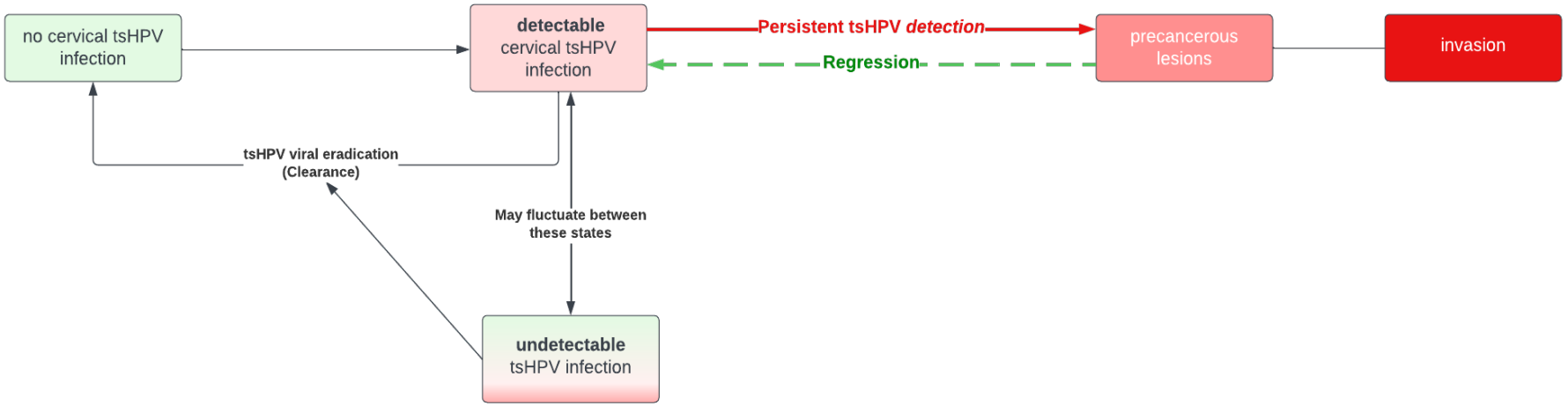
Further implications given revised natural history understanding



THANK YOU

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