HealthCare
MARKEY CANCER CENTER
An NCI-Designated Comprehensive Cancer Center

Recent Advances Toward Developing Screening for Oropharyngeal Cancer

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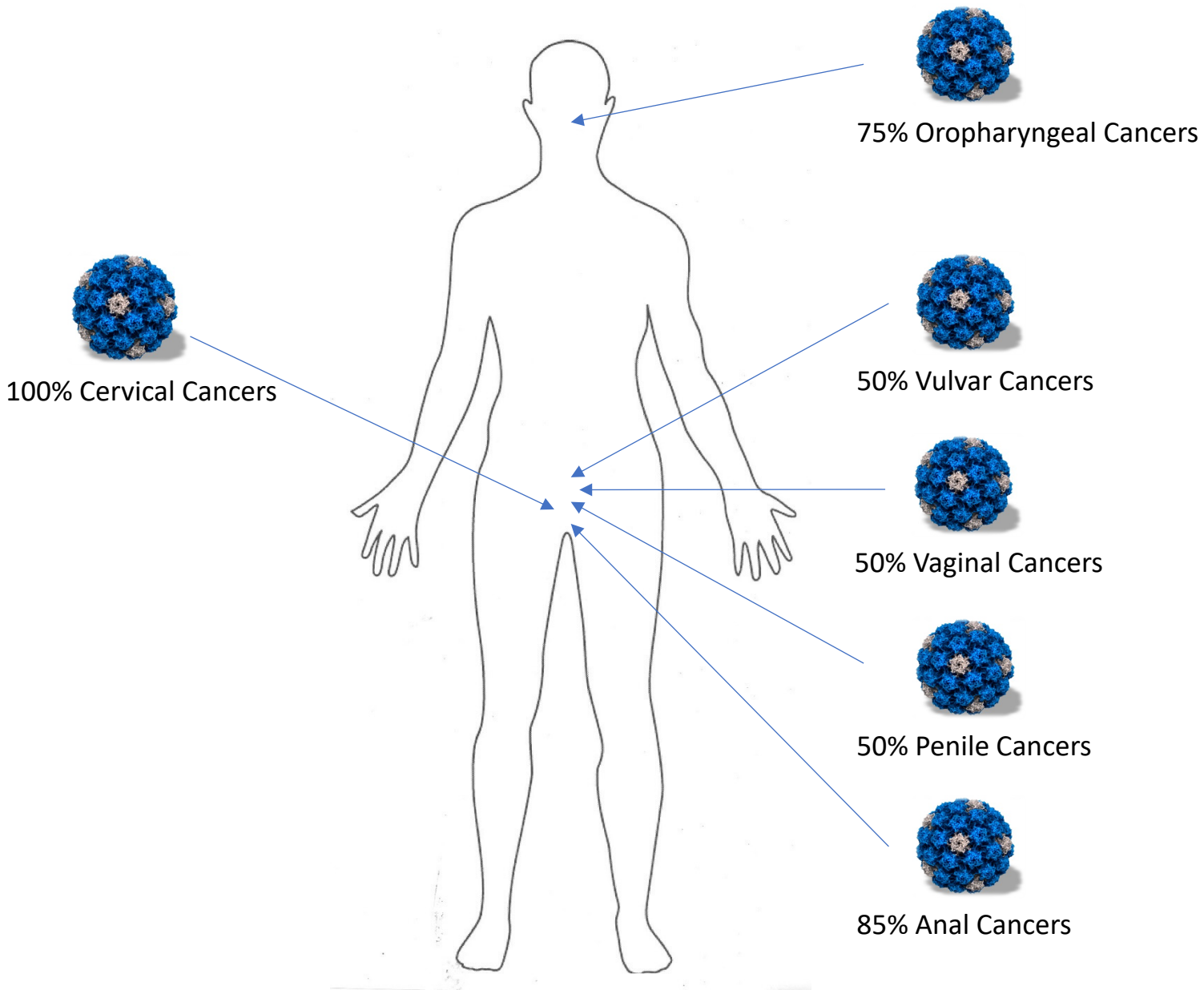
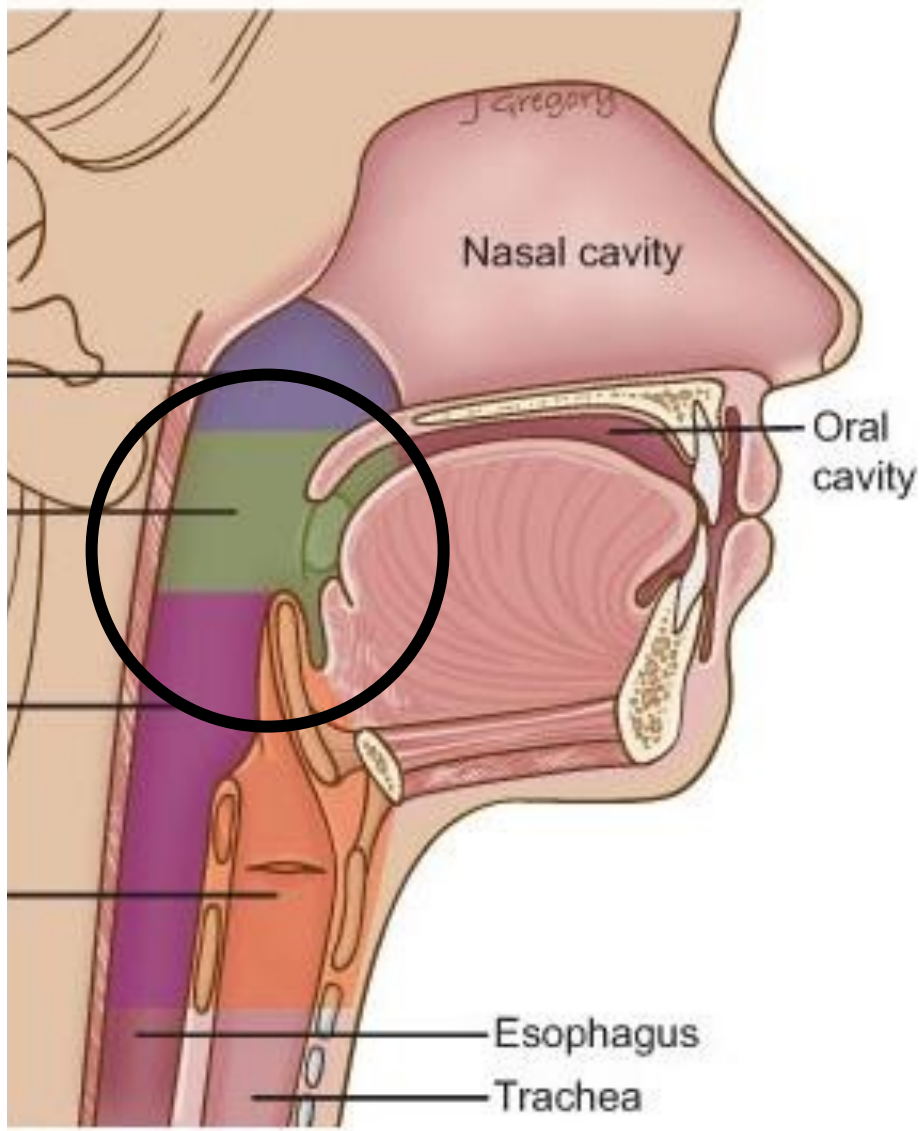
Cancers caused by human papilloma virus (HPV)



Oropharyngeal cancer

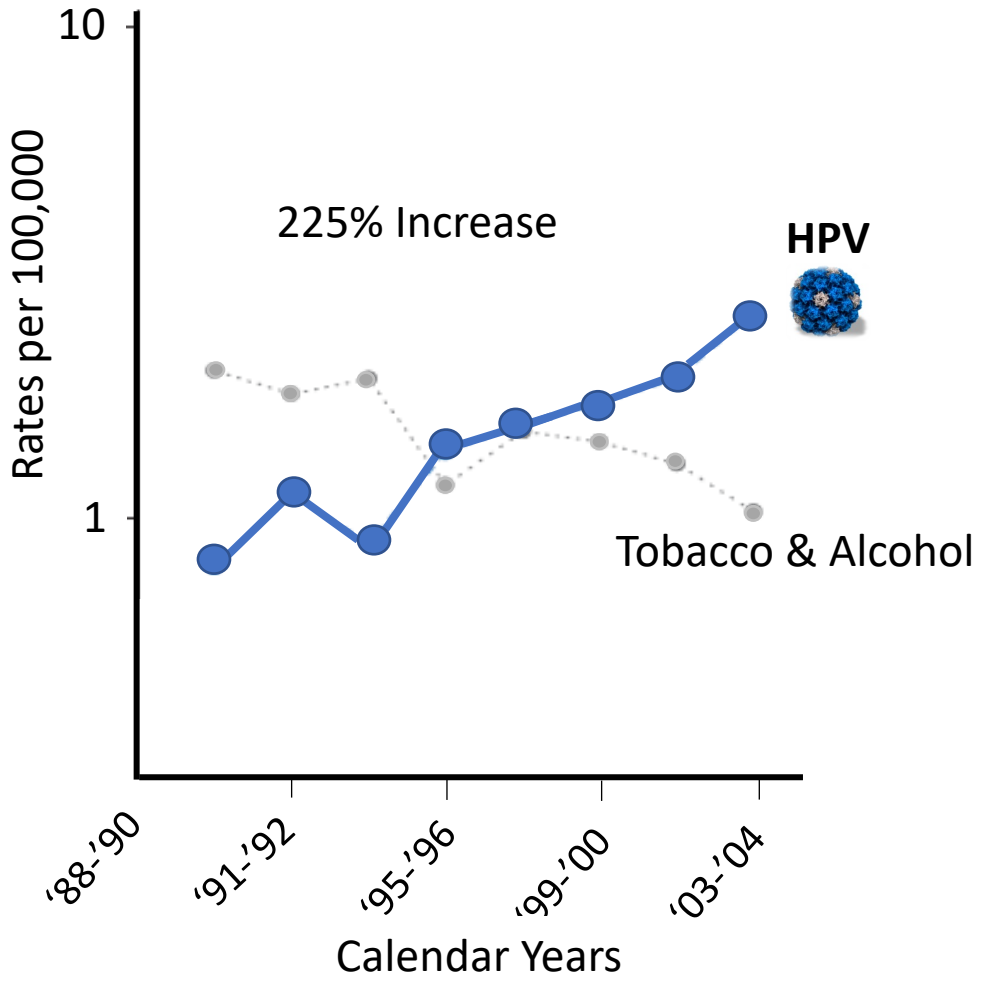
- Back and side walls of the throat
- Soft palate
- Waldeyer’s ring
- Palatine tonsils
- Tonsils in the base of the tongue



Gillison Vaccine 2012; headandneckcancerguide.org

HPV-driven Oropharyngeal Cancer (HPV-OPC)

- US is at the epicenter of emerging epidemic
- ~90% of cases are due to just 1 high-risk HPV type – HPV16
- 85% of cases are among white men
- Cases of OPC outnumber cervical cancer cases
- Currently there are no methods for early detection



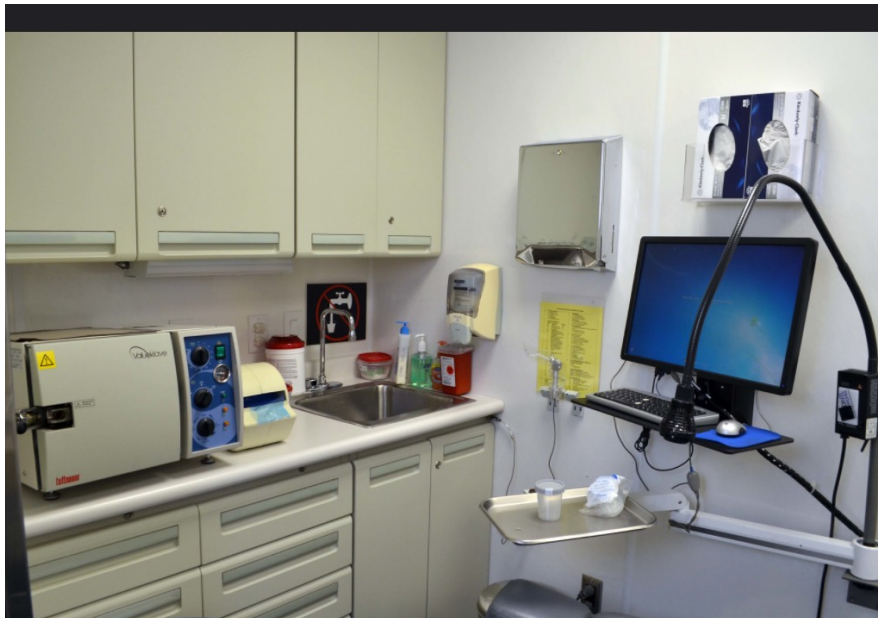
Adapted from: Chaturvedi et al, J Clin Onc, 2011

Causes of HPV-OPC:
Oral HPV Prevalence in the US

NHANES – Studying the US population

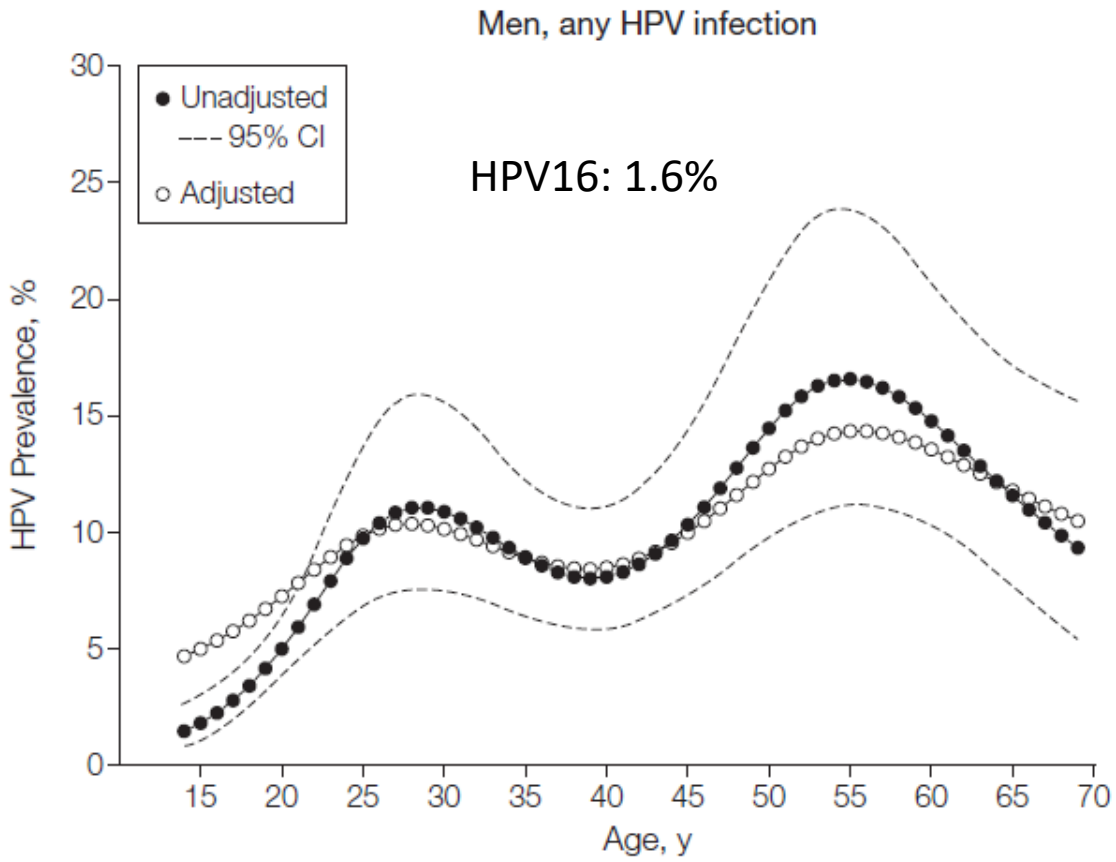
nhanes

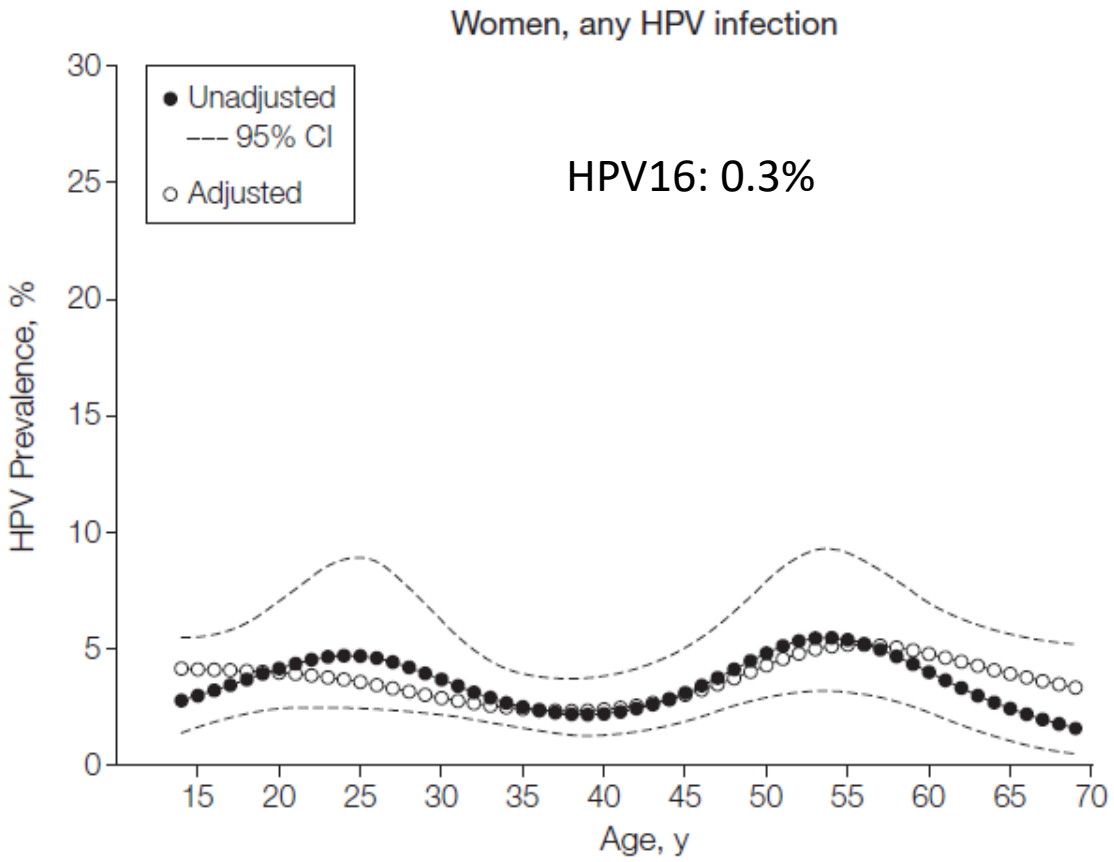
National Health and Nutrition Examination Survey



https://www.cdcfoundation.org/blog-entry/behind-scenes-nhanes

Prevalence of Oral HPV infection in the US (NHANES)



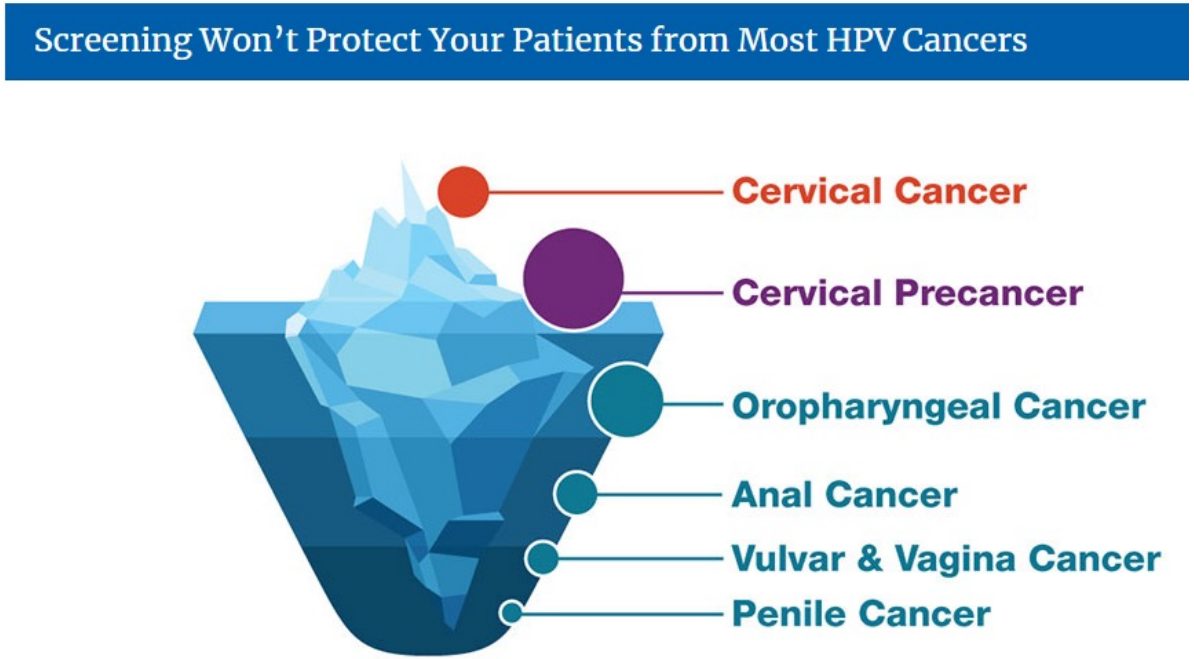


Risk Factors for Oral HPV: Age, sex, number of sexual partners and current number of cigarettes smoked per day

Chaturvedi et al, *JAMA*, 2012

Prevention

HPV Vaccines for Prevention of HPV-driven Cancers



Vaccine	Coverage (HPV types)	Gender and age range
Cervarix (bivalent)*	HPV16 & 18	Females, 9-25 years
Gardasil (quadrivalent)	HPV 6, 11, 16 and 18	Females and males, 9-26 years
Gardasil 9 (nonavalent)	HPV 6, 11, 16, 18, 31, 33, 45, 52, 58	Females and males, 9-26 years

https://www.cdc.gov/hpv/hcp/protecting-patients.html

*Taken off US market

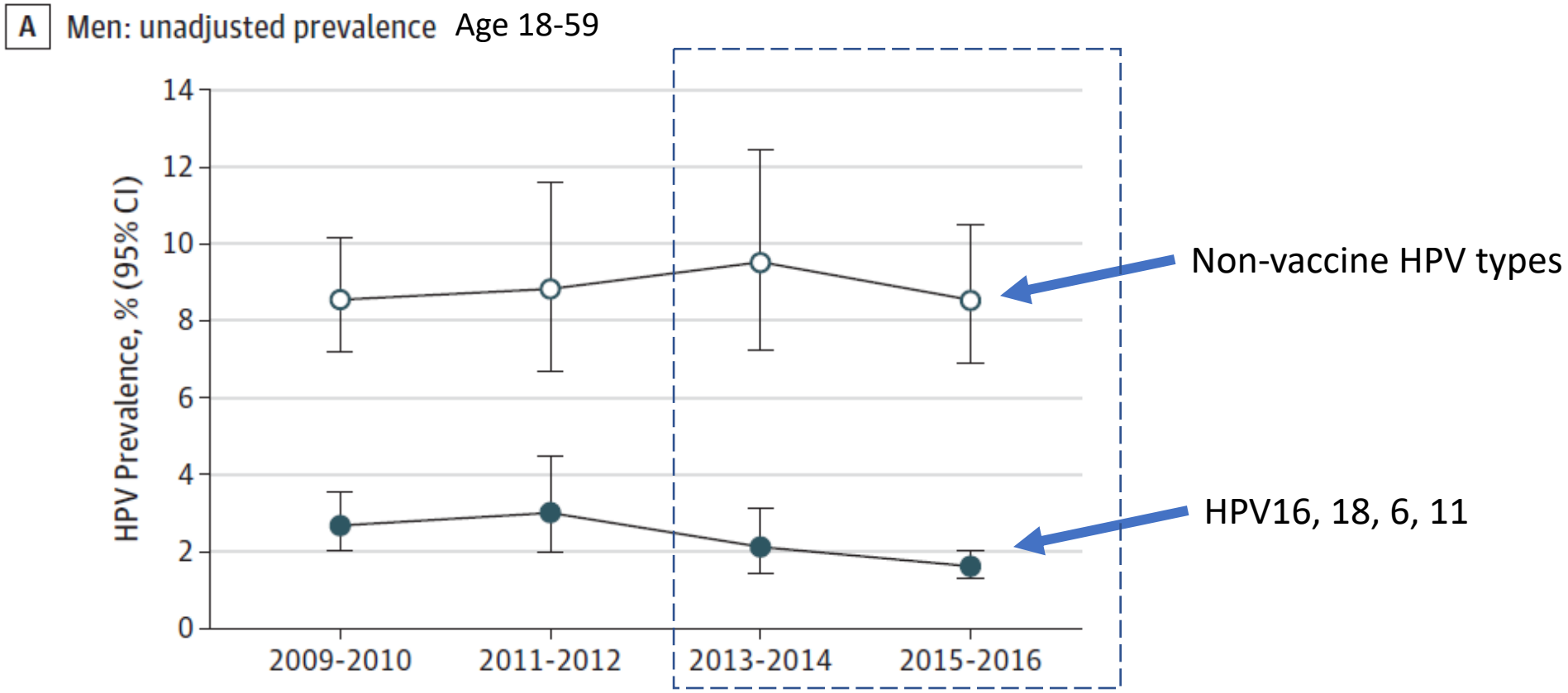
Vaccine Efficacy Results from the Costa Rica Vaccine Trial

Aimee Kreimer, NCI

Arm	No. Women	HPV 16/18	Prevalence	Vaccine Efficacy	95% CI
Vaccine	2924	1	0.0%	93.3%	62.5% to 99.7%
Control	2910	15	0.5%		

Herrero et al, *PlosOne*, 2013

Reduced prevalence of oral HPV infection following vaccination in US (NHANES)



≥1 Dose of HPV Vaccine

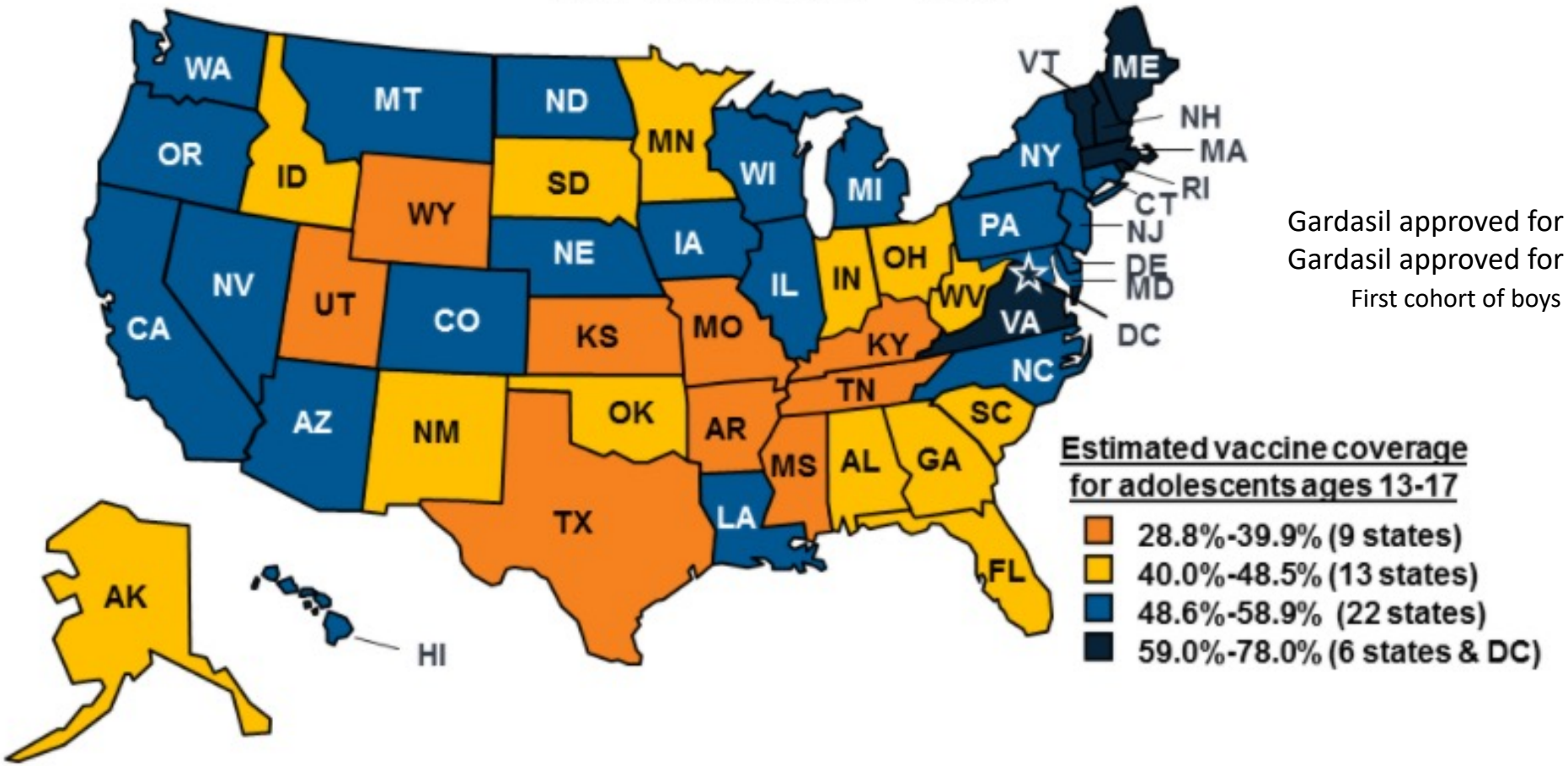
Men	0%	2.0%	4.1%	5.8%	P<0.001
Women	7.3%	10.2%	14.2%	15.1%	

Chaturvedi et al, *JAMA*, 2019

HPV Vaccination Rates of Adolescents, by State

Adolescents ages 13-17 with HPV Up-To-Date (UTD) Vaccination Series, 2017

2017 US Average = 48.6%



Gardasil approved for girls: 2006
Gardasil approved for boys: 2009
First cohort of boys now aged 24

NOTES: HPV UTD includes those with ≥3 doses, and those with 2 doses when the first HPV Vaccine dose was initiated before age 15 years and time between the first and the second dose was at least 5 months minus 4 days.
SOURCE: CDC. (2018). National, Regional, State, Selected Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years—United States, 2017. *MMRW* 67(33).

KFF
HENRY J KAISER FAMILY FOUNDATION

Can we find HPV-driven oropharyngeal cancer earlier?

Barriers to oropharyngeal cancer screening

- No easily identifiable high-risk population
- No precursor lesion
- Usually small tumors buried deep within tonsillar crypts

New Discovery:
HPV16 E6 as an early marker of HPV-OPC

1990s

100,000 Healthy Individuals
Aged 50-75 Donated Blood

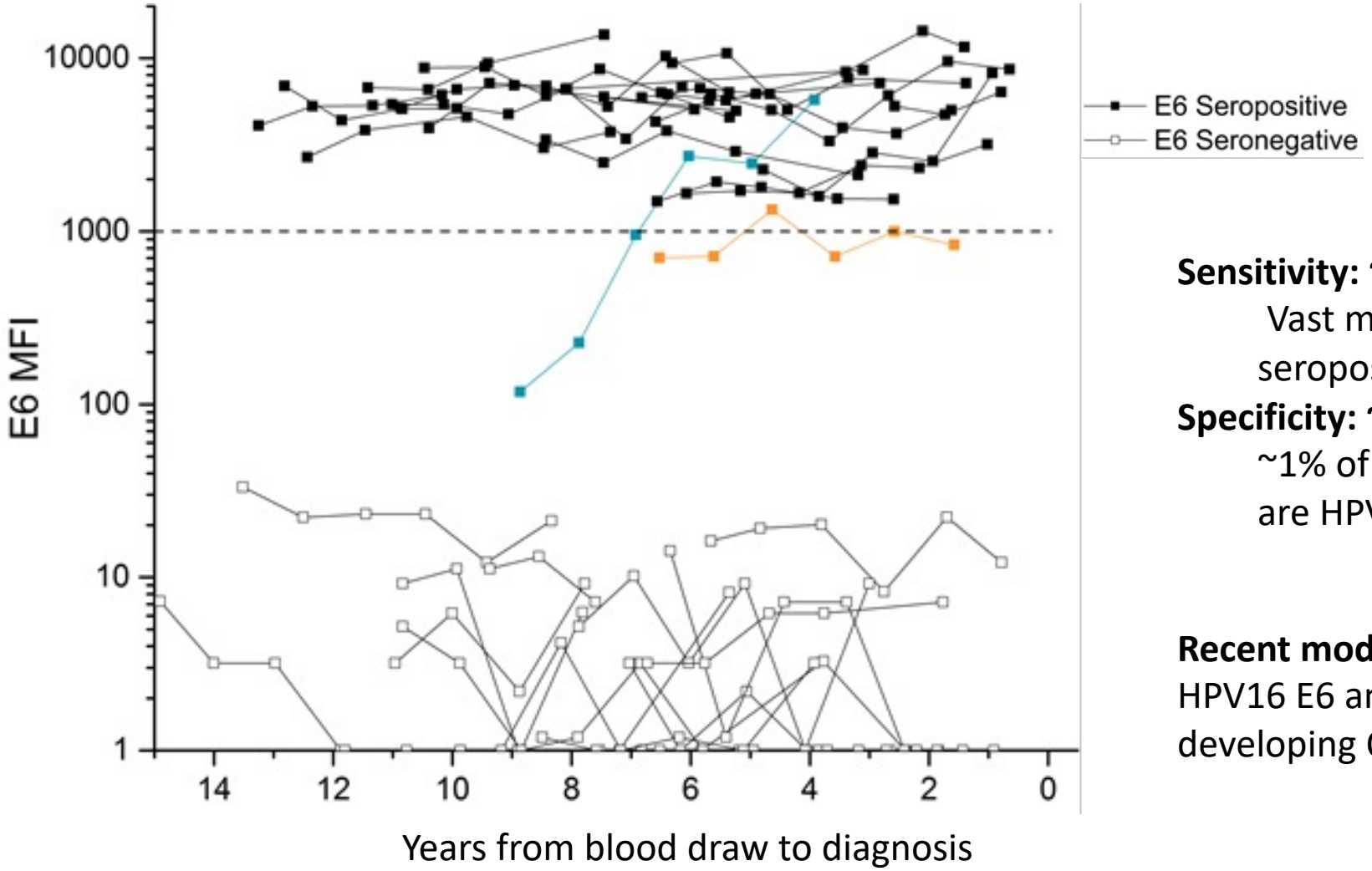
?

2013

Who developed oropharyngeal cancer?

And did they have detectable HPV antibodies in their blood prior to diagnosis?

HPV16 E6 antibodies as an early marker for OPC



Sensitivity: ~90%

Vast majority of patients are HPV16 E6 seropositive at diagnosis

Specificity: ~99%

~1% of healthy people without caner are HPV16 E6 seropositive

Recent modelling study: Man aged 50 with HPV16 E6 antibodies has 50% chance of developing OPC in his lifetime

Kreimer…Lang Kuhs et al, *JNCI*, 2017; Lang Kuhs KA, et al *Cancer* 2017
Lang Kuhs KA & Anantharaman D, et al *CEBP* 2015

Can we use the HPV16 E6 blood marker to find people at highest-risk for HPV-OPC?

Test blood from healthy middle aged males

HPV16 E6 seropositives

Full Head and Neck Exam

Potential Barriers

- Although rapidly increasing, OPC is considered an uncommon cancer nationally (<40 per 100,000)
- Large recruitment effort to find a small number of E6 seropositives (seroprevalence in general population <1%)

Nested cohort studies with permission to recontact.

HPV16 E6 as a screening tool in the general population

Hamburg City Health Study

IMPACT: First evidence that HPV serology could be used for screening in the general population

First 5,000 participants screened for HPV16 E6 antibodies

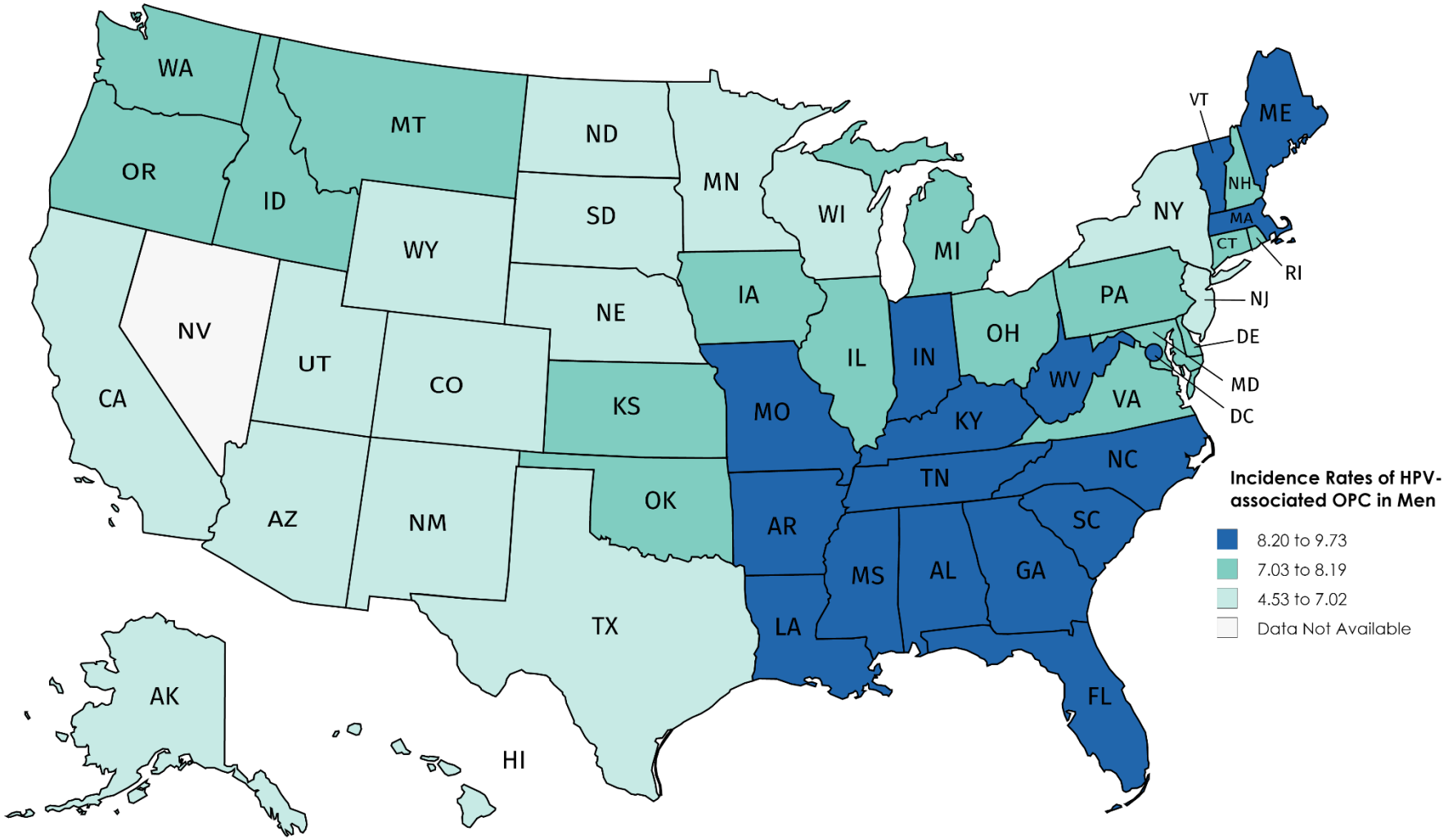
ID	E6	E2	E7	E1	age at blood draw	sex	diagnosis	
1					56-65	male	HPV16-OPC	invited to clinical follow-up
2					56-65	male	HPV16-OPC	
3					66-76	male	-	
4					56-65	male	NA	
5					46-55	male	-	
6					66-76	male	-	
7					56-65	female	HPV16-OPC	
8					46-55	male	-	
9					66-76	male	NA	
10					56-65	male	-	
11					46-55	male	-	
12					46-55	female	NA	not invited to clinical follow-up
13					46-55	male	NA	
14					46-55	female	NA	
15					66-76	male	NA	
16					66-76	male	NA	
17					66-76	female	NA	
18					66-76	male	NA	
19					56-65	male	NA	
20					46-55	female	NA	
21					66-76	female	NA	
22					66-76	male	NA	
23					46-55	male	NA	
24					46-55	female	NA	
25					56-65	male	NA	
26					56-65	male	NA	
27					66-76	male	NA	
28					66-76	female	NA	
29					66-76	male	NA	
30					66-76	male	NA	
31					66-76	female	NA	
32					66-76	male	NA	
33					56-65	female	NA	
34					56-65	female	NA	
35					46-55	female	NA	

3 Individuals diagnosed with early stage HPV16+OPC

Busch… Lang Kuhs et al, *EClinical Medicine*, 2022

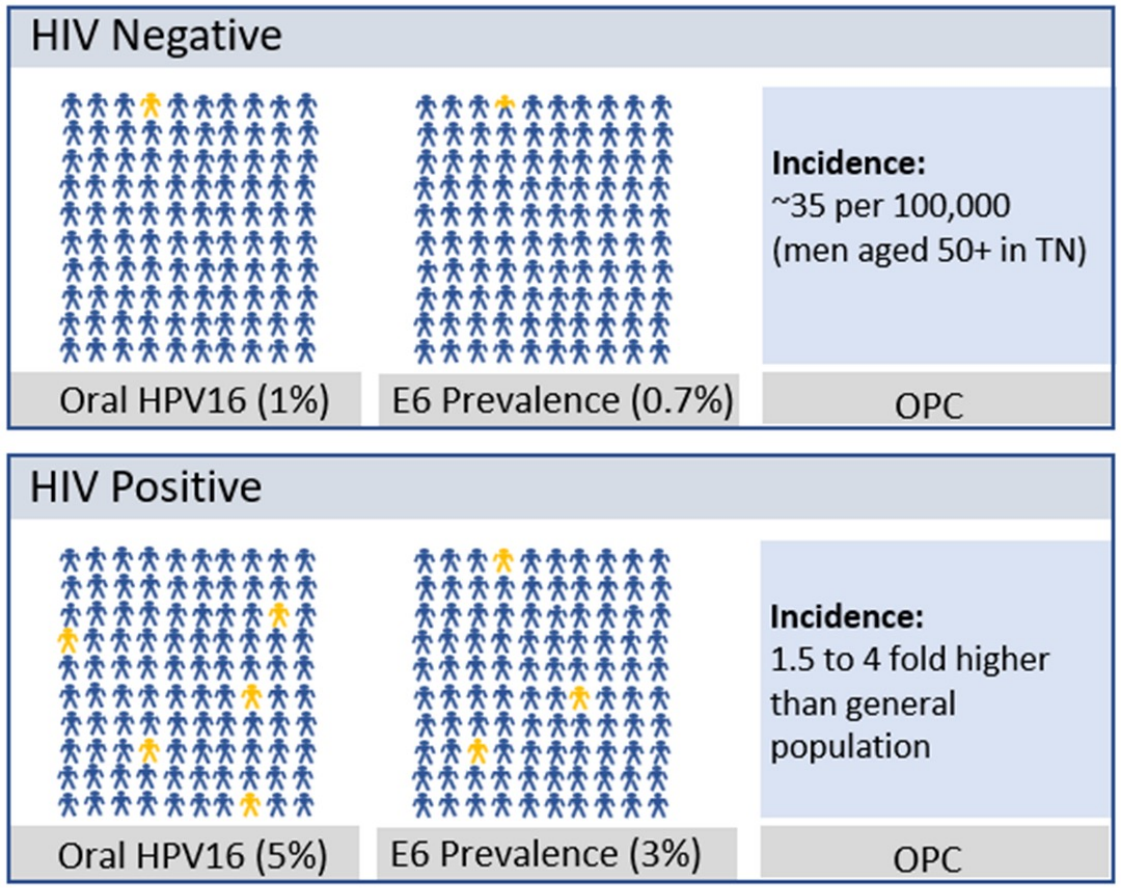
What about the United States?

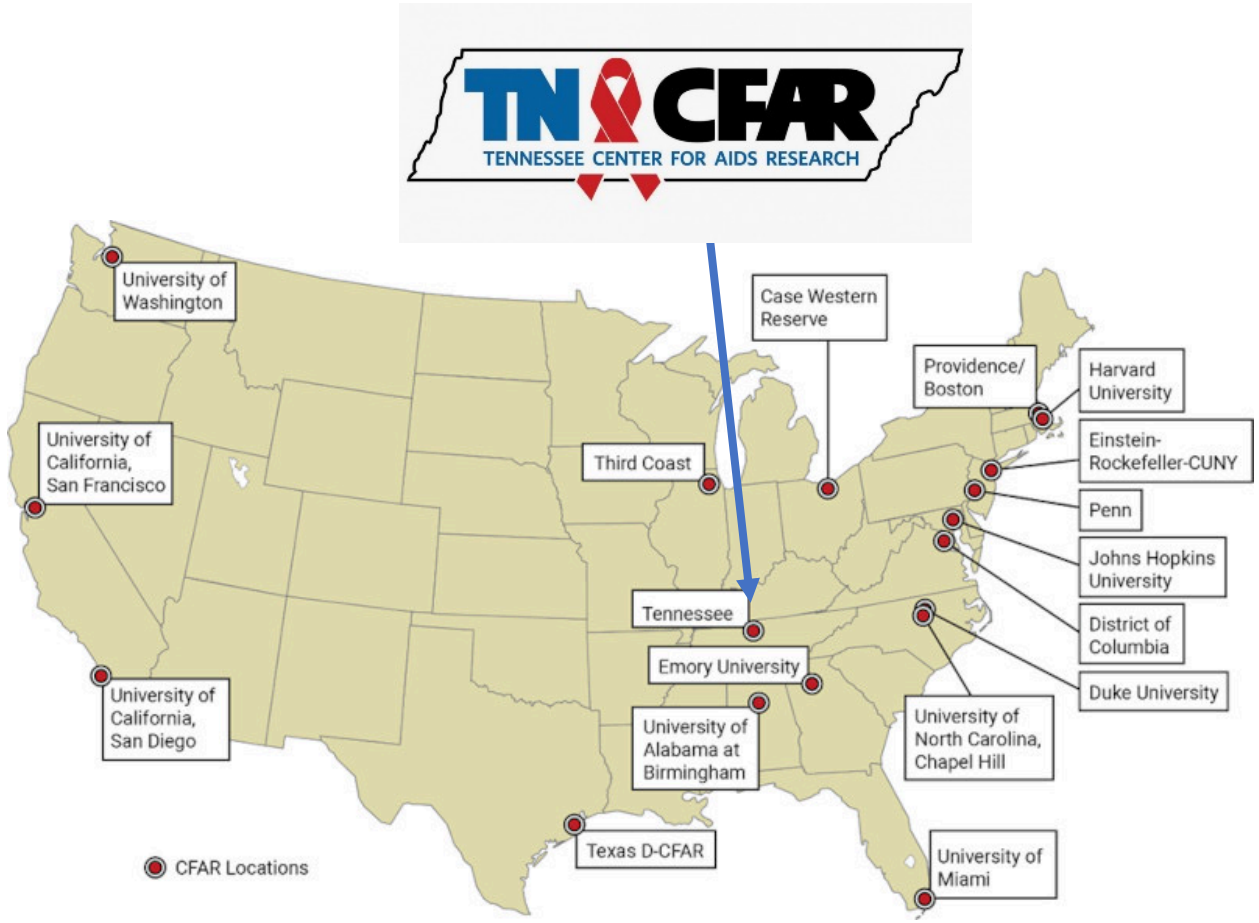
Southeast has the highest incidence of OPC in the country



Source: https://www.cdc.gov/cancer/hpv/statistics/state/oropharyngeal.htm
Rates are per 100,000 and age-adjusted to the 2000 US Std. Population

Men Living with HIV at High Risk





Men living with HIV:

- 5-fold greater prevalence of oral HPV16
- >3-fold HPV16 E6 seroprevalence
- Up to 4-fold greater incidence of HPV-OPC

TN-CFAR Biorepository

- ~3,000 blood samples from men living with HIV aged 40+
- Allows for recontact of participants

HIV-ENDEAVOR STUDY DESIGN

PARTICIPANTS N=3,000

Specimen Selection

3,000+ plasma samples
from males aged 40+

TESTING N=3,000

E6 Marker Testing

DKFZ

RECRUITMENT N=180

Approached for Study

(All E6 positives and subset of E6 Negatives)

CLINICAL EXAM 4 Yearly Exams

Vanderbilt Head and Neck Clinic

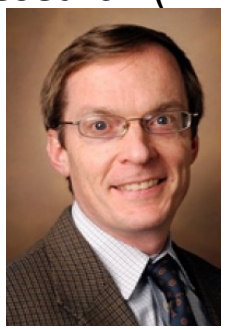
Clinical Head and Neck Exam

- One-time questionnaire
- Visual inspection of head and neck
- Laryngoscope and ultrasound
- Biospecimen collection for oral HPV detection

TN- Center for AIDS Research (TN-CFAR)

Staci Sudenga

David Haas



Timothy Sterling

Vanderbilt Head and Neck Surgeons

James Netterville

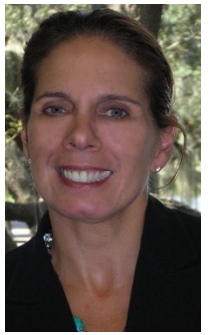
Kyle Mannion

Michael Topf

DKFZ

Tim Waterboer

Moffitt



Anna Giuliano

R01 DE029650, NIDCR; Lang Kuhs (PI)

HIV-ENDEAVOR: Preliminary Results

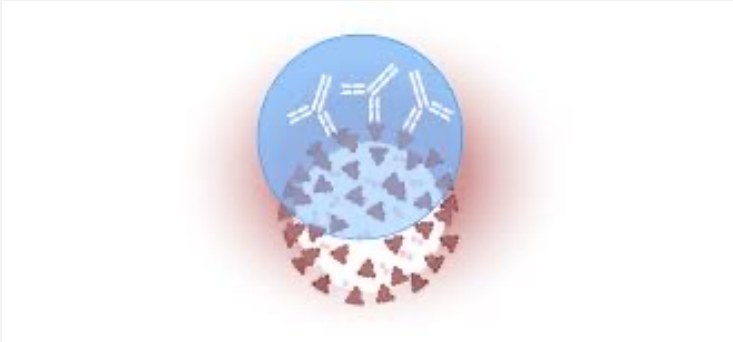
HPV16 E6 Testing Phase

1,465 samples from men aged 40+ tested to date

4.5% were HPV16 E6 seropositive (N=66)

61% levels as high as OPC patients

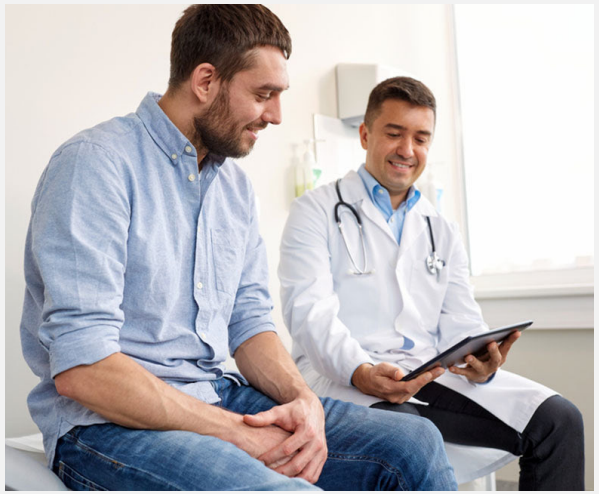
24% seroreactive against 1 other E antigens



Head and Neck Clinical Exam

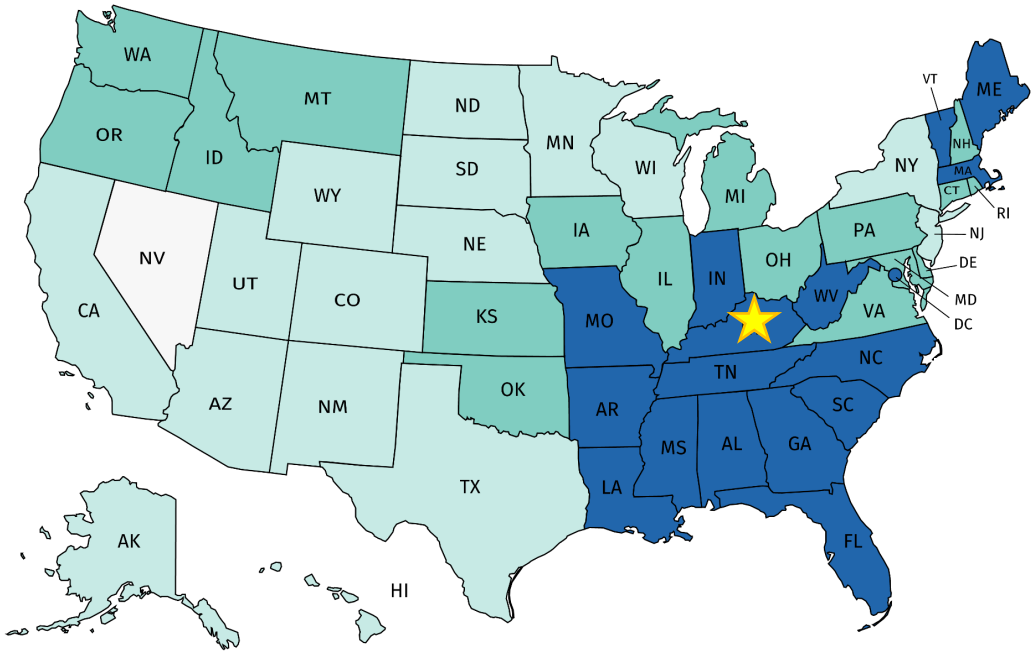
20 participants have undergone exam

1 suspicious lesion is being monitored in a seronegative participant



What about the general population?

VOYAGER Study



How feasible it is to conduct large scale screening of the general population?

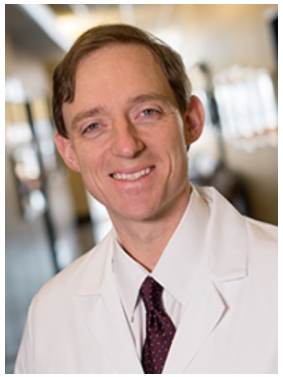
(1) How common is the HPV16 E6 marker in the general male population in Kentucky?

(2) Is oral HPV more common among men with the HPV16 E6 marker?

(3) Can we diagnosis HPV-OPC in men with the HPV16 E6 marker?

UK Primary Care

Neelima Kale



Key Douthitt

Head & Neck

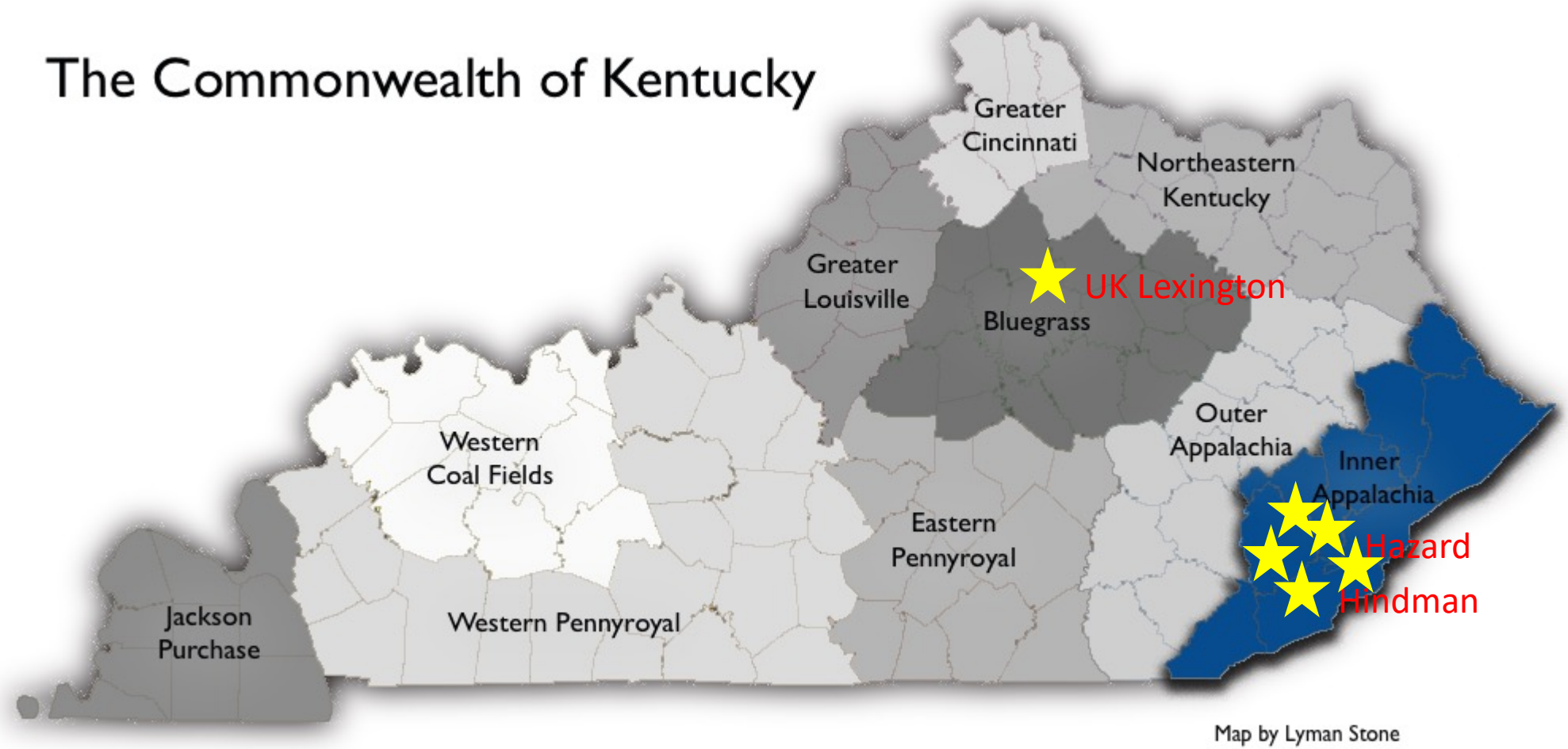
Melvyn Yeoh

Kuhs Lab

Soma Bose

Shaina Campbell

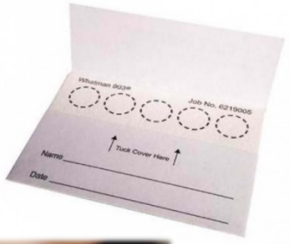
Recruiting healthy men aged 45+ across 6 primary care clinics in Kentucky



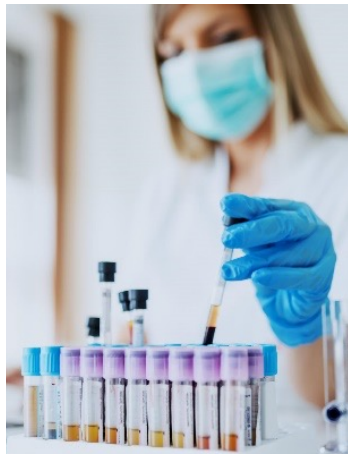
VOYAGER STUDY DESIGN

Phase 1: Screening (N=2,000)

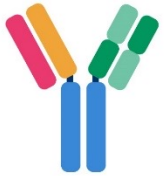
Blood Spot Card and Oral Rinse Collection in Clinic



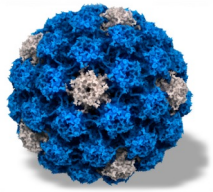
Laboratory Testing



HPV16 E6 Antibody Testing



Oral HPV Testing



All HPV16 E6+ men and subset of HPV16 E6- men (1:2) will invited for head and neck cancer screening

Phase 2: Screening Exam (N=45)

Physical Head and Neck Exam

Laryngoscope Exam

Biospecimen Collection

Oral rinse for HPV testing

Blood for in depth HPV serologic and liquid biopsy testing

Innovations to streamline and scale recruitment

Efficient enrollment

Only 10 mins are needed for consent and biospecimen collection

All data capture is conducted on iPad with centralized REDCap database

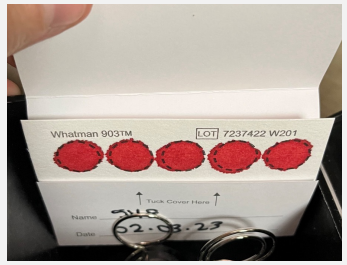
Non-invasive specimen collection

Inexpensive collection

Minimum lab processing required

Scalable: Possibility for self-collection

Blood Sample



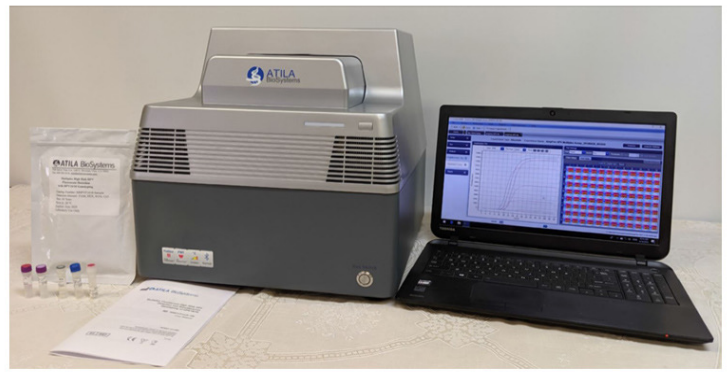
Oral Sample

Inexpensive oral HPV testing

Originally designed for HPV screening in low resources settings

1/10 cost of conventional testing

Strong reproducibility and agreement with conventional testing in ongoing pilot studies

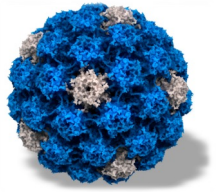


Progress to Date: Over 1,300 men enrolled!

Lexington Launch

Feb 2022

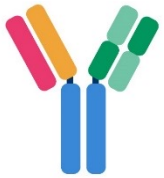
Oral HPV Testing Ongoing

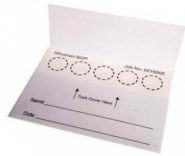


Hazard Launch

Feb 2023

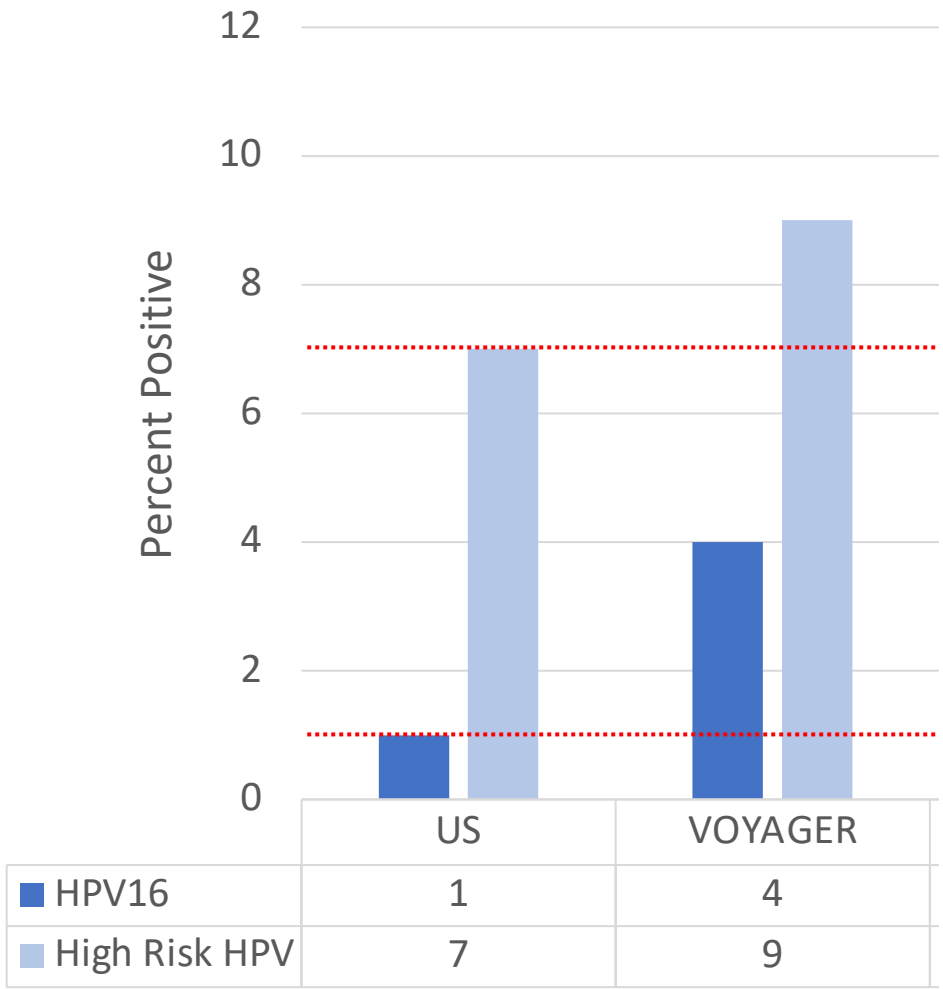
E6 Testing & Optimization Ongoing



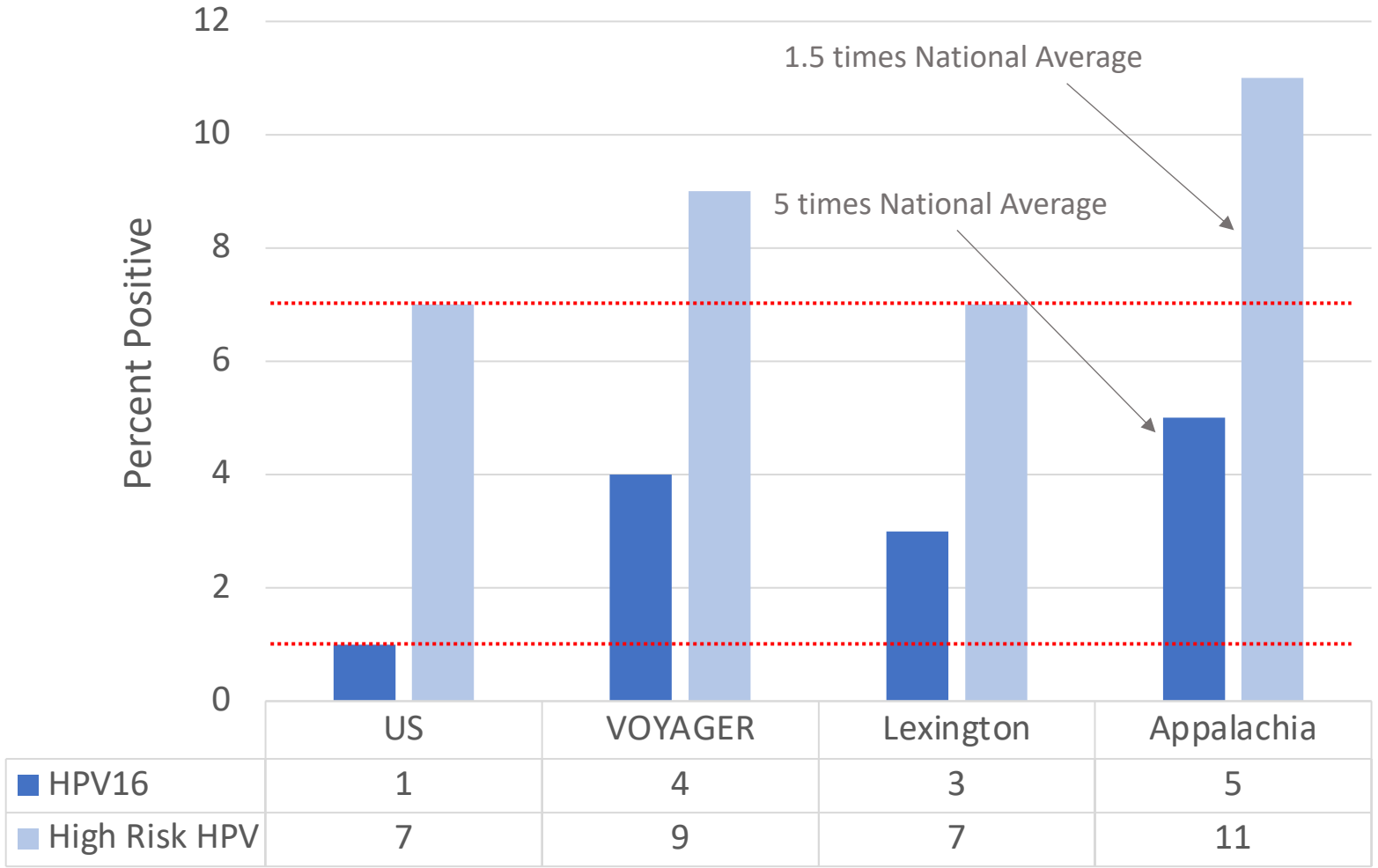


May 2023

Preliminary Oral HPV Results (N=1,188)



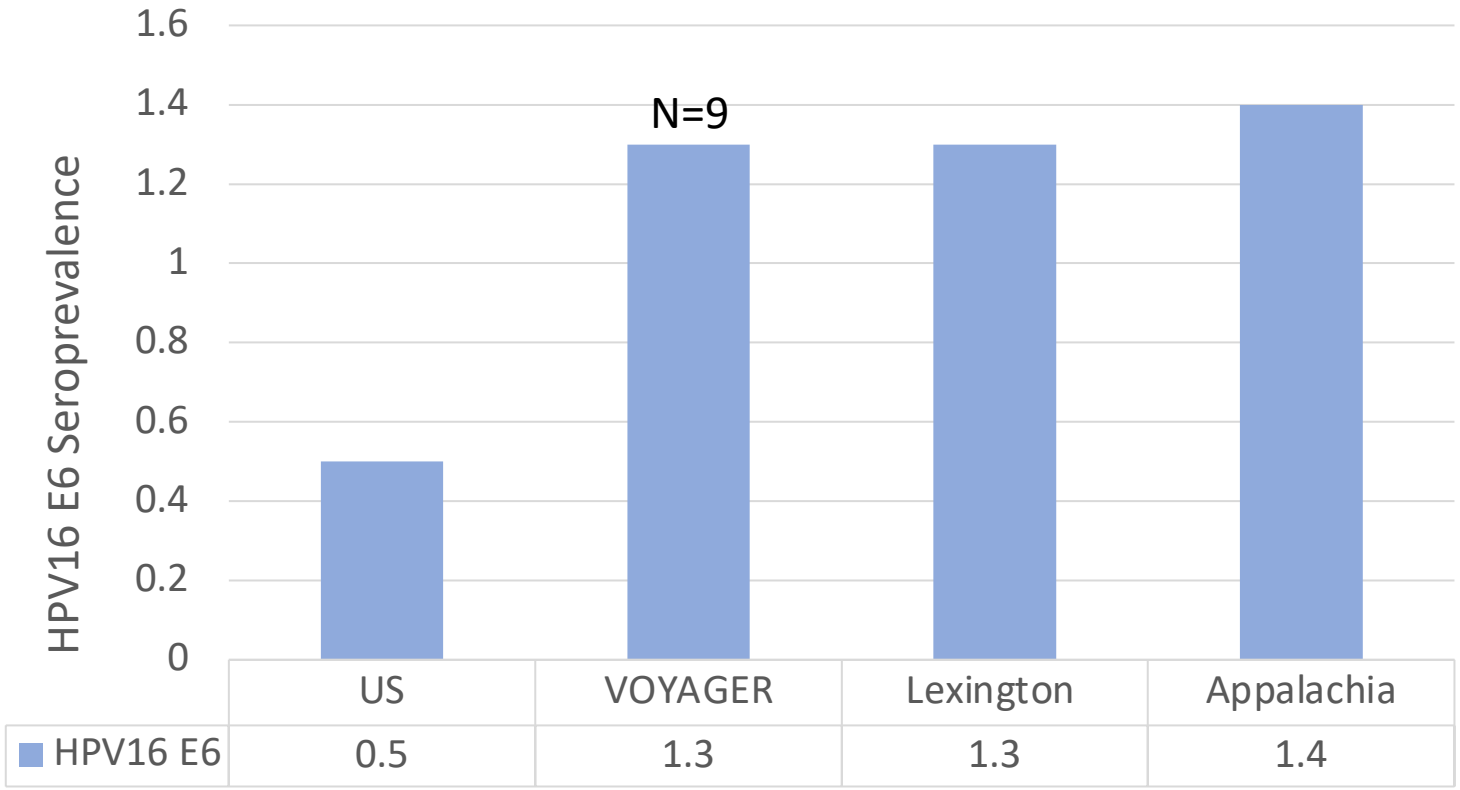
Preliminary Oral HPV Results (N=1,188)



Ever Smokers

66% for Appalachia
vs.
41% for Lexington

Preliminary HPV16 E6 Antibody Results (N=683)



Limitations: No nationally representative data for comparison
(NHANES has restriction on foreign testing)
Small numbers

3 out of 9 HPV16 E6 seropositives were reactive against other HPV16 E6 proteins
Currently working to get these patients screened for oropharyngeal cancer

Summary

- US is at the epicenter of the emerging epidemic with the southeast region having the highest incidence in the country
- 85% of cases occur among men and 90% of cases of due to HPV16
- HPV vaccination is highly effective at preventing oral HPV infection, but vaccine uptake is still low
- There is no screening for available; however, a promising early marker has been identified
- Early detection is an active area of research, but we still have long way to go…

Acknowledgements

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Birgitta Michels

Moffitt Cancer Center

Anna Giuliano

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Pamela Stein

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Questions?