Cancer Research and Saving Lives: The Example of HPV-associated Cancer

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CPRIT innovations in Cancer Research Conference

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Disclosures

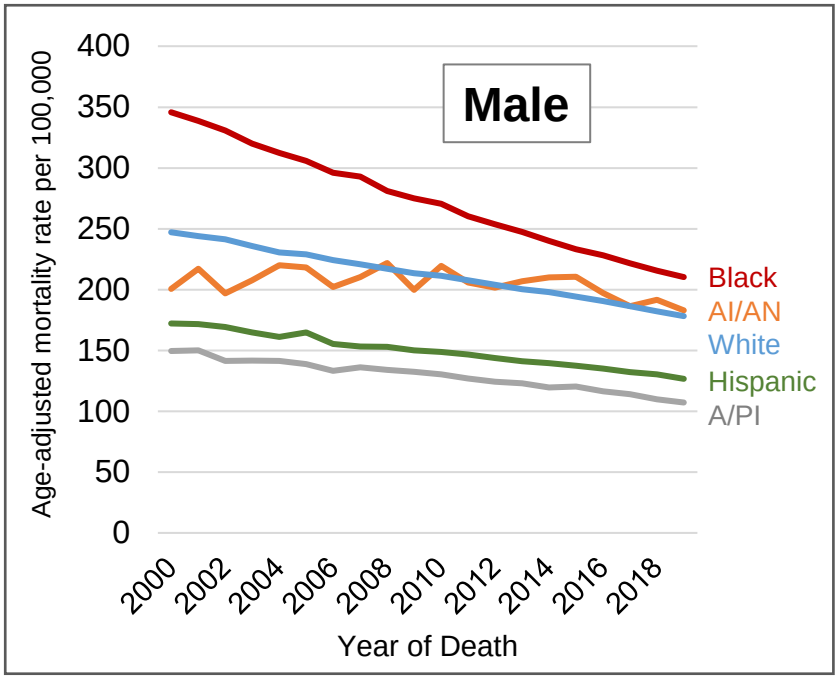
- National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. I am an inventor.
- NIH has licensed L1 VLP technology to Merck and GlaxoSmithKline, the two companies with FDA-approved versions of the vaccine.
- **I will mention two possible non-FDA approved interventions: 1) fewer HPV vaccine doses, 2) A "see-and-treat" approach for cervical cancer screening**
- Licensees of other NIH technologies of which I am an inventor: GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax.

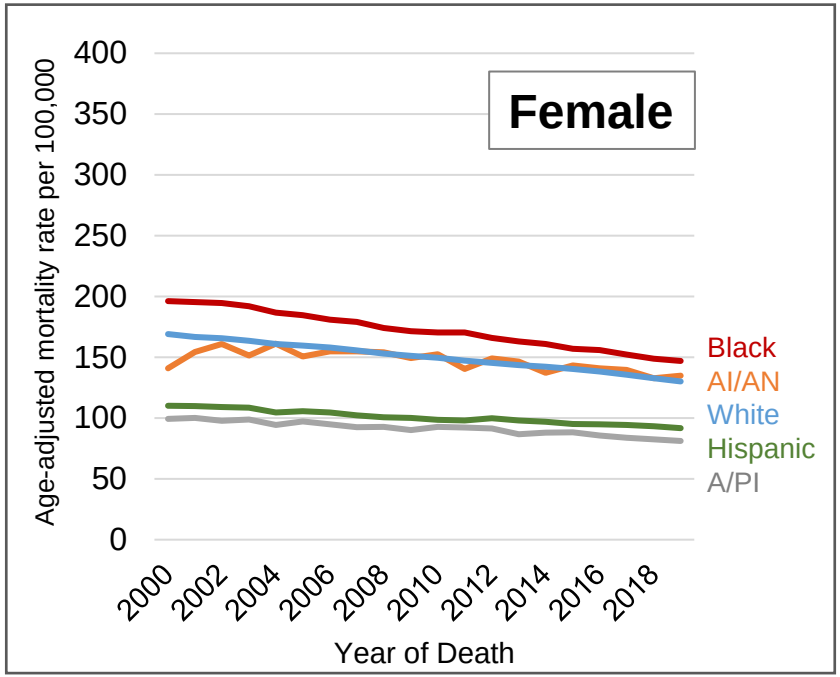
Today's Talk

- **Evidence of Progress… but much remains to be done**
  - The "reignited" Cancer Moonshot
  - Persistent poverty
  - Lung cancer
  - Cervical cancer and other HPV-associated cancers

Evidence of progress
…but much remains to be done

Cancer Mortality Trends by Race/Ethnicity (2000-19)



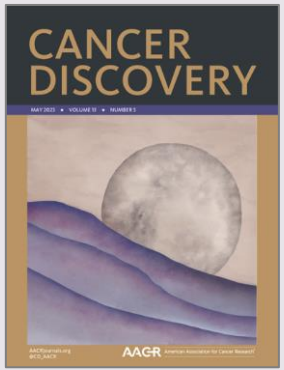


Source: NCI Surveillance, Epidemiology, and End Results Program (SEER), seer.cancer.gov

For more, see Lawrence, et al: Trends in Cancer Mortality Among Black Individuals in the U.S. From 1999 to 2019 – *JAMA Oncology*, May 19, 2022

Goals of the reignited Moonshot: NCI jump-started it in FY23 with funds from initial Moonshot:

- Reduce U.S. cancer death rate by 50% in the next 25 years (hard)
- Overcome cancer disparities (harder)
- End cancer as we know it, for all (hardest)



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Opportunities for Achieving the Cancer Moonshot Goal of a 50% Reduction in Cancer Mortality by 2047

Meredith S. Shiels, Stanley Lipkowitz, Nicole G. Campos, Mark Schiffman, John T. Schiller, Neal D. Freedman, Amy Berrington de González

Accomplishing the Goals of the Cancer Moonshot

&

- Need wider dissemination of current standards of care
- Ensure everyone benefits
- Requires implementation research

- Need more research advances that change standard of care
- Must include poor prognosis cancers, rare cancers, and childhood cancers

New Persistent Poverty Initiative – Underway

The first major program to address the structural and institutional factors of persistent poverty associated with higher cancer mortality rates

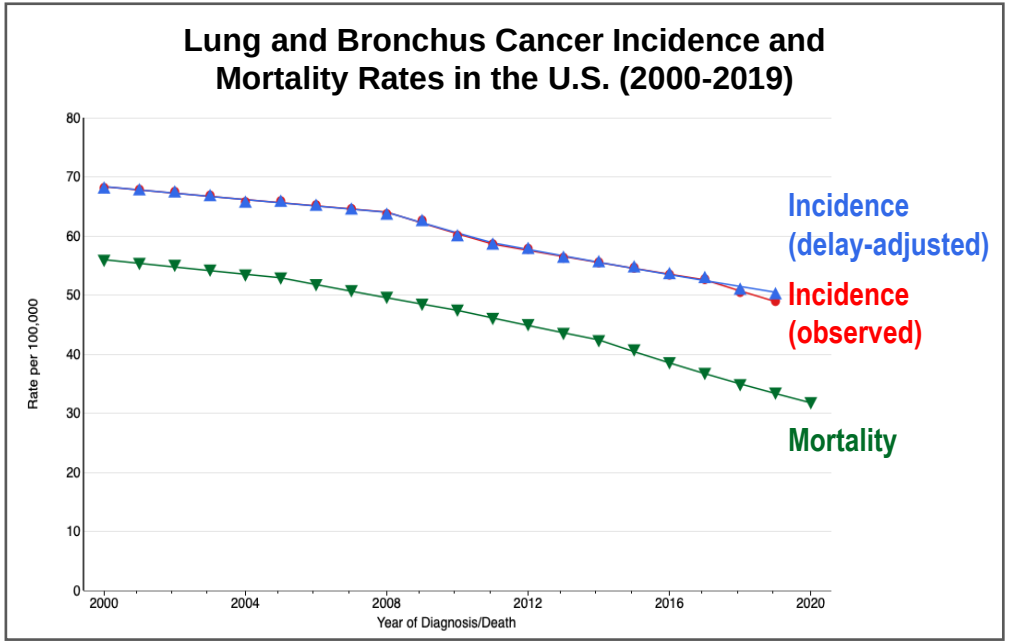
- $50 million total funding to 5 centers
- Goals: To improve cancer outcomes in low-income areas by:
  - Building research capacity
  - Fostering cancer prevention research
  - Promoting the implementation of community-based programs

Funded Centers:

- University of Texas MD Anderson Cancer Center, Houston
- University of Alabama at Birmingham,
- Stanford University, Palo Alto
- Weill Cornell Medicine and Columbia University, New York City
- Huntsman Cancer Institute at the University of Utah, Salt Lake City

Lung cancer

Lung Cancer Incidence and Mortality in the U.S.



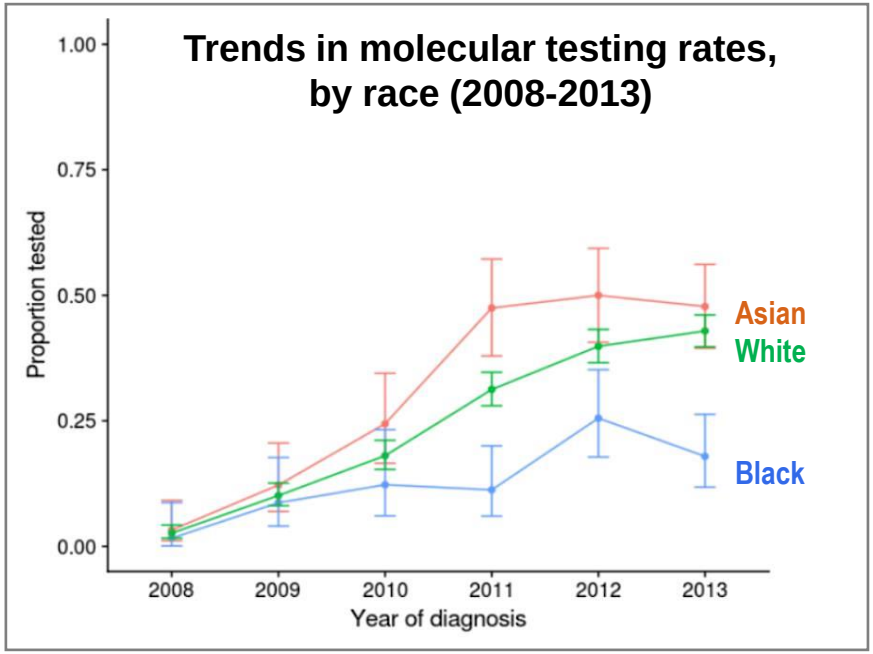
Change in:	2015	2016	2017	2018	2019
Incidence rates	-2.4	-2.4	-2.4	-2.4	-2.2
Mortality rates	-4.6	-4.6	-4.6	-4.6	-4.6

Improvements in treatment lead to mortality rates decreasing faster than incidence rates

Data: seer.cancer.gov

For more: Howlader et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. *New England Journal of Medicine.* August 13, 2020.

Black patients with lung cancer have received molecular testing less frequently than White or Asian patients



- 5,556 patients
- 26% had molecular testing*

Molecular Testing Rates (2008-2013)	
Asian/other	33%
White	26%
Black patients	14%

**Testing within 60 days of diagnosis of stage IV lung adenocarcinoma*

Equitable precision medicine requires concerted implementation efforts.

Kehl et al. Race, Poverty, and Initial Implementation of Precision Medicine for Lung Cancer. *Journal of the National Cancer Institute.* 2019

Under-enrollment of Black patients to immunotherapy trials

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Population with *EGFR* and *ALK* Wild-Type Tumors).*

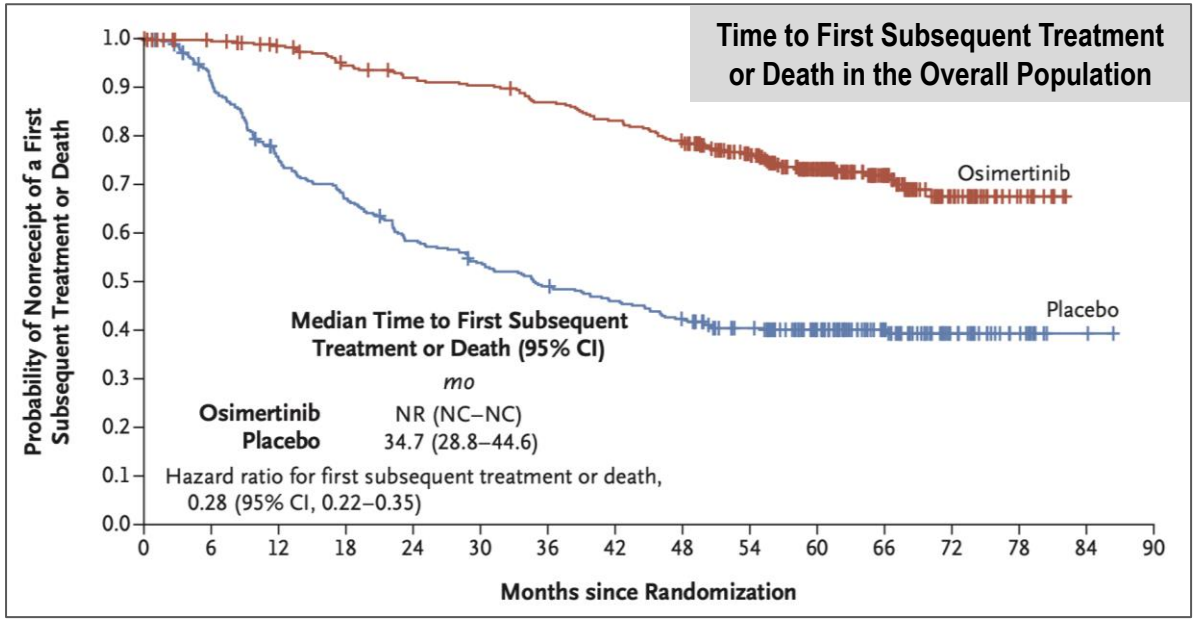
Characteristic	Any PD-L1 Expression		High or Intermediate PD-L1 Expression		High PD-L1 Expression	
	Atezolizumab (N=277)	Chemotherapy (N=277)	Atezolizumab (N=166)	Chemotherapy (N=162)	Atezolizumab (N=107)	Chemotherapy (N=98)
Median age (range) — yr	64 (30–81)	65 (30–87)	63 (33–81)	65 (33–87)	63 (33–79)	66 (33–87)
Male sex — no. (%)	196 (70.8)	193 (69.7)	122 (73.5)	107 (66.0)	79 (73.8)	64 (65.3)
Race — no. (%)†						
White	227 (81.9)	240 (86.6)	133 (80.1)	139 (85.8)	87 (81.3)	82 (83.7)
Asian	45 (16.2)	30 (10.8)	31 (18.7)	20 (12.3)	20 (18.7)	15 (15.3)
Black	2 (0.7)	2 (0.7)	1 (0.6)	0	0	0
Unknown	2 (0.7)	5 (1.8)	1 (0.6)	3 (1.9)	0	1 (1.0)

Herbst et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. *New England Journal of Medicine*, 2020.

Significant Survival Benefit with Adjuvant Therapy Osimertinib in Resected EGFR-Mutated NSCLC

Adjuvant osimertinib provided a **significant overall survival benefit** among patients with completely resected, *EGFR*-mutated, stage IB to IIIA NSCLC.

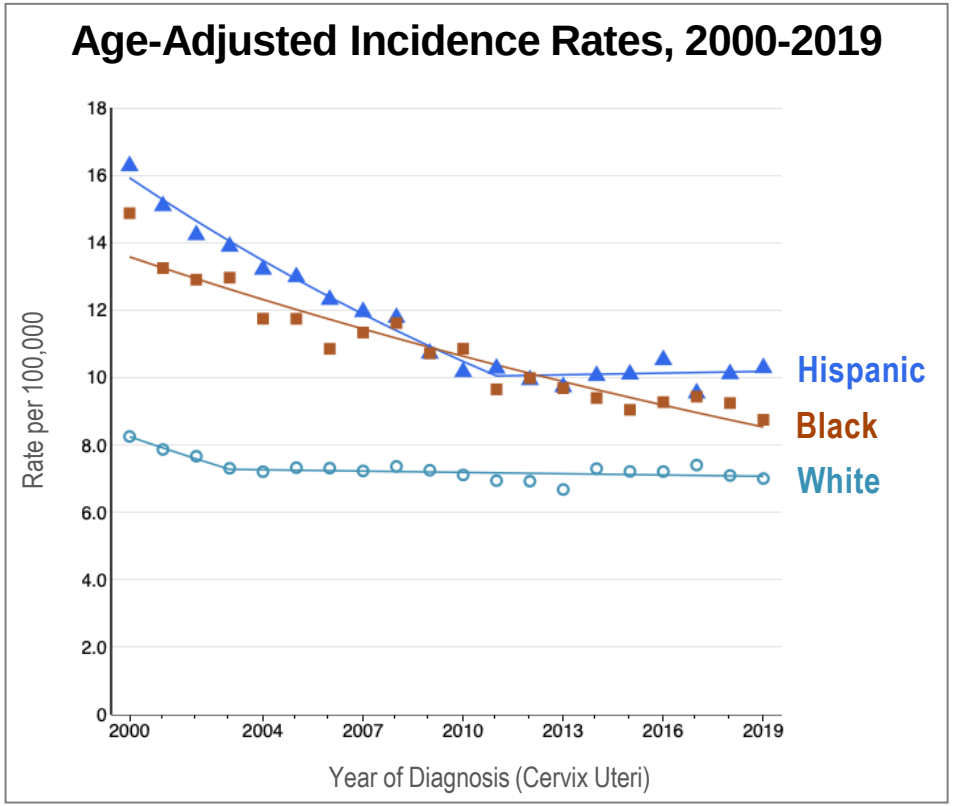
Source: Tsuboi, et al. *NEJM*. June 4, 2023.



EGFR: epidermal growth factor receptor
NSCLC: non–small-cell lung cancer

Cervical cancer: Epidemiology, HPV vaccination, and cervical cancer screening

U.S. Cervical Cancer Incidence and Mortality



Est. new cases/deaths in 2022:

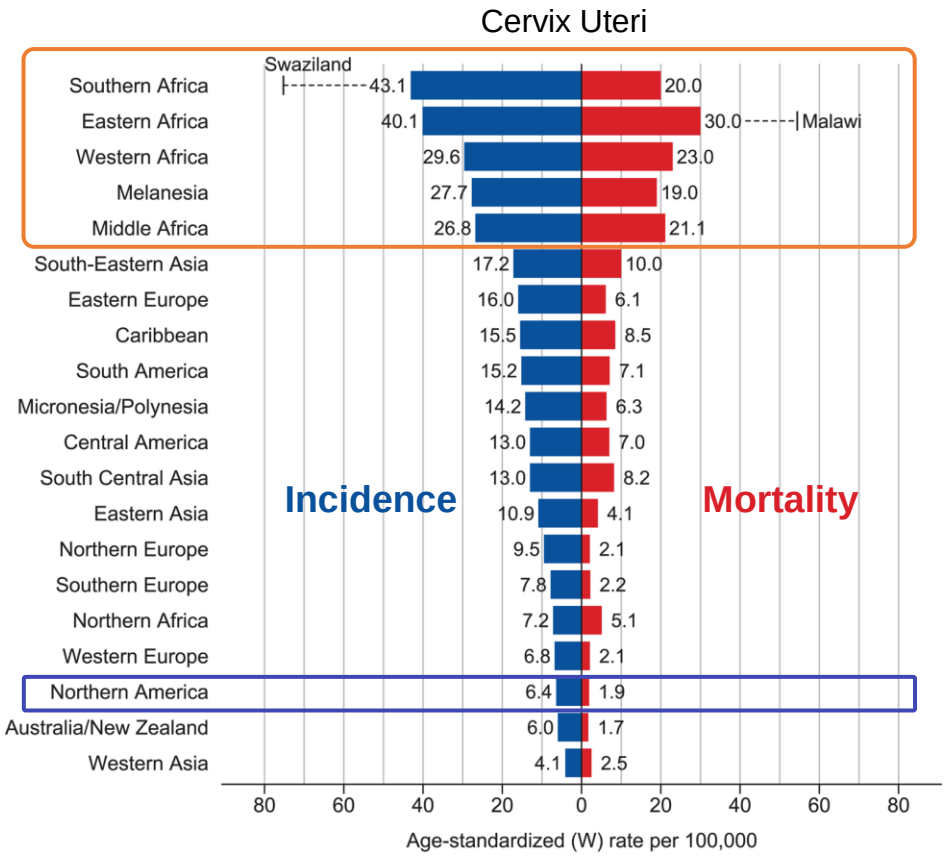
- **New cases: 14,100**
- **Deaths: 4,280**

Current Mortality Rates (2020) per 100,000	
Black women	3.2
Hispanic	2.5
White	2.1
American Indian / Alaska Native	2.1
Asian / Pacific Islander	1.7

Source: seer.cancer.gov

Global Disparities in Cervical Cancer Cases & Deaths:

Many-fold higher in Africa than in U.S.



Low- and middle-income countries:

- ~90% of cervical cancer cases and deaths (projected to increase by 2% each year)
- **Africa vs. North America: >5-fold higher incidence rates, >8-fold higher mortality rates**
- Cervical cancer represents 90% of HPV-associated cancer

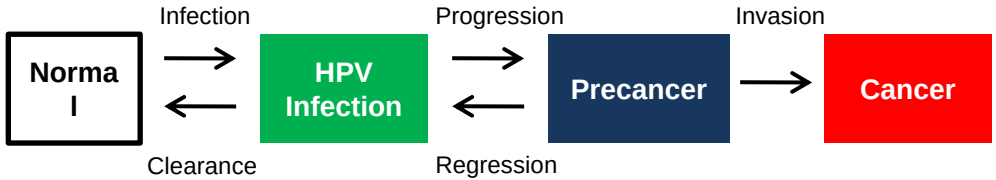
Bray et al, Global cancer statistics 2018, Cancer J Clin 2018.

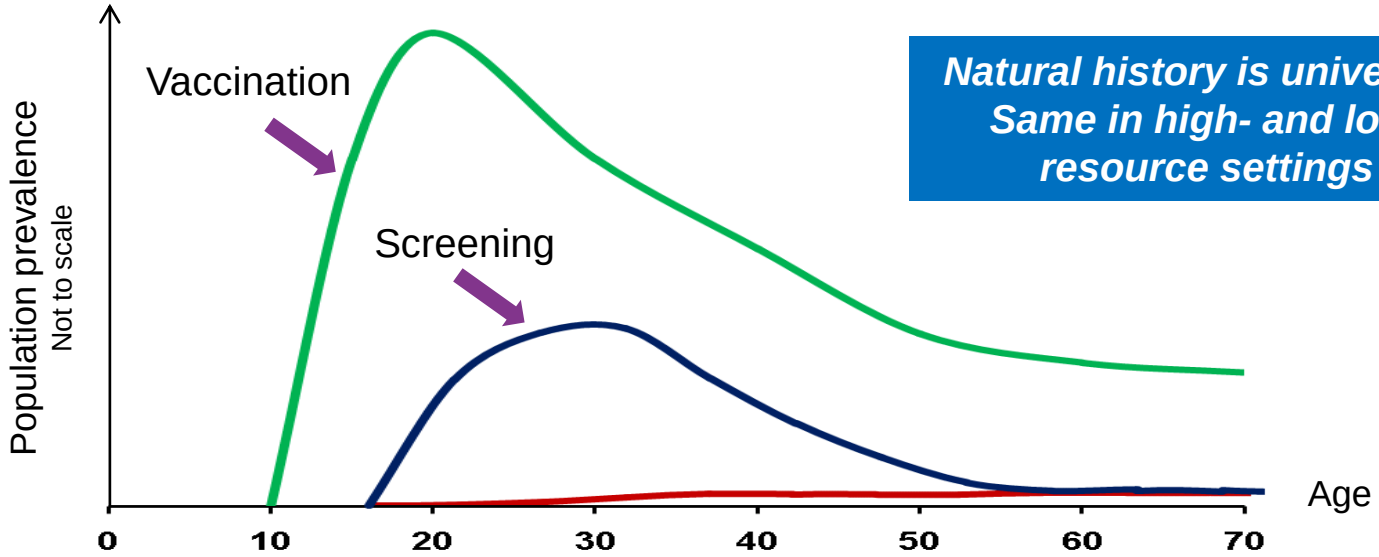
Interventions against cervical cancer

Opportunities at each step of the process

HPV vaccination	***Primary prevention***
Cervical cancer screening	***Secondary prevention***
Treatment of invasive cervical cancer	***To save more lives***

Cervical cancer natural history and prevention: Intervene before cancer develops



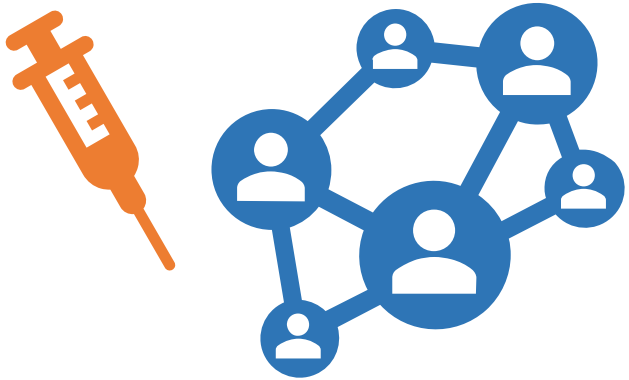


Natural history is universal: Same in high- and low-resource settings

Source: Wentzensen and Schiffman. *The Lancet Public Health*. 2017

Goals of HPV Vaccination

- Directly reduce risk of infection and disease in vaccinees
- Indirectly reduce risk by reducing prevalence of “HPV vaccine types” in general population (herd protection)

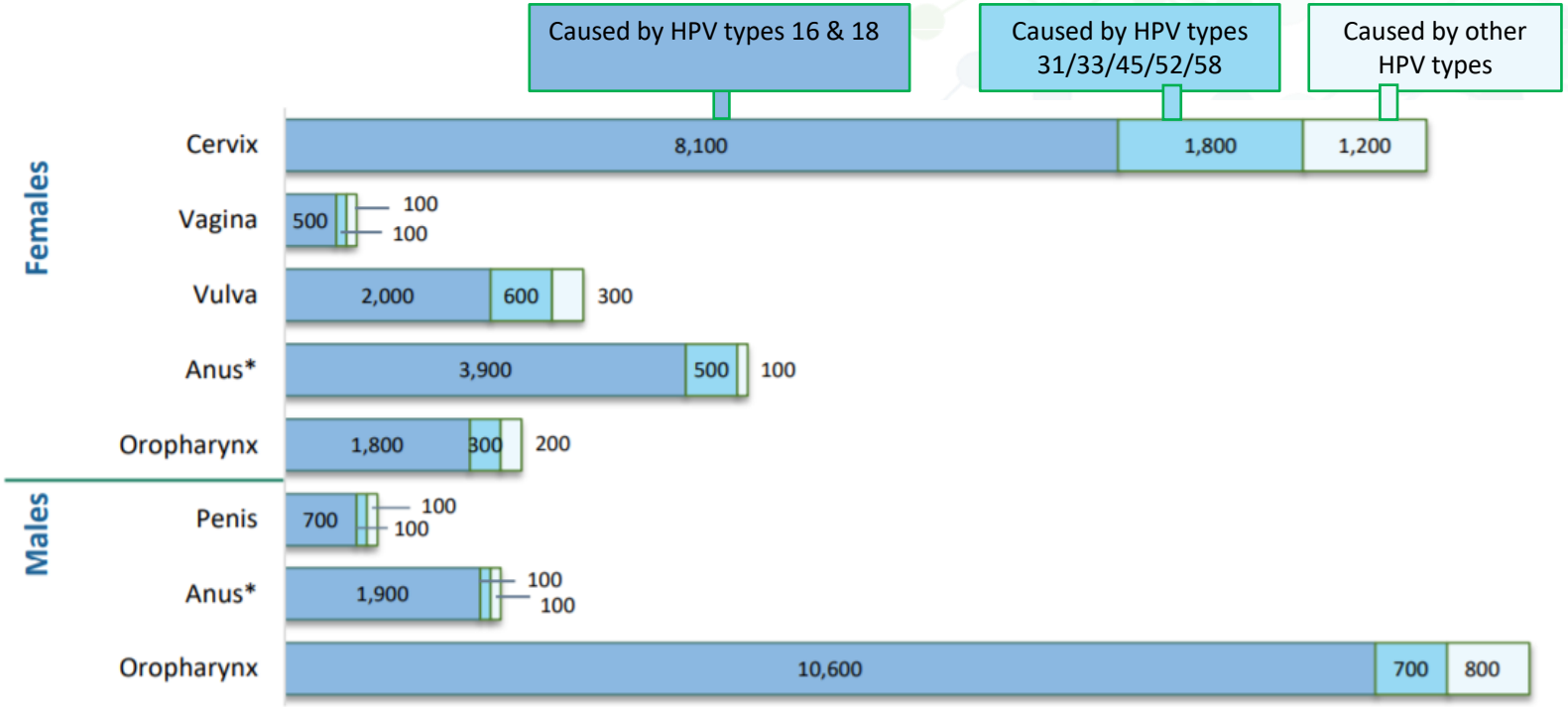


Disease prevention goals of HPV vaccination:
Less developed countries vs. more developed countries

A question of who gets HPV-associated cancer, priorities, and resources

Less developed countries	Mainly to protect against cervical cancer (>90% HPV-associated cancer in women) • Female vaccination is the most cost-effective
More developed countries	Protect both males and females against a range of HPV-associated cancer (~40% HPV-associated cancer in men) • Female vaccination with high uptake: most cost-effective, but adding male vaccination can confer even greater protection for vaccinees than can herd immunity alone • Male vaccination: the fastest way to reduce HPV prevalence in men who have sex with men

HPV causes a range of cancers, ~36,000/year (U.S.)



Centers for Disease Control and Prevention. Cancers Associated with Human Papillomavirus, United States—2014–2018 USCS Data Brief, no. 26. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2021.

Some important clinical results against HPV types targeted by the vaccine

Vaccine has very high efficacy (>95%) and long duration of protection (>10 years)

Vaccine confers sterilizing immunity

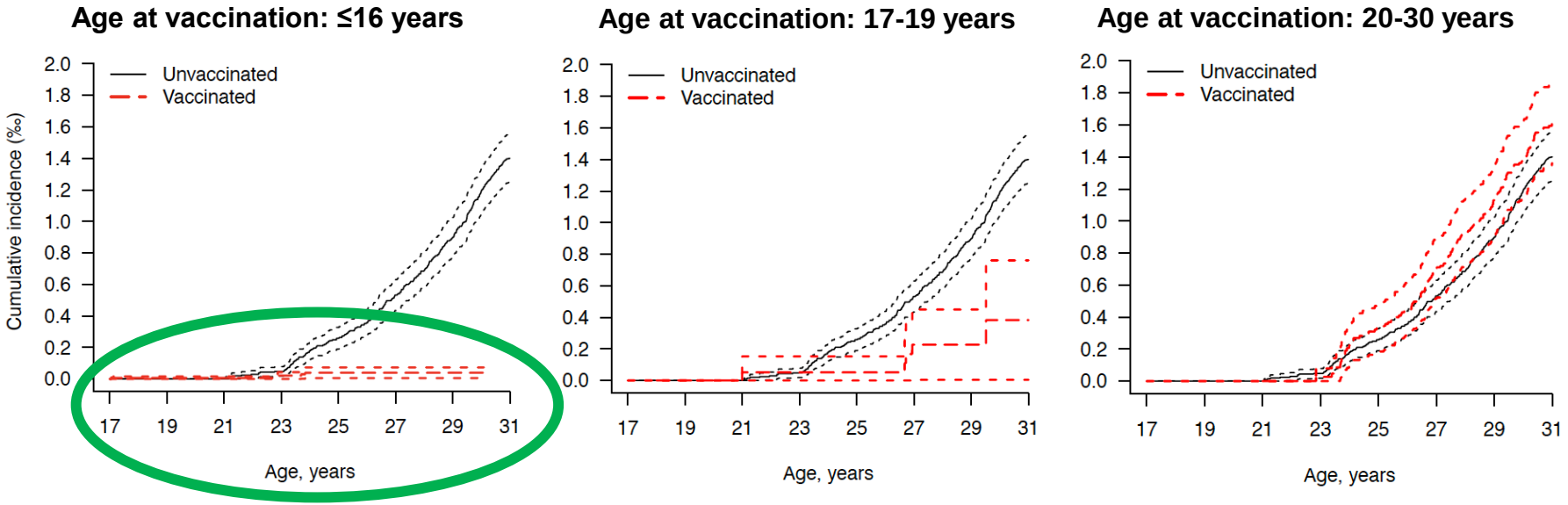
Prevents infection in most vaccinees

Vaccine induces herd immunity even with sub-optimal vaccine uptake

Vaccine does not treat established infection

Schiller & Lowy, Vaccine, 2018; *Hildesheim et al, American Journal of Obstetrics and Gynecology, 2016; Rosenblum et al, CDC Morbidity and Mortality Weekly Report (MMWR), 2021*

Cervical cancer incidence decreased ~90% in Danish women vaccinated at 16 years old or younger



Kjaer, et al. Real world effectiveness of human papillomavirus vaccination against cervical cancer. *Journal of the National Cancer Institute*, 2021.

HPV vaccine: U.S. Advisory Committee on Immunization Practices (ACIP) Recommendations

Age group	ACIP Recommendation
9-14 years	Routine vaccination, 2-doses
15-26 years	Routine “catch-up” vaccination, 3-doses
27-45 years	Shared decision, 3-doses*

Adolescents are the main target group for the vaccine because **HPV infection occurs commonly soon after sexual debut**.

For more, see:

- *Ho et al, NEJM, 338:423-8, 1998*
- *Winer et al, Cancer Epidemiol Biomarkers Prev 20:699-707, 2011*

**www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html*

HPV Vaccine Uptake in the U.S.

National vaccination coverage among adolescents 13-17 years

Increases in HPV vaccine coverage (2019 to 2022):

	2019	2020	2021	2022
≥1 dose* of HPV vaccine	72%	75%	77%	76%
Adolescents who were up to date with HPV vaccination	54%	59%	62%	63%

Urban areas have higher vaccine uptake than rural areas.

Includes receipt of **any HPV vaccine; does not distinguish between 9-valent, quadrivalent, or bivalent vaccines.*

Source: Pingali et al. CDC Morbidity and Mortality Weekly Report (MMWR). September 2, 2022 and August 25, 2023.

HPV vaccination rates for adolescents 13-17 years

Uptake is higher in metropolitan/urban areas than rural areas

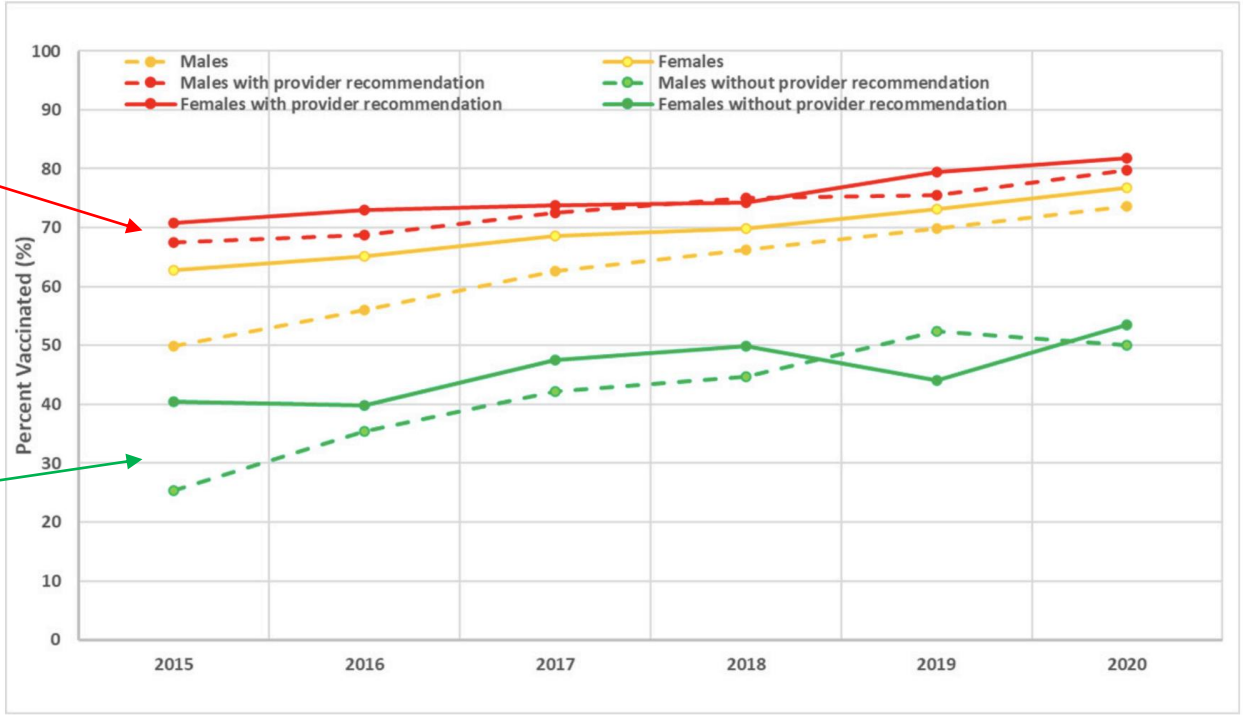
	HPV vaccine ≥ 1 dose	Cervical cancer (2016-2020)	
		Incidence (per 100,000)	Mortality (per 100,000)
United States	76%	7.5	2.2
Texas (state)	70%	9.4	2.8
Houston	81%		
Rest of Texas	69%		

Sources: statecancerprofiles.cancer.gov; Pingali et al. CDC Morbidity and Mortality Weekly Report (MMWR). August 25, 2023.

Health care provider recommendation improves HPV vaccine uptake

Health care provider recommendation for HPV vaccination

No provider recommendation

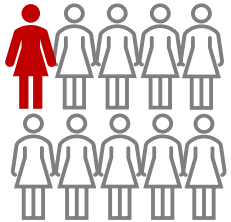


Source: Lu et al, Human papillomavirus vaccination trends among adolescents: 2015 to 2020. Pediatrics, 2022.

Developing evidence for one-dose HPV vaccine* efficacy & durability

*Not yet FDA-approved

To Increase Worldwide HPV Vaccine Uptake



Currently, only ~**10%** of adolescent girls in LMICs are vaccinated against HPV

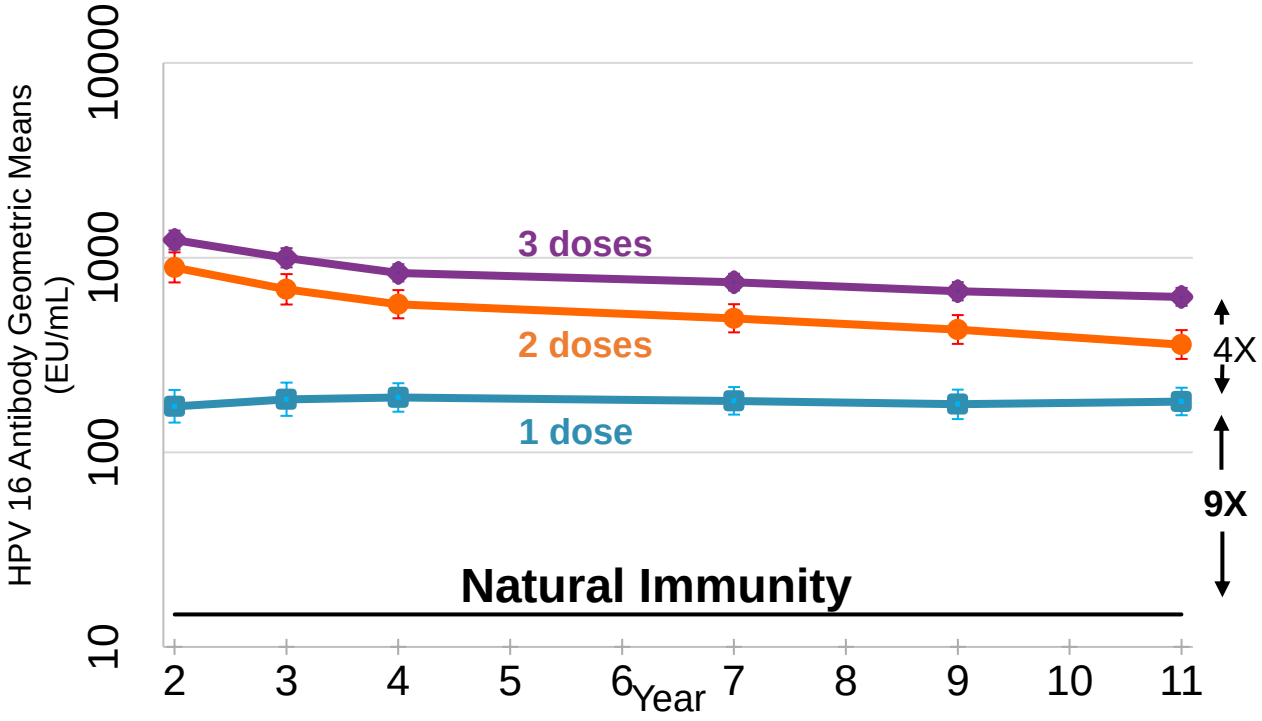
WHO Strategic Advisory Group of Experts on Immunization (SAGE) **recommends one or two doses** for 9-20 year-old women (2022)

Compile more evidence that **one dose** of HPV vaccine can induce long-term protection

Single dose HPV vaccination

- Less expensive than two doses
- Logistically easier than two doses
- Not yet fully standard of care

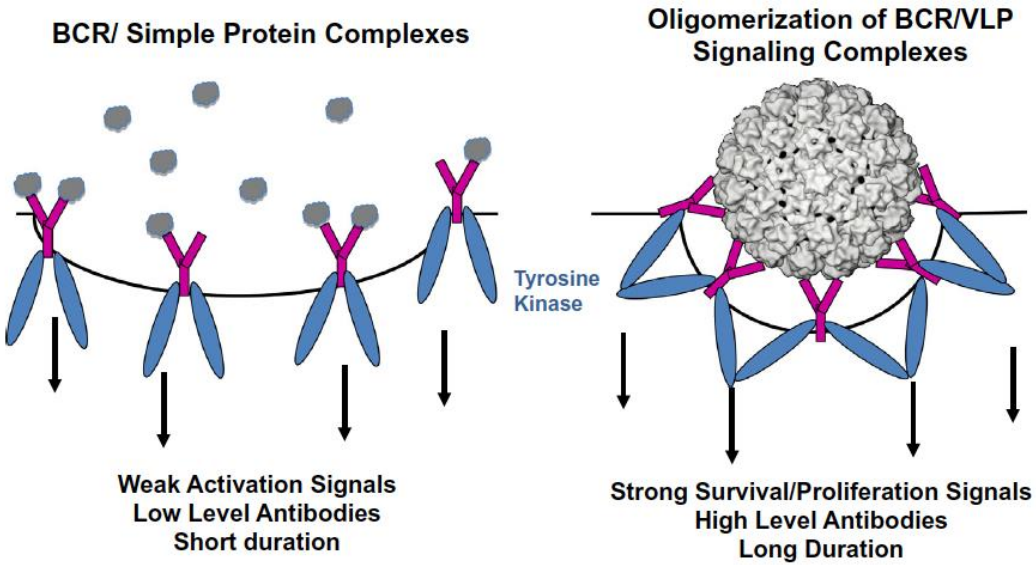
Costa Rica HPV Vaccine Trial: Stable HPV16 serum antibodies 11 years after one dose of bivalent vaccine (post-hoc analysis)



- At 11 years, 100% of one dose recipients remain seropositive with efficacy as high as 2 or 3 doses
  - Similar data at 15 years (unpublished)
- These results are unprecedented for a sub-unit vaccine
- Similar results seen in IARC trial with Gardasil

Kreimer et al, JNCI, 2020

Probable mechanism of durable immune response: Repetitive structure of virus-like particle (VLP) vaccine



B cell recognition of dense repetitive protein arrays promotes induction of exceptionally durable antibody responses

Schiller & Lowy. Explanations for the high potency of HPV prophylactic vaccines. *Vaccine*. 2018

Costa Rica “One Dose” HPV vaccine trial:

Compare efficacy of one dose vs. two doses of two FDA-approved vaccines (Gardasil 9 & Cervarix)

Aimée R. Kreimer, Ph.D.
U.S. National Cancer Institute

Rolando Herrero, M.D.
Costa Rica

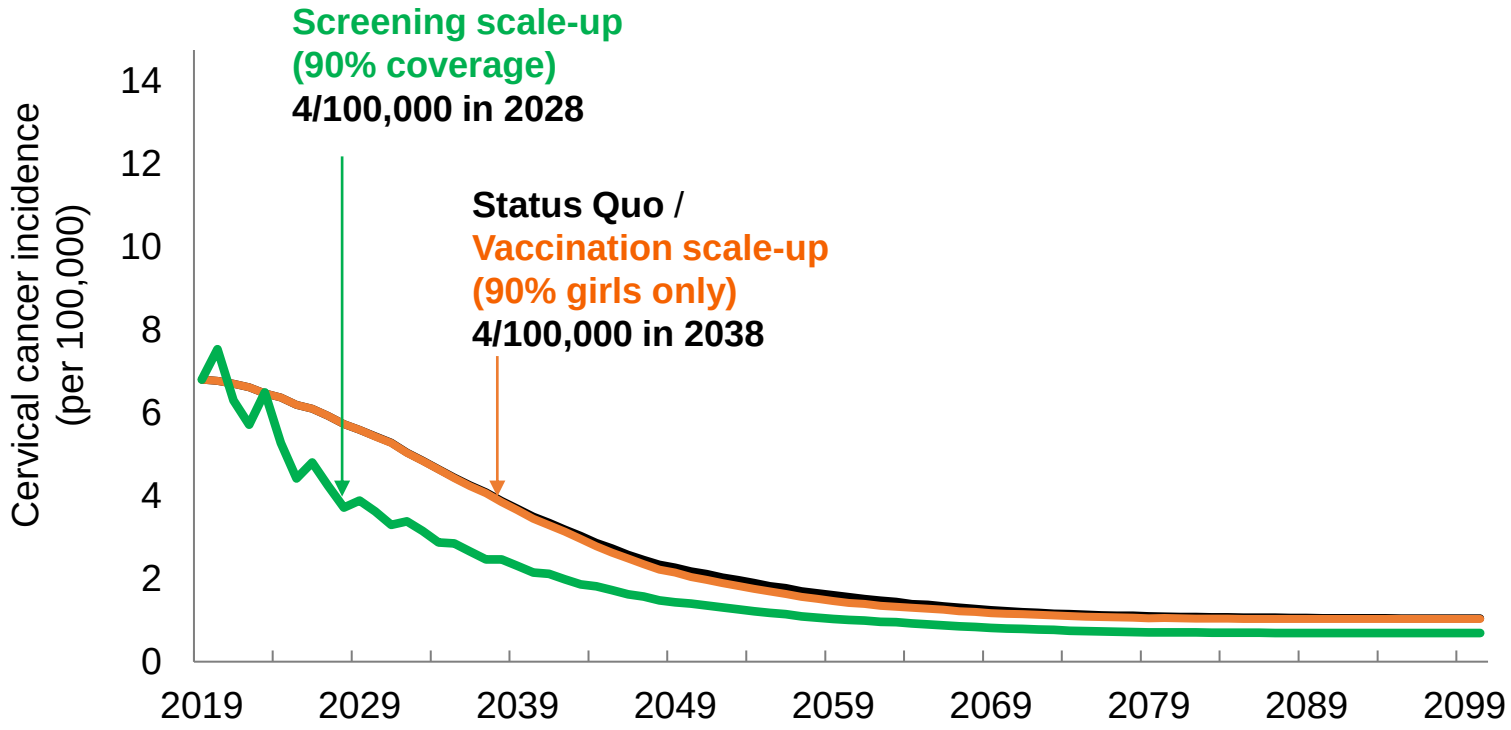
Trial is supported by The Bill & Melinda Gates Foundation and by the U.S. National Cancer Institute

Current research is evaluating efficacy of a single HPV vaccine dose

Research / Update	References
Post-hoc analyses: >10 years of strong protection (Cervarix or Gardasil)	Kreimer et al, JNCI, 2020; Basu et al, The Lancet Oncology, 2021
Ongoing NCI ESCUDDO efficacy trial of 12-16 year-old girls comparing one dose vs. two doses of Cervarix or Gardasil-9	Porras et al, Vaccine, 2022
Ongoing NCI PRISMA efficacy trial of 18-30 year-old women evaluating one dose of Cervarix or Gardasil-9 vs. DPT vaccine	Kreimer (principal investigator); trial NCT05237947
18 month KEN-SHE trial >95% efficacy (Cervarix or Gardasil-9)	Barnabas et al, NEJM Evidence, 2022
WHO now recommends 1 or 2 doses for females 9-20 years old (April 2022)	WHO news release (April 11, 2022): One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer

Cervical cancer screening

Cervical cancer incidence in the U.S. will decline more rapidly by increasing screening rates than by increasing vaccination rates



Source: Burger et al, Lancet Public Health, 2020

Cervical Cancer Screening Guideline Update 2020
(American Cancer Society)

- **Begin screening at 25 years instead of 21**

  Herd immunity in the U.S. enables identical screening guidelines for vaccinated and non-vaccinated women

- **Prefer HPV-based screening every 5 years if a woman is HPV-negative**

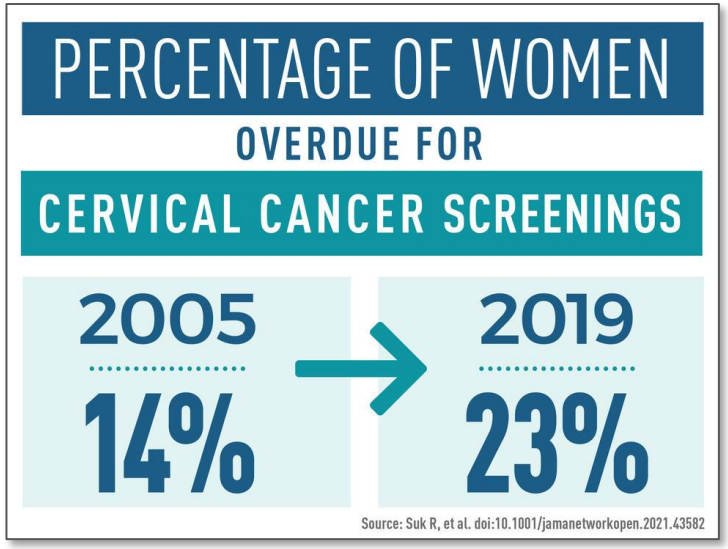
- **Managing HPV+ result is risk-based**
  - Based on molecular biomarkers related to HPV cause and disease development, not cytology (Pap smear).

- *USPSTF recommendations have not changed (yet).*

Fontham et al, CA: A Cancer Journal for Clinicians. July 30, 2020.

Many women overdue for cervical cancer screening; increasing over time

Rates of overdue cervical cancer screening (2019)	
Black	22%
White	20%
Uninsured	42%
Public insurance	28%



Suk R, et al. Assessment of US Preventive Services Task Force Guideline–Concordant Cervical Cancer Screening Rates and Reasons for Underscreening by Age, Race and Ethnicity, Sexual Orientation, Rurality, and Insurance, 2005 to 2019. *JAMA Network Open.* January 18, 2022

NCI's Cervical Cancer 'Last Mile' Initiative

A public-private partnership bringing together federal agencies, industry, and professional societies to contribute ***evidence about the accuracy and clinical effectiveness of self-sampling-based HPV testing for cervical cancer screening.***

Goal:

Overcome barrier of lack of FDA approval for self-sampling approaches for HPV testing-based cervical cancer screening

Approach:

Engage public and private sector stakeholders to facilitate regulatory approvals for self-sampling

Outcome:

Increase screening access and reduce cervical cancer incidence in underserved and high-burden populations

The initiative is supporting the "Self-sampling for HPV testing to Improve Cervical Cancer Prevention" Trial ('SHIP Trial'), slated to open late 2023.

Technology & health disparities, and cervical cancer screening

Technology Development & Health Disparities

Technology can
decrease disparities,
increase disparities, or
be neutral

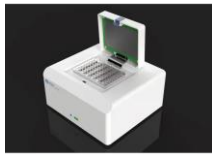
To increase the likelihood of a technological development decreasing disparities, **think about disparities *from the beginning* of the process**

Don't wait until the end to consider the possible impact on disparities

Even more direct: develop technology whose **goal includes reducing disparities**

Cost-effective, high quality, candidate “See and Treat” approach for cervical cancer screening

Undergoing international large-scale clinical trials for low- and middle-income AND high-income countries



Rapid, inexpensive, on-site HPV DNA test

On-site automated visual evaluation of cervix with smartphone and AI algorithm (HPV-positive women)

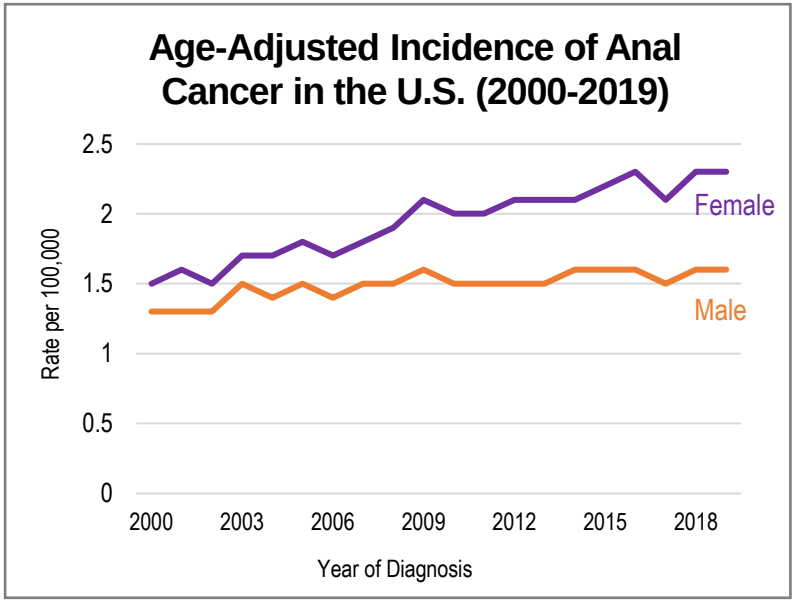
On-site thermal ablation

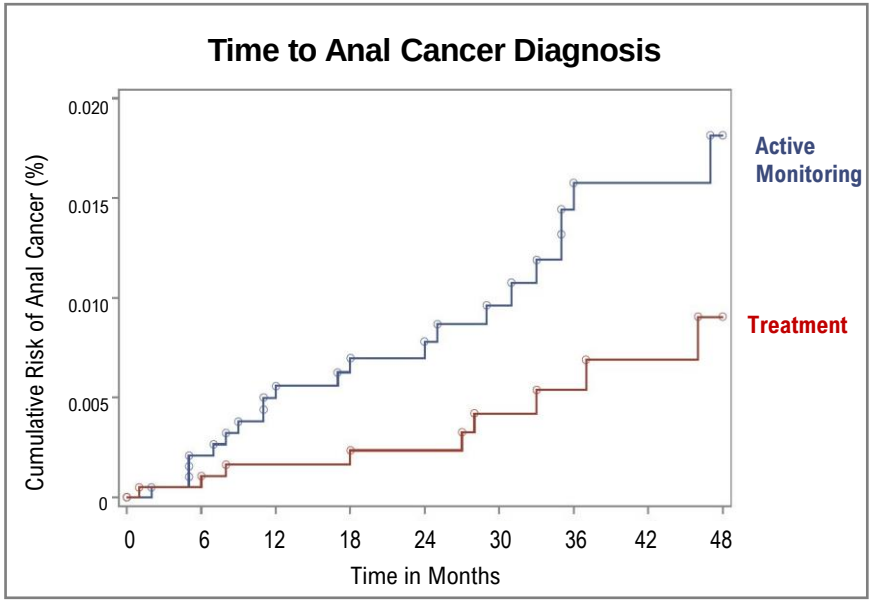
Mark Schiffman, MD, MPH

For more: Desai et al, Int J Cancer, 2022: “Redesign of a rapid, low-cost HPV typing assay to support risk-based cervical screening and management” and "The development of “automated visual evaluation” for cervical cancer screening”

Anal cancer screening: likely to become standard of care in the near future, at least for HIV-positive individuals

ANCHOR Trial: Treatment of high-grade anal epithelial dysplasia reduces risk of progression to invasive anal cancer (HIV-positive patients)





Source: seer.cancer.gov

Palefsky, et al. Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer. *New England Journal of Medicine. 386: 2273-82*, 2022

Some take-home messages

Cancer mortality rates continue to decrease but far too many people still die from cancer

We need wider dissemination of standard of care plus new interventions, especially for cancers with poor prognosis, including rare cancers

When developing new technology, consider implications for health disparities from the beginning

HPV vaccination for long-term control of HPV-associated cancers; cervical cancer screening for controlling this cancer faster; we should ensure all countries benefit from both interventions

Thank you!

www.cancer.gov

www.cancer.gov/espanol

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