

Advances in 1° and 2° Prevention of HPV-Related Cancers

Philip E. Castle, PhD, MPH

Director, Division of Cancer Prevention

Acting Director, Cancer Prevention Fellowship Program

Senior Investigator, Division of Cancer Epidemiology and Genetics,

NCI/NIH/DHHS

Disclaimers

- Opinions expressed are mine alone and should **not** be interpreted as representing the official viewpoint of the U.S. Department of Health and Human Services, the National Institutes of Health, the National Cancer Institute, or the Division of Cancer Prevention.
- My comments are informal and should **not** be taken as a “signal” for funding priorities.
- If I mention specific products to illustrate my points, my comments should **not** be taken as an endorsement of said products

Disclosures

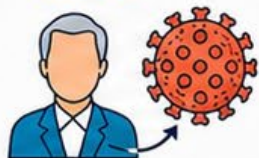
- I conduct research on effectiveness of and new delivery strategies for HPV vaccination and HPV testing-based screening for the prevention of cervical cancer, especially in women with HIV
- I have received HPV tests and assays at a reduced or no cost for research use only from Roche, Cepheid, and Atila Biosystems.

Agenda

1. *Background/History*
2. *HPV Vaccination*
3. *HPV Testing-Based Cervical Cancer Screening*
4. *Anal Cancer*
5. *Oropharyngeal Cancer*
6. *Remaining Gaps/Opportunities*

TIMELINE OF KEY MILESTONES IN HPV RESEARCH & CANCER PREVENTION

1976



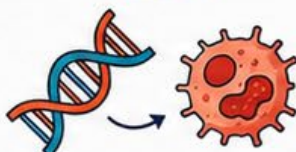
Zur Hausen Proposes HPV Role in Cervical Cancer

1983-1984



Zur Hausen Isolates HPV-16 & HPV-18

1986



HPV Genome Characterized; Oncoproteins E6/E7 Identified

1991



Bethesda System for Cytology Reporting

1995



IARC Classifies HPV-16/18 as Group 1 Carcinogens

1999



Proof-of-Concept for Virus-Like Particles (VLPs)

2006



ACIP Recommends HPV Vaccination for Females (First ACIP Recommendation)

2006



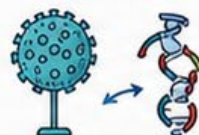
FDA Approves Gardasil® (Merck)

2008



Zur Hausen's Nobel Prize

2009



FDA Approves First HPV DNA Test for Co-testing

2009

Cervarix®

FDA Approves Cervarix® (GSK)

2011



ACIP Expands Vaccine Recommendation to Males

2012



USPSTF Recommends Co-testing

2014

FDA APPROVES GARDASIL® 9 Cover More Types with More Types

2014

FDA APPROVES COBAS HPV TEST FOR STANDALONE PRIMARY SCREENING

Key to Capres About Catriira and Strestops

2014-2019



ANCHOR STUDY ENROLLMENT

2014-2019



Professional Guidance and Expanded Approval to Ages 27-45

2020s

2022



ANCHOR STUDY RESULTS: TREATING ANAL HSIL PREVENTS CANCER



57% Reduction

2021



WHO Strategy Reaffirmation

2021



USPSTF Reaffirmation

2023



FDA APPROVES IN-CLINIC SELF-COLLECTION FOR HPV TESTING

2024



Studies for Home Collection

2024



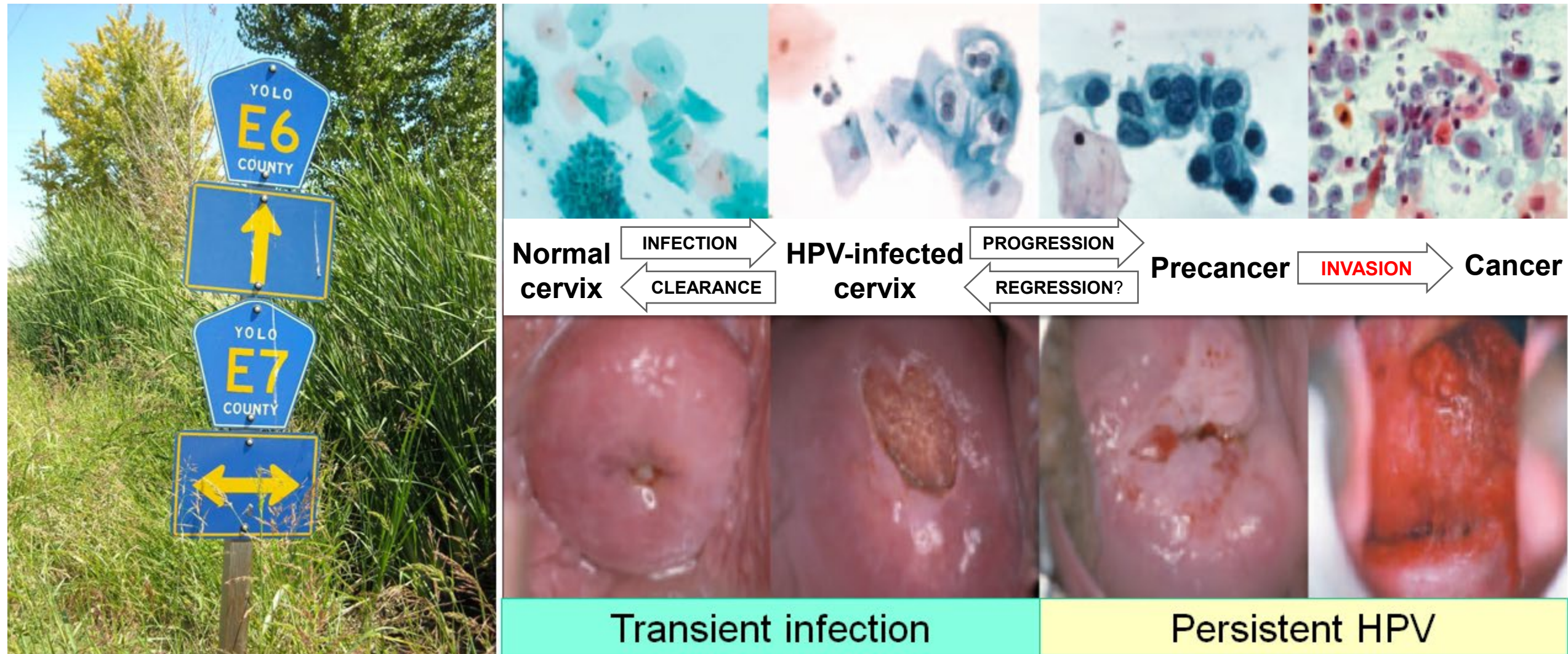
WHO Single-Dose Recommendation

2026

FDA APPROVES HOME-BASED SELF-COLLECTION & HPV TESTING FOR CERVICAL CANCER SCREENING



Cervical (Anogenital) Carcinogenesis



Key Facts

- ~4.5% of all cancers are caused by HPV (de Martel *et al.*, *Int J Cancer*, 2017 (PMID: 28369882):

HPV-related cancer site (ICD-10 code)	Number of incident cases ^{1,2}	Number attributable to HPV	AF (%)	Number attributable to HPV by gender	
				Males	Females
Cervix uteri (C53)	530,000	530,000	100.0	0	530,000
Anus ³ (C21)	40,000	35,000	88.0	17,000	18,000
Vulva ³ (C51)	34,000	8,500	24.9	0	8,500
Vagina ³ (C52)	15,000	12,000	78.0	0	12,000
Penis ³ (C60)	26,000	13,000	50.0	13,000	0
Oropharynx ³ (C01, C09–10)	96,000	29,000	30.8	24,000	5,500
Oral cavity ³ (C02–06)	200,000	4,400	2.2	2,900	1,500
Larynx (C32)	160,000	3,800	2.4	3,300	460
Other pharynx ³ (C12–C14)	78,000	0	0	–	–
Total HPV-related sites	1,200,000	630,000	54.0	60,000	570,000

- High-Risk HPV Types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68

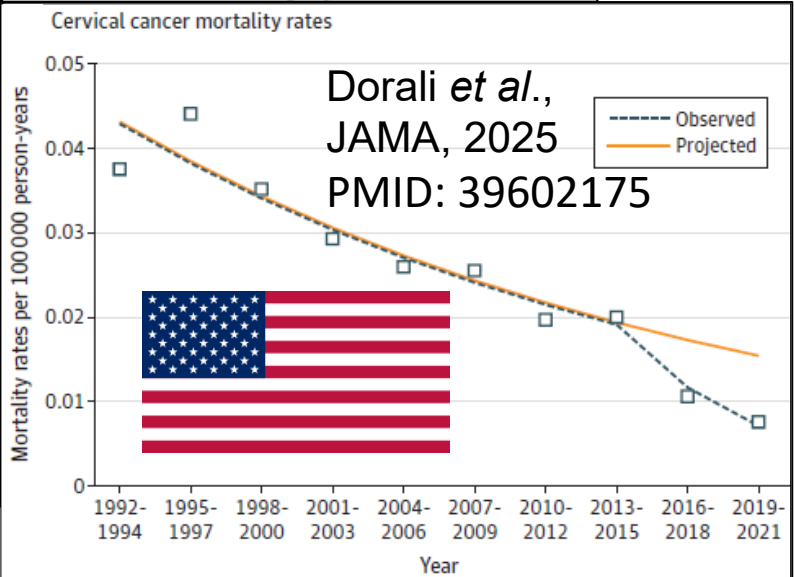
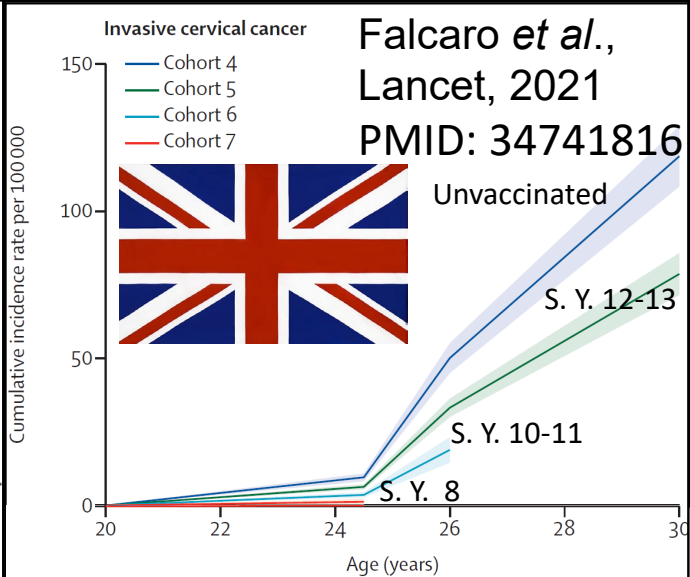
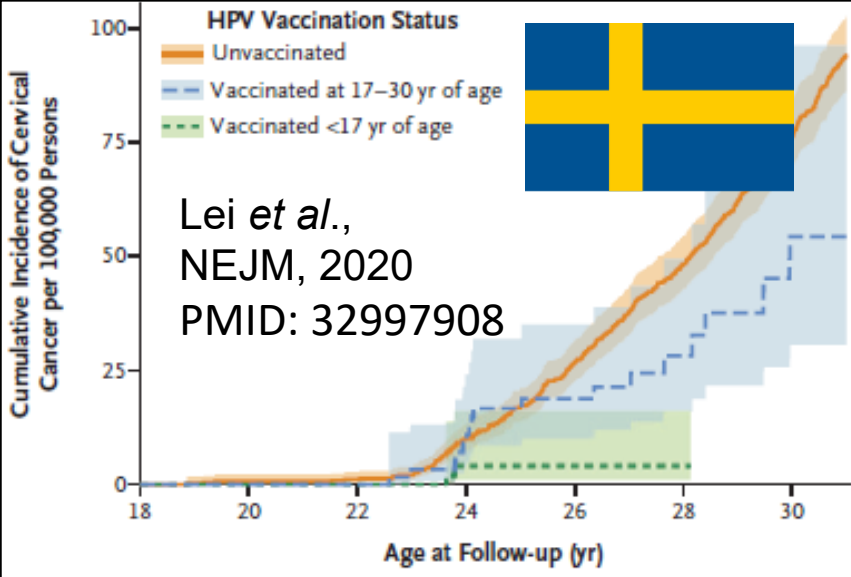
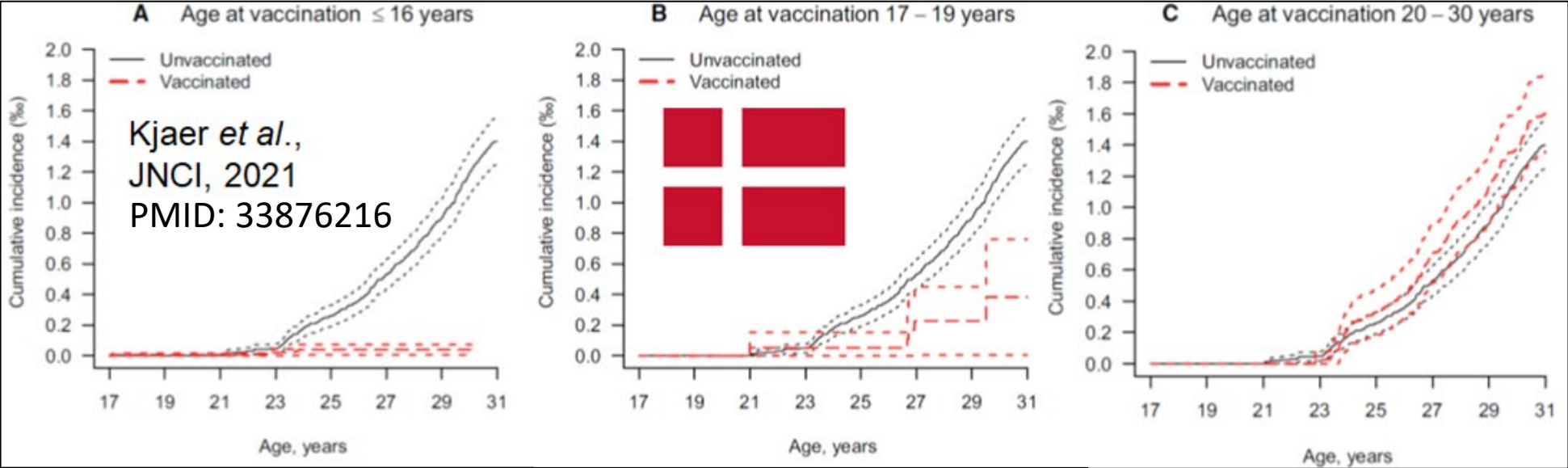
Agenda

1. *Background/History*
2. *HPV Vaccination*
3. *HPV Testing-Based Cervical Cancer Screening*
4. *Anal Cancer*
5. *Oropharyngeal Cancer*
6. *Remaining Gaps/Opportunities*

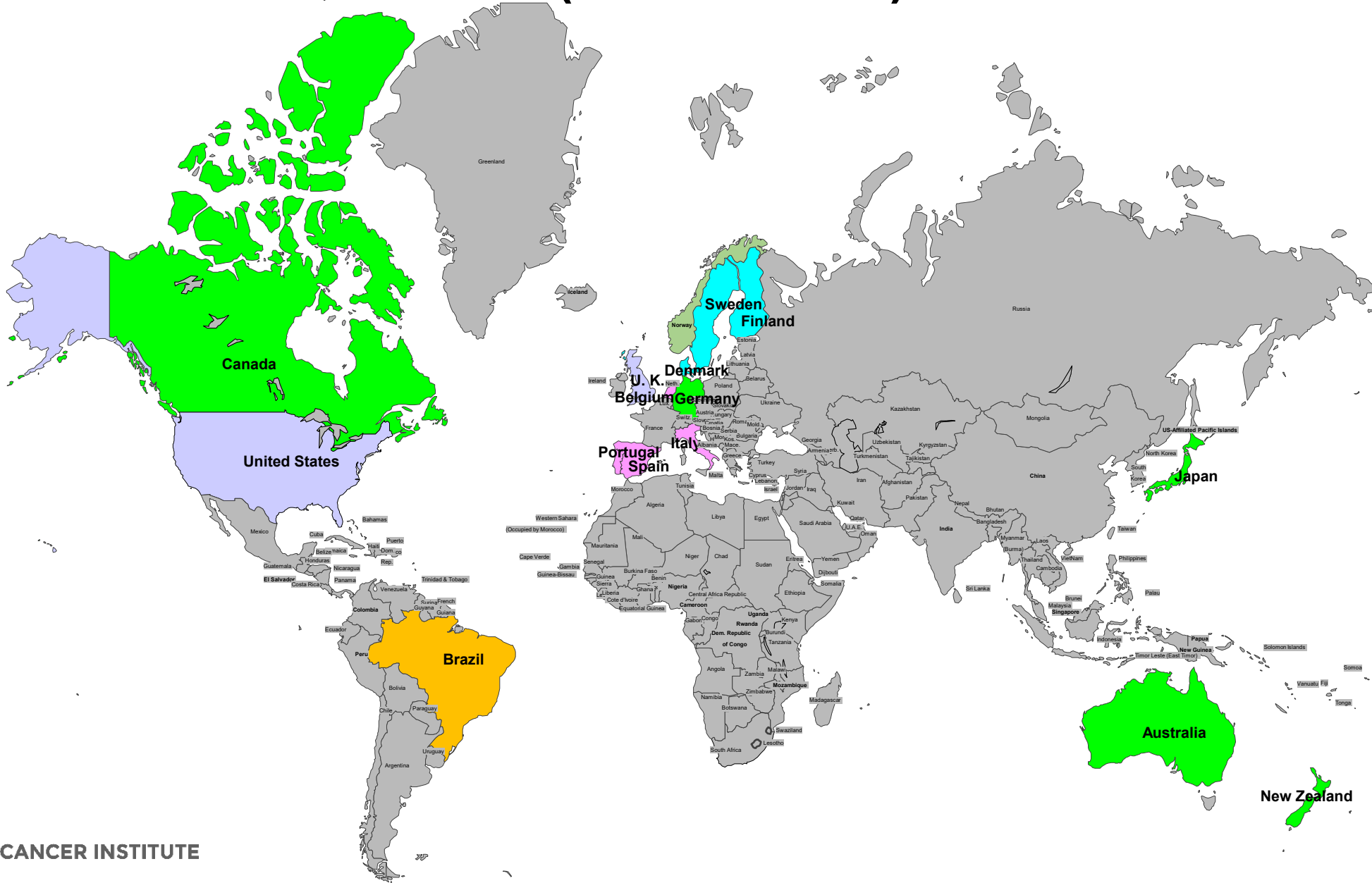
Currently Available Prophylactic HPV Vaccines

	Gardasil	Cervarix	Gardasil-9
Manufacturer	Merck	GSK	Merck
Types and Virus-Like Particle (VLP) Dosing	40 mg HPV16; 20 mg HPV18; 20 mg HPV6; 40 mg HPV11	20 mg HPV16; 20 mg HPV18	60 mg HPV16; 40 mg HPV18; 30 mg HPV6; 40 mg HPV11; 20 mg HPV31; 20 mg HPV33; 20 mg HPV45; 20 mg HPV52; 20 mg HPV58
Schedule	0, 2, and 6 months	0, 1, and 6 months	0, 2, & 6 months
Adjuvant	225 mg amorphous aluminum hydroxyphosphate sulfate	500 mg aluminum hydroxide & 50 mg 3-O-desacyl-4' monophosphoryl lipid A (MPL)	500 mg amorphous aluminum hydroxyphosphate sulfate
Projected Prevention Benefits	70% Cervical Cancer; 90% Warts	84% Cervical Cancer	90% Cervical Cancer; 90% Warts
Biosimilars	Cervavac (Serum Institute of India (SII), Pune, India)	Cecolin® (Xiamen Innovax Biotech Co. Ltd; China), and Walrinvax (Walvax Biotechnology Co.; China)	Cecolin 9® (Xiamen Innovax Biotech Co. Ltd; China)

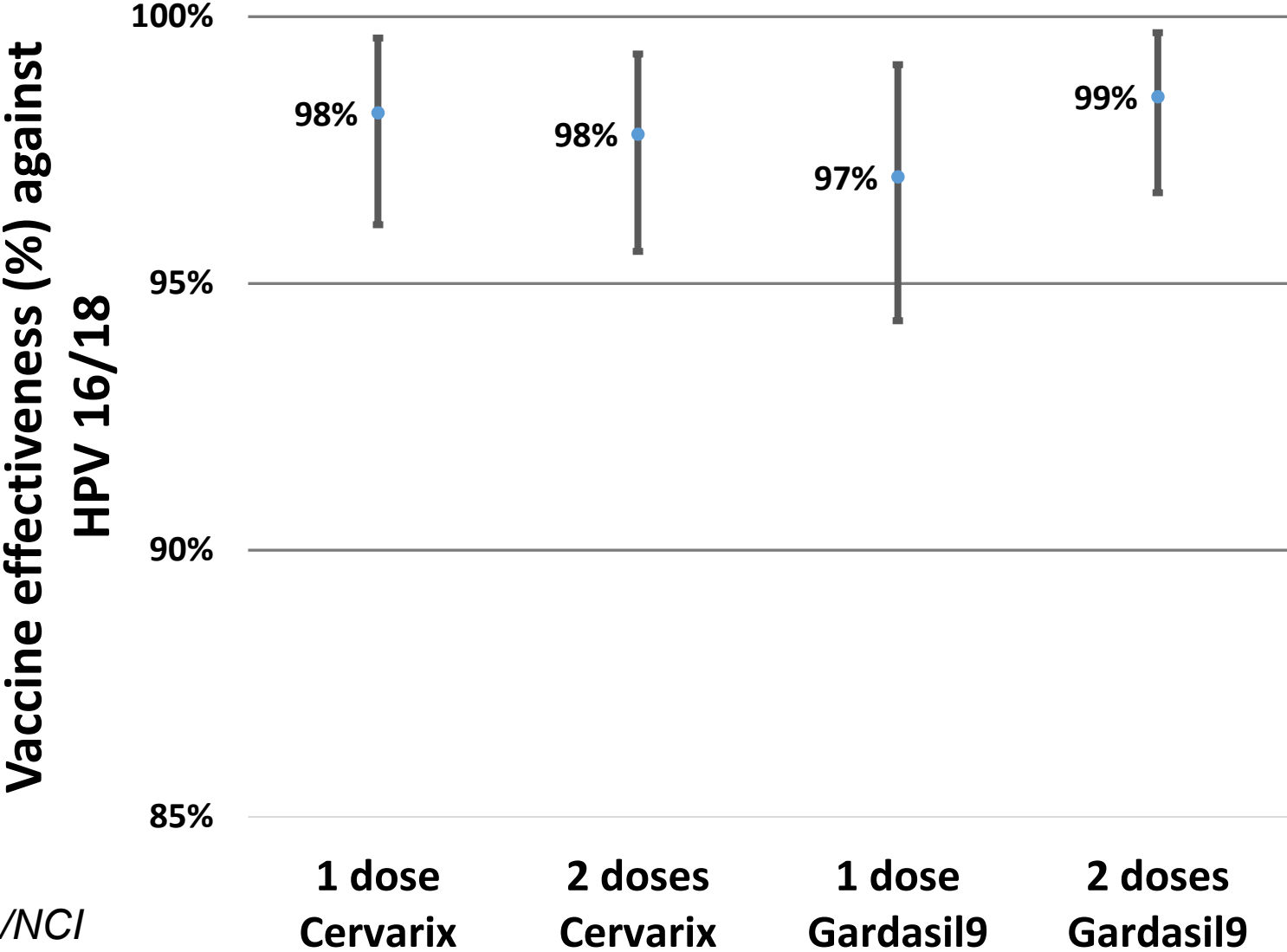
Impact on Cervical Cancer Incidence and Mortality



National Reductions in Cervical Cancer Mortality, Incidence, HSIL, Genital Warts, or HPV (hierarchical) due to HPV Vaccination



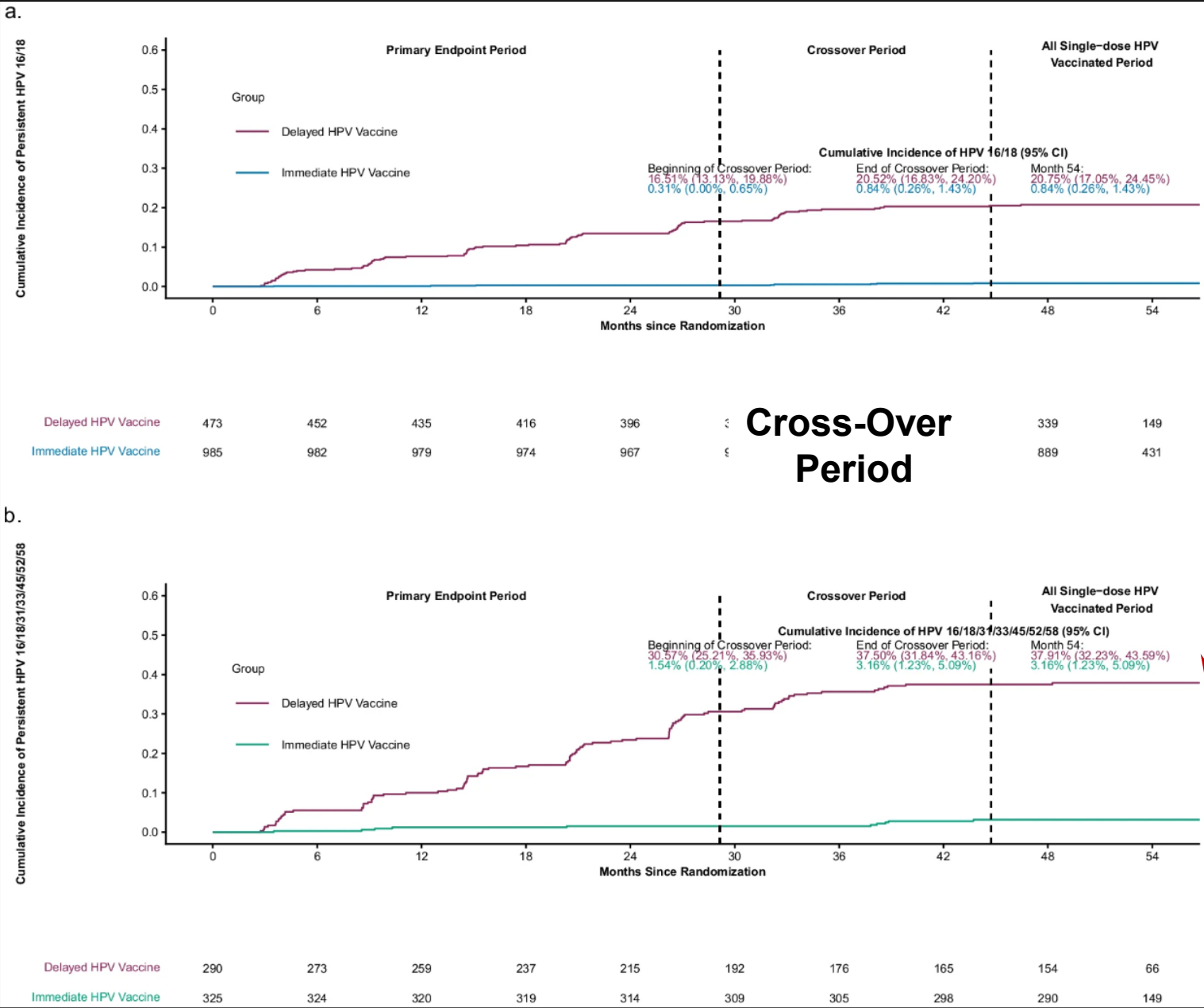
ESCUDDO Trial in Costa Rica: HPV16/18 Vaccine Effectiveness by Number of Doses (vs. No HPV Vaccination)



Courtesy of
Dr. Aimée R. Kreimer, DCEG/NCI

KEN-SHE Trial: One-Dose HPV Vaccination in Kenya

HPV16 & 18



Initially
Unvaccinated,
then crossed
over

Vaccinated

HPV31,
33, 45, 52,
& 58

Australia Adopts Single-Dose HPV Vaccination



Ministers

Department of Health and Aged Care

February 6, 2023

[Home](#)

[Media centre](#)

[Mark Butler](#)

[Anika Wells](#)

[Ged Kearney](#)

[Emma McBride](#)

[Malarndirri McCarthy](#)

[Home](#) > [The Hon Mark Butler MP](#) > [Minister Butler's media](#)

Change to single dose HPV vaccine

From today, Australia will move from two doses to a single dose of the Gardasil®9 human papillomavirus (HPV) vaccine for routine immunisation of young people under the National Immunisation Program.

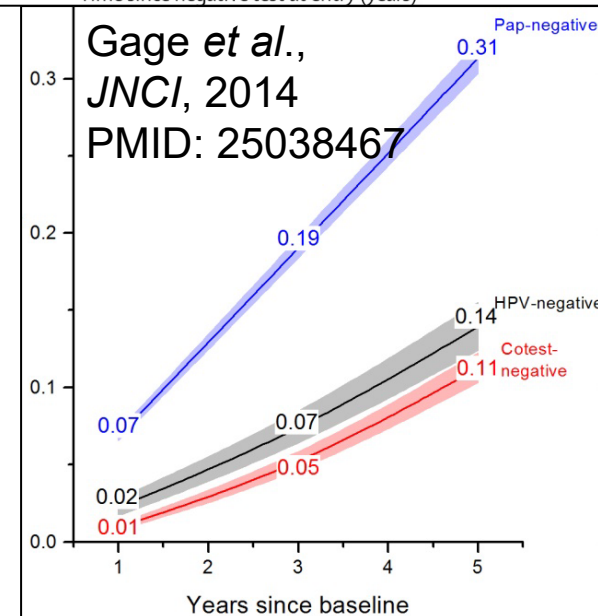
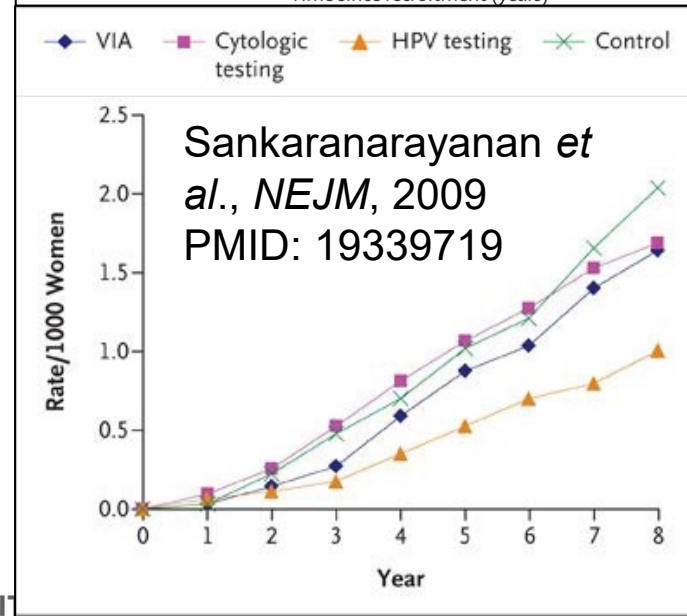
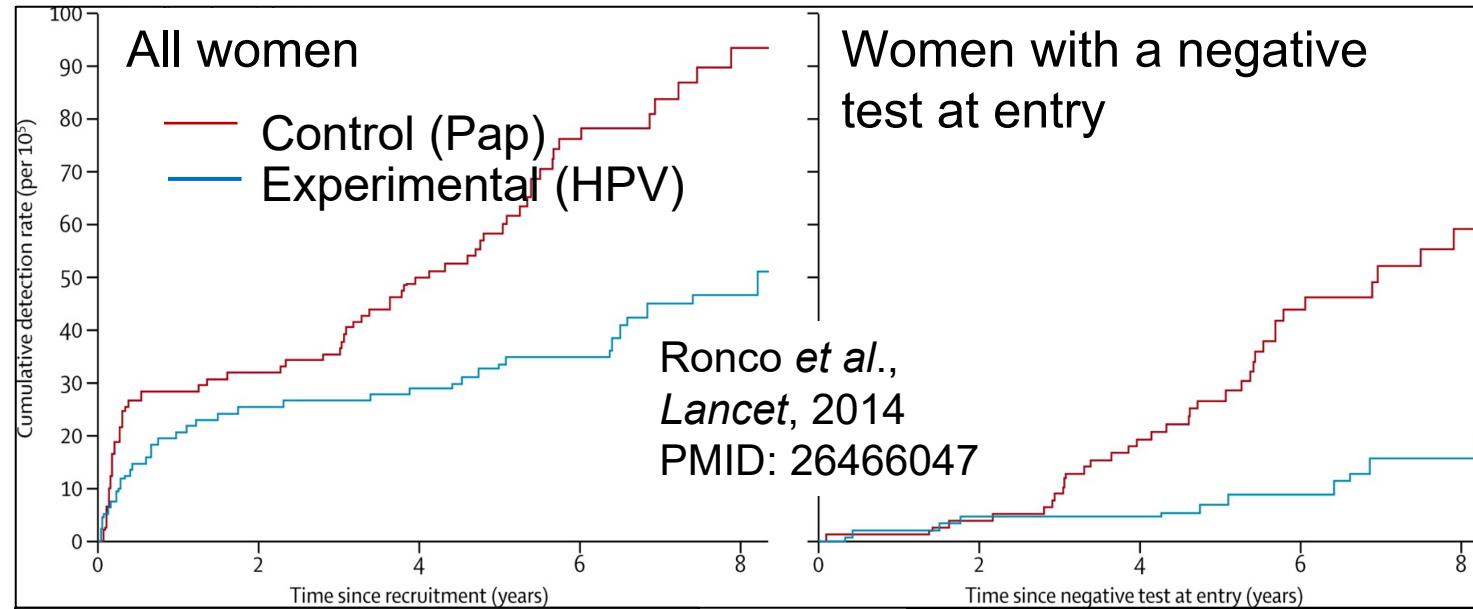


The Hon Mark Butler MP
Minister for Health and Aged Care

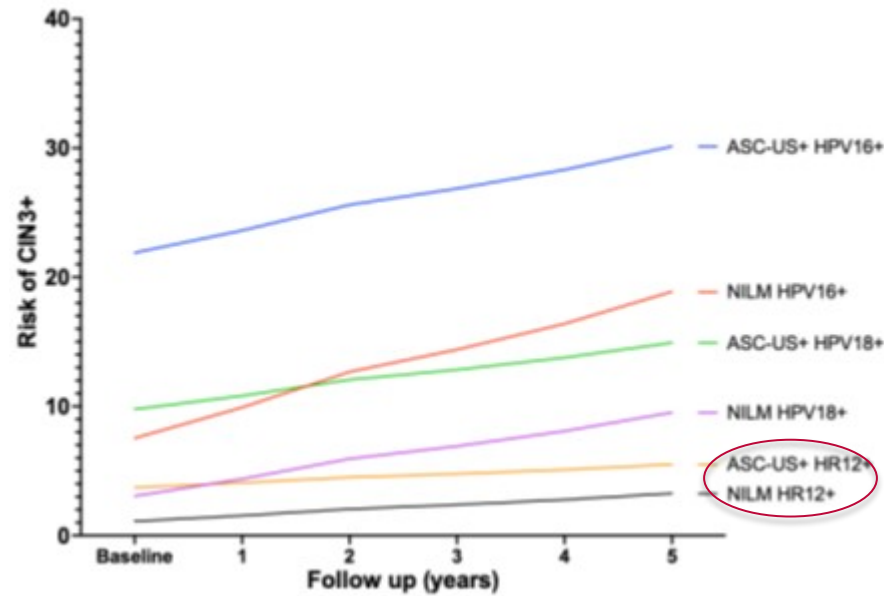
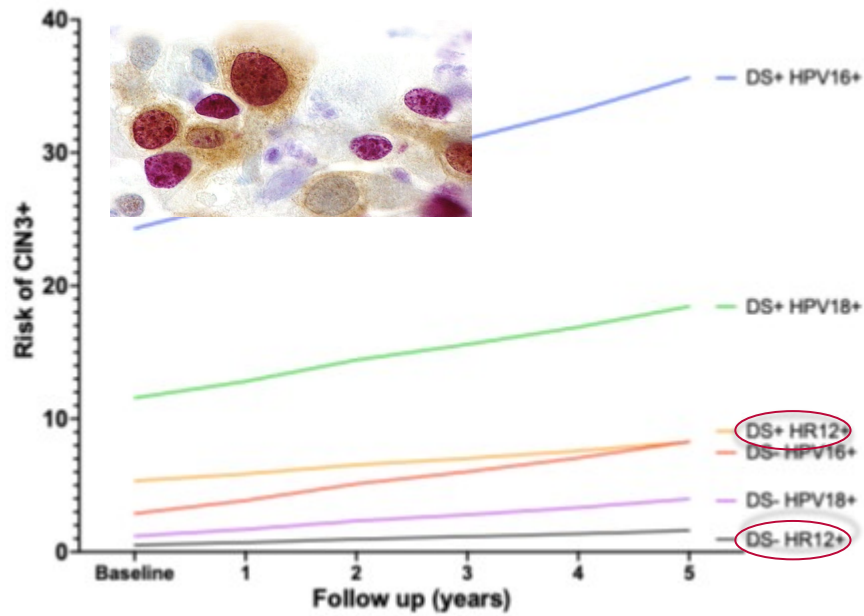
Agenda

1. *Background/History*
2. *HPV Vaccination*
3. *HPV Testing-Based Cervical Cancer Screening*
4. *Anal Cancer*
5. *Oropharyngeal Cancer*
6. *Remaining Gaps/Opportunities*

Evidence for HPV Testing-Based Cervical Cancer Screening



Triage of HPV-positives with HPV Genotyping and p16/Ki-67 Dual Stain



- Superior risk stratification of Dual Stain compared to cytology
- Long-term reassurance of low risk from negative DS results for all HPV results
- Dual stain will perform better than cytology in vaccinated populations

Slide scanning

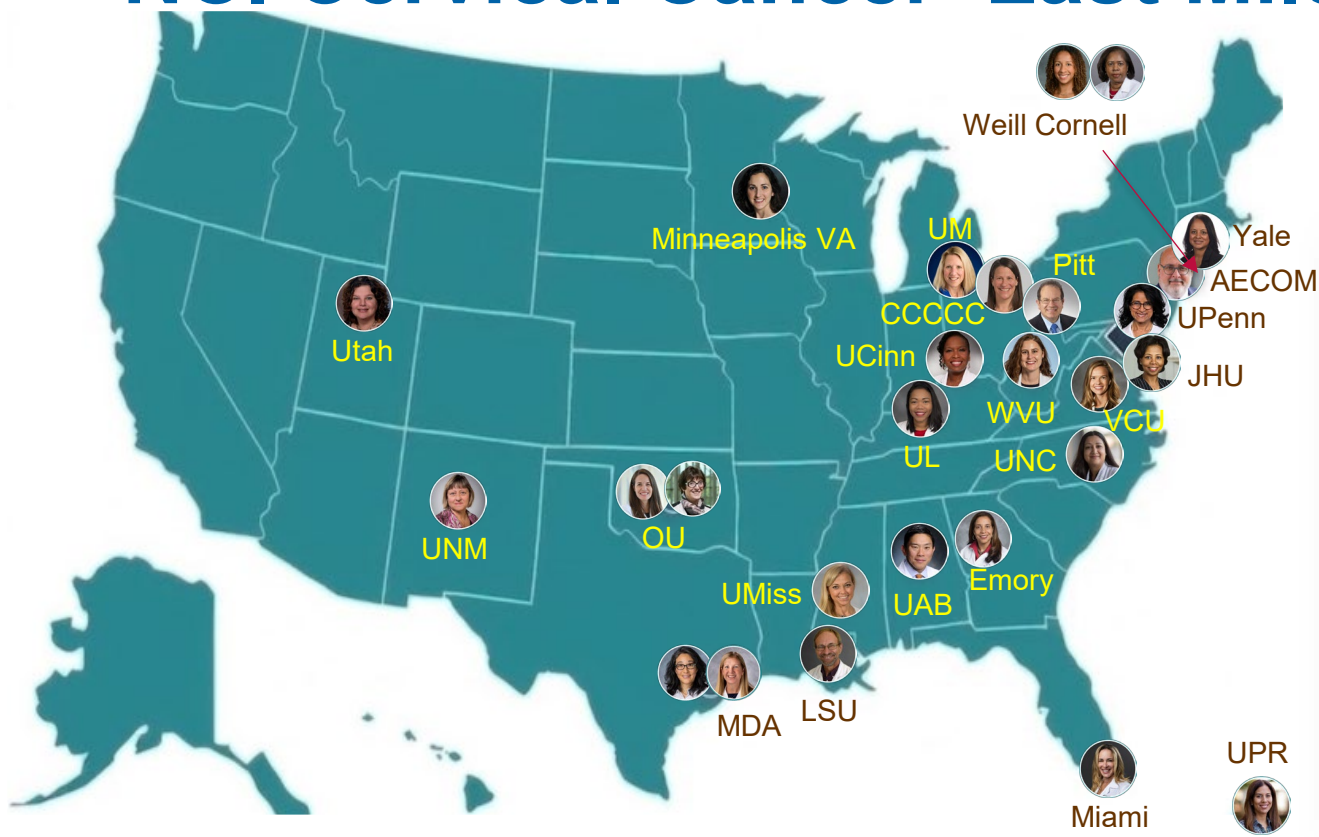


Evaluation	Sensitivity	Specificity	Colposcopy Referral
Pap cytology (188 CIN3+)	85.8% (81.2-90.5)	41.9% (40.1-43.7)	1,860 (60.1%)
Manual DS (197 CIN3+)	90.0% (86.0-93.9)	52.6% (50.8-54.5)	1,536 (50.4%)
Automated DS (≥2 cells) (192 CIN3+)	88.1% (82.5-91.7)	61.5% (59.7-63.3)	1,298 (41.9%)

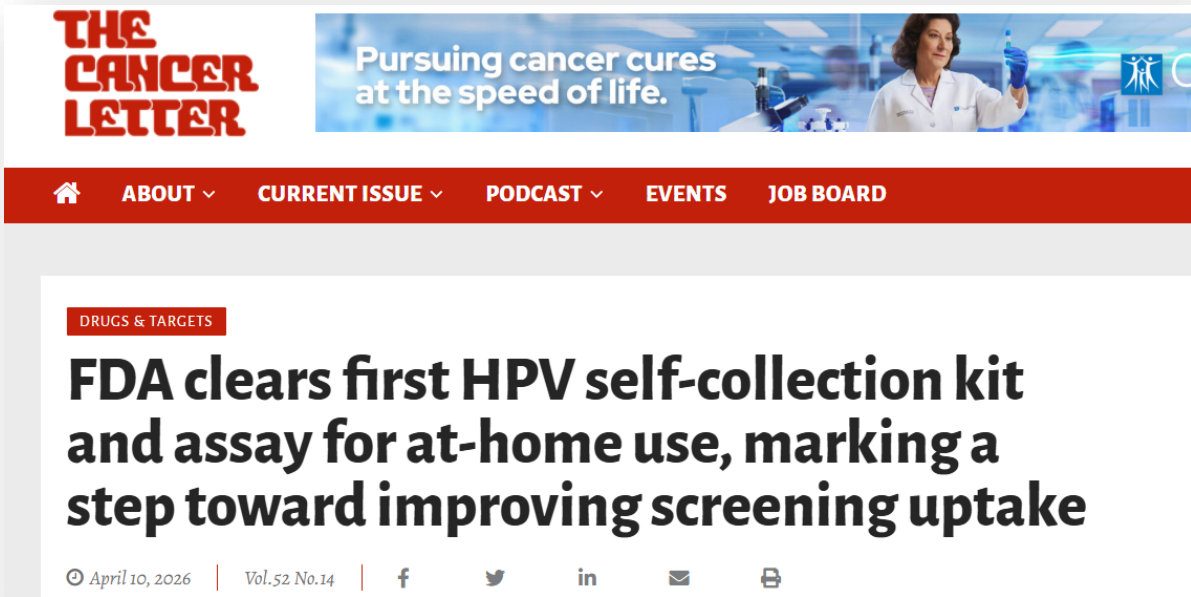
Courtesy of
Dr. Nicolas Wentzensen,
DCEG/NCI

Wentzensen *et al.*, JCO, 2026 (PMID: 41701950)
Wentzensen *et al.*, JNCI, 2021 (PMID: 32584382)
Lahrman NEJM AI in press

NCI Cervical Cancer ‘Last Mile’ Initiative



Total n=2124 participants enrolled (Sept 2024 - April 2026) across 4 SHIP Trial sub-protocols at 24 Clinical Sites across 21 US States and Puerto Rico

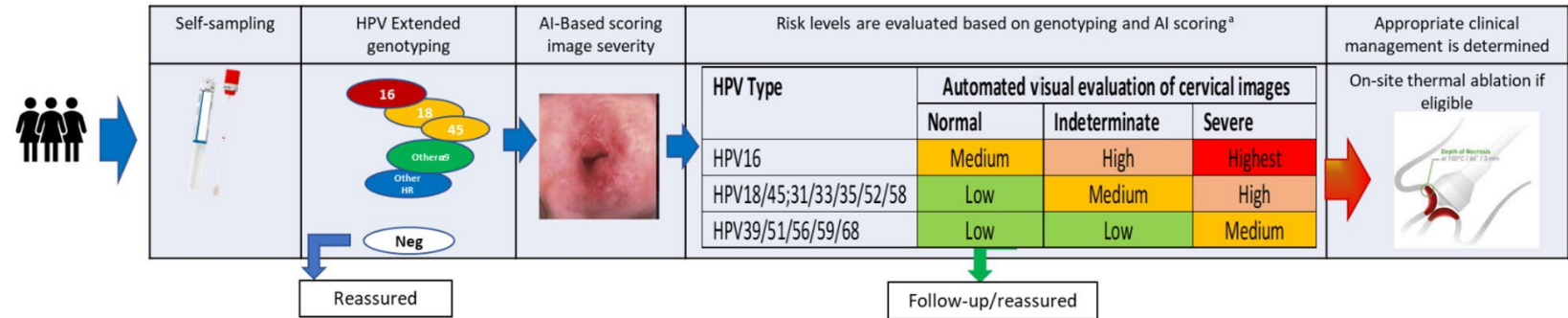


Courtesy of
Dr. Vikrant
Sahasrabudde,
DCP/NCI

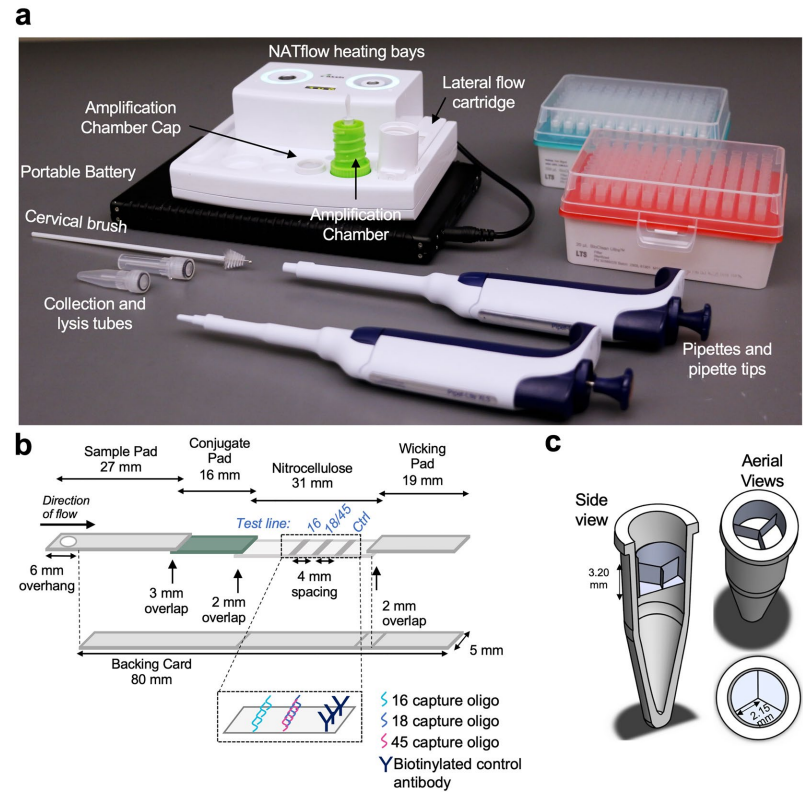


SHIP Sub-protocol and Industry Partner	HPV assay	NCT number	Status of enrollment and FDA review
S01: Waters (BD)	Onclarity HPV	NCT06498661	Enrollment complete (n=554), FDA approval granted
S02: Roche	Cobas HPV	NCT06611553	Enrollment complete (n=529), FDA review underway
S03: Roche	Cobas HPV	NCT06611553	Enrollment complete (n=533), FDA review underway
S04: Abbott	Alinity m HR-HPV	NCT07281430	Enrollment complete (n=508), FDA review underway
S05: Roche	Cobas HPV	In development	

Low-Cost HPV Testing-Based Cervical Screening for LMICs



de Sanjosé *et al.*, *eLife*, 2024
(PMID: 38224340)
Befano *et al.*, *JNCI*, 2025
(PMID: 40104876)



Chang *et al.*, *Sci Rep*, 2023
(PMID: 37989845)
Barra *et al.*, *Nat Commun*, 2025
(PMID: 40774968)

Agenda

1. *Background/History*
2. *HPV Vaccination*
3. *HPV Testing-Based Cervical Cancer Screening*
4. *Self-Collection for HPV Testing*
5. *Anal Cancer*
6. *Oropharyngeal Cancer*
7. *Remaining Gaps/Opportunities*

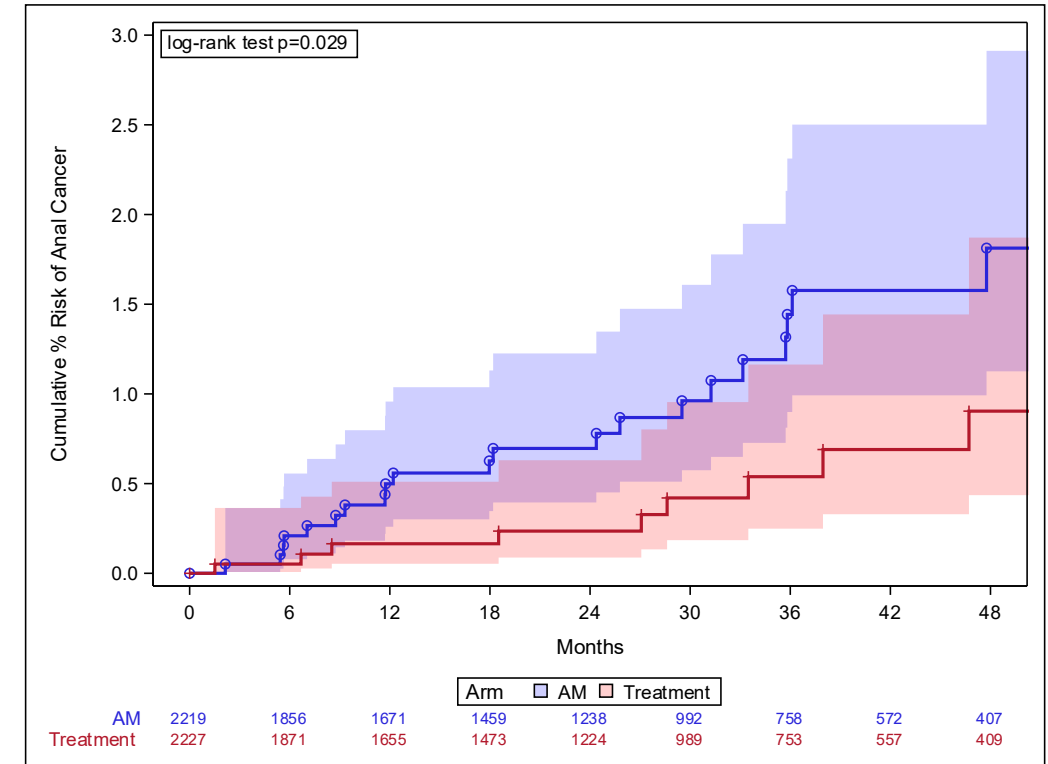
Key Findings from the Anal Cancer HSIL Outcomes Research (ANCHOR) Study

- Anal HSIL was very common in 10,723 screened men (53%) and women (47%) living with HIV
- Anal cancer can be prevented by treating anal HSIL with a 57% reduction compared with no treatment (95% CI, 6-80; P = 0.03 by log-rank test)
- Developed and validated the ANCHOR Health-Related Symptom Index (A-HRSI), health-related quality of life symptom index for persons diagnosed with and either treated or monitored for anal HSIL
- Treatment of HSIL (office-based targeted lesion ablation) is safe, well tolerated and, in an analysis including ANCHOR data, cost-effective in the U.S. setting
- Based on ANCHOR findings, HHS published guidelines recommending screening for and treatment of anal HSIL as standard of care in PWH



the
ANCHOR
study

The ANCHOR Investigators Group
Protocol A01 of the AIDS Malignancy Consortium
UM1CA121947



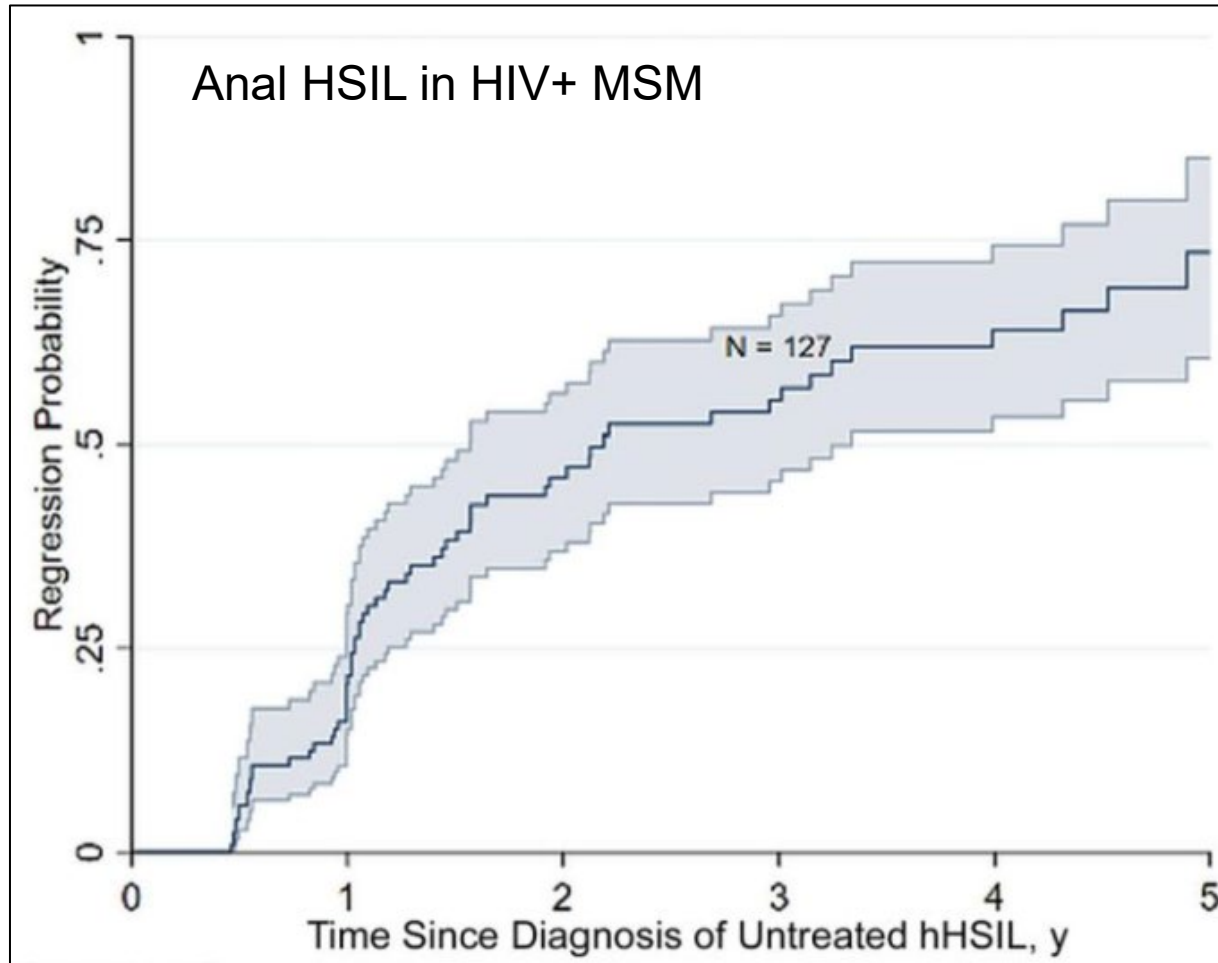
Palefsky *et al.*, *NEJM*, 2022 (PMID: 35704479)

Deshmukh *et al.*, *Ann Intern Med*, 2025 (PMID: 40523287)

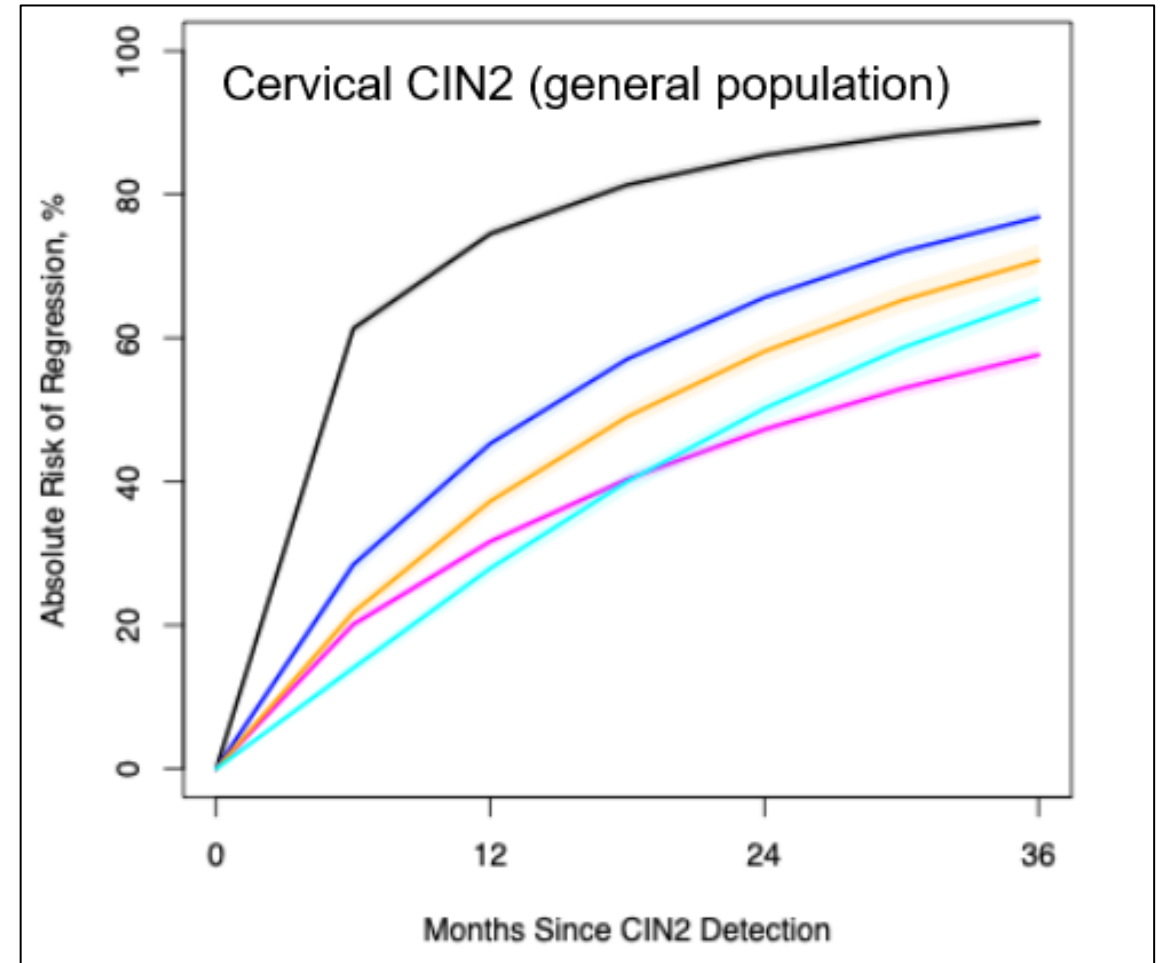
Atkinson *et al.* *JCO Oncol Pract*, 2025 (PMID: 40048673)

<https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/human>

“Precancer” Regression & Overtreatment



Etienney *et al.*, *Clin Infect Dis*, 2026



Cheung *et al.*, *JNCI*, in Press

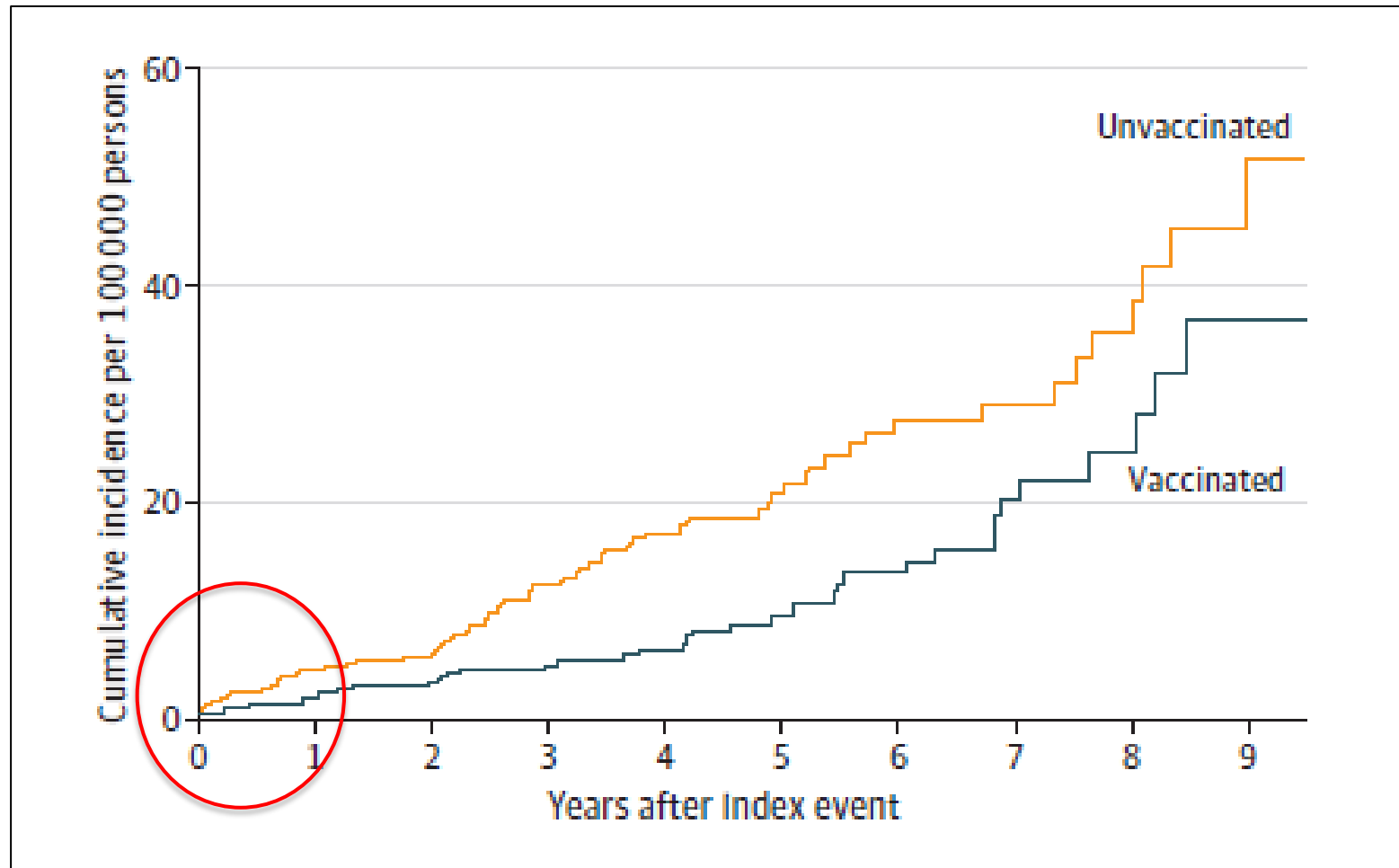
Agenda

1. *Background/History*
2. *HPV Vaccination*
3. *HPV Testing-Based Cervical Cancer Screening*
4. *Anal Cancer*
5. *Oropharyngeal Cancer*
6. *Remaining Gaps/Opportunities*

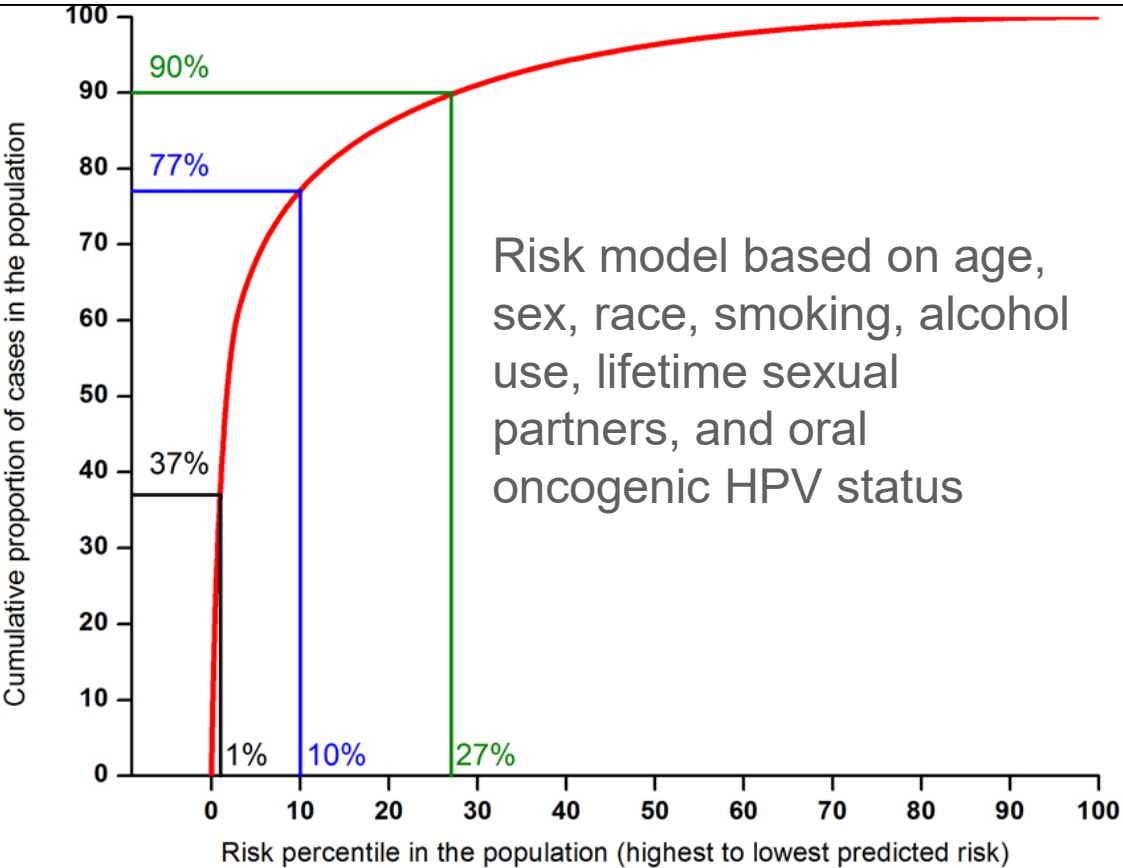
Maura L. Gillison (1965-2026)



Evidence of HPV Vaccination Preventing Oropharyngeal Cancer in Males? Caveat Emptor!



Precision, Early Detection of Oropharyngeal Cancer (?)



Risk decile	10	9	8	7	6	5	4	3	2	1
Decile-specific % cancers in population	77.1	9.0	5.0	3.2	2.1	1.5	1.0	0.6	0.4	0.2
Decile-specific absolute risk (per 100,000)	63.0	7.3	4.0	2.6	1.8	1.2	0.8	0.5	0.3	0.1
Cumulative population proportion, %	10	20	30	40	50	60	70	80	90	100
Cumulative NNR* for 1 cancer case	1,586	2,841	4,041	5,212	6,349	7,501	8,677	9,843	11,026	12,195

*NNR=Number needed to recruit

	Whole Pop	10% Highest Risk	1% Highest Risk
NNR=	12,195	1,586	323
% of Cancers=	100%	77%	37%
Se/Sp	Cancers among Screen+		
90%/99%	1 in 136	1 in 19	1 in 5
90%/98%	1 in 273	1 in 36	1 in 8
70%/99%	1 in 175	1 in 24	1 in 6
70%/98%	1 in 349	1 in 46	1 in 10
83%/95%* (HPV E6 Serology)	1 in 735	1 in 96	1 in 20

Tota *et al.*, *Cancer*, 2019 (PMID: 31454434)

*Hibbert *et al.*, *Cancers (Basel)*, 2021 (PMID: 34208476)²⁵

Agenda

1. *Background/History*
2. *HPV Vaccination*
3. *HPV Testing-Based Cervical Cancer Screening*
4. *Anal Cancer*
5. *Oropharyngeal Cancer*
6. *Remaining Gaps/Opportunities*

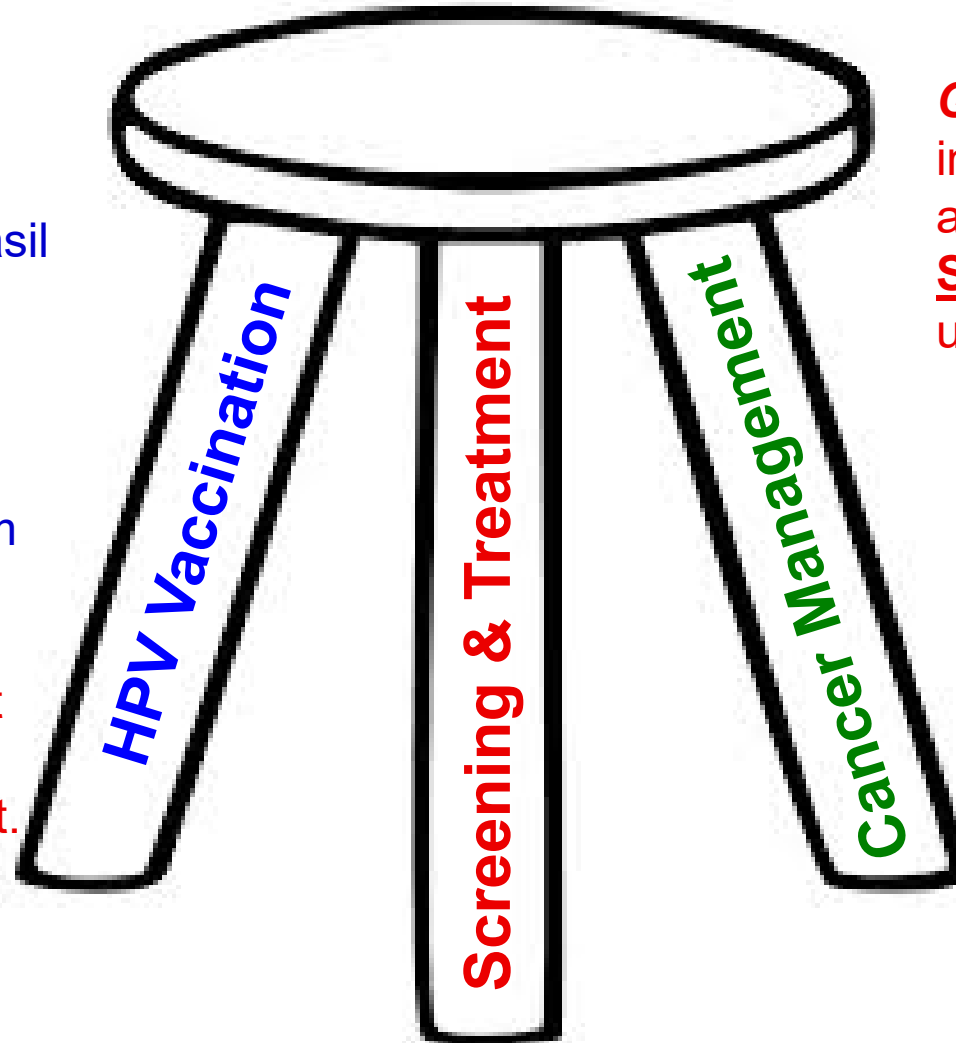
WHO Cervical Cancer Elimination as a Public Health Problem: Three-Legged Stool of Global Cervical Cancer Control

Gap: Availability of subsidized nonavalent HPV vaccine for LMICs

Solution: Biosimilars and/or Gardasil 9 made available through GAVI. Expand access to subsidized HPV vaccines to lower-middle-income countries and upper-lower-income countries (that have graduated from GAVI)

Gap: Availability of low-cost, robust HPV testing

Solution: Tests are in development. Alternatively/Complementary---develop a GAVI-like organization/procurement system for IVDs.



Gap: Can we identify those HPV+ individuals at the highest risk without a pelvic exam?

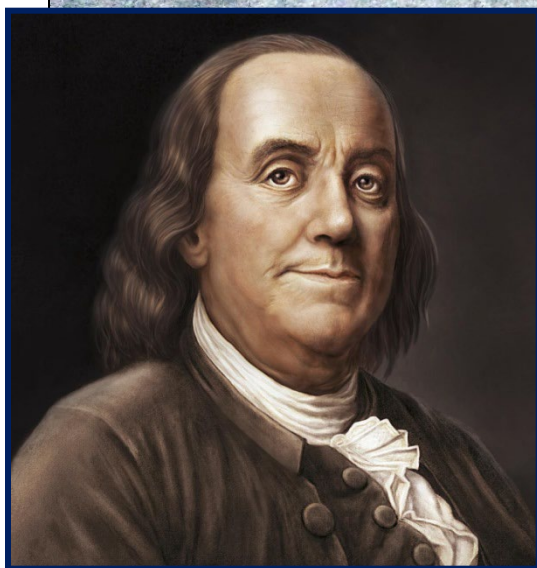
Solution: Molecular triage of HPV+ using the self-collected specimen.

Gap: Non-provider methods of treating cervical precancer/HPV

Solution: HPV Therapeutic Vaccines; HPV Anti-Virals

Gap: If you are scaling up screening, you will cause a spike of (screen-detected) cancers. Who will treat/take care of them?

Solution: Training of Gynecologic Oncologists!



Benjamin Franklin

Signatory, *Declaration of Independence*
Founder, University of Pennsylvania

Courtesy of
Dr. Robert Vonderheide, U Penn 28