



UK HealthCare Markey Cancer Center

Human papillomavirus-driven oropharyngeal cancer (HPV-OPC)

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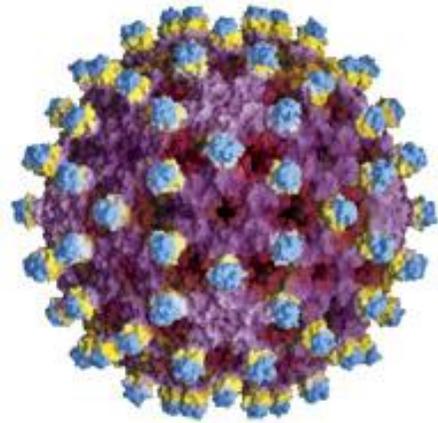


Outline

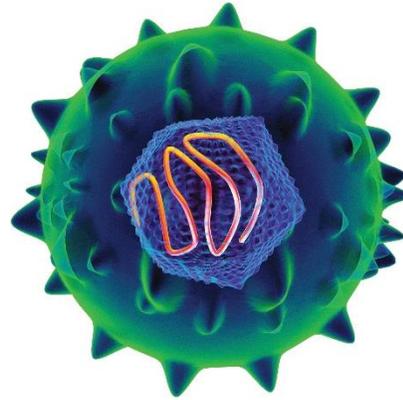
- Epidemiology
- Causes
- Prevention
- Diagnosis, Treatment, and Survival
- Staging
- Up and Coming Advances

Epidemiology

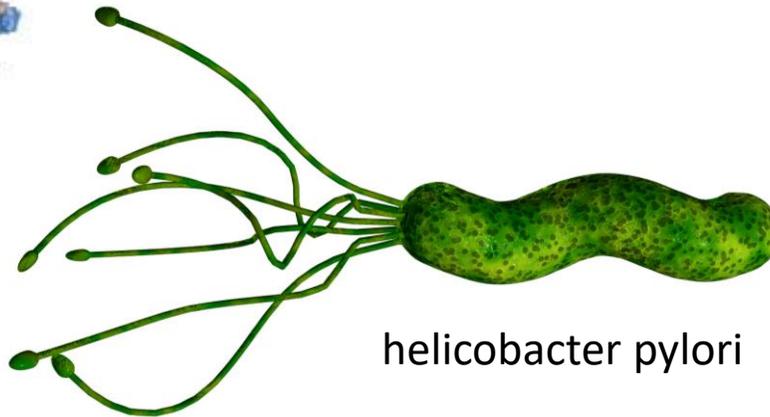
2 million cases cancers are caused by infections each year



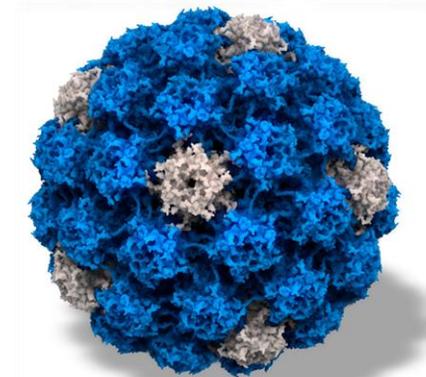
hepatitis B virus



hepatitis C virus

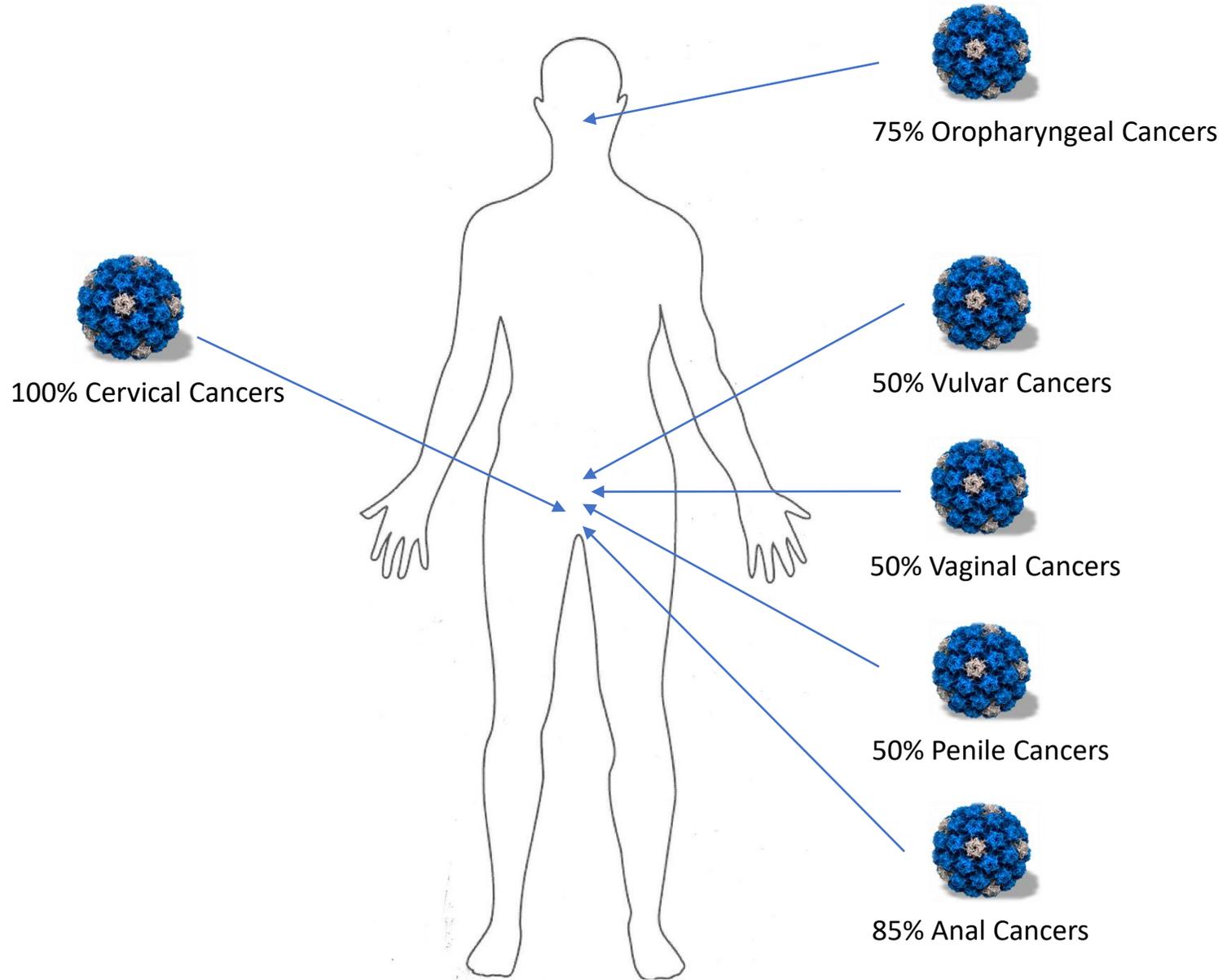


helicobacter pylori



human papillomavirus

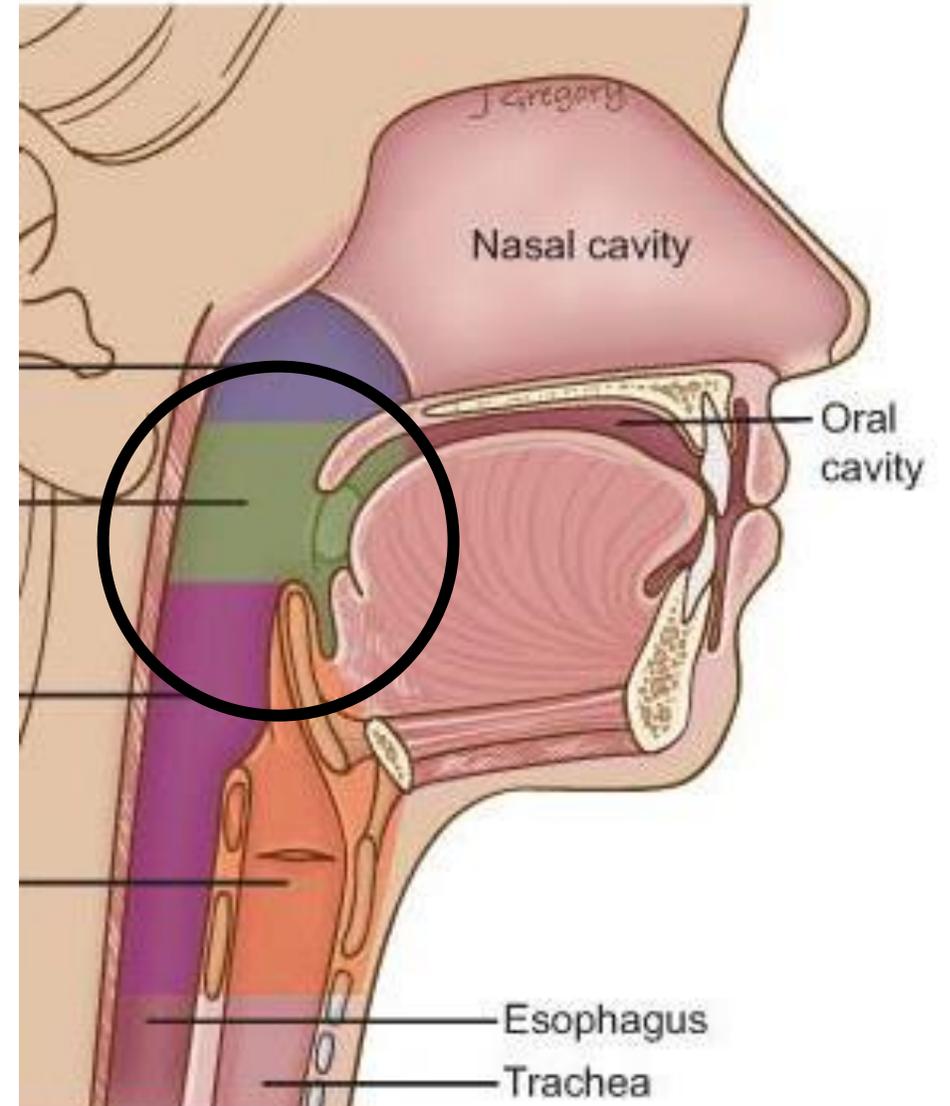
Cancers caused by HPV



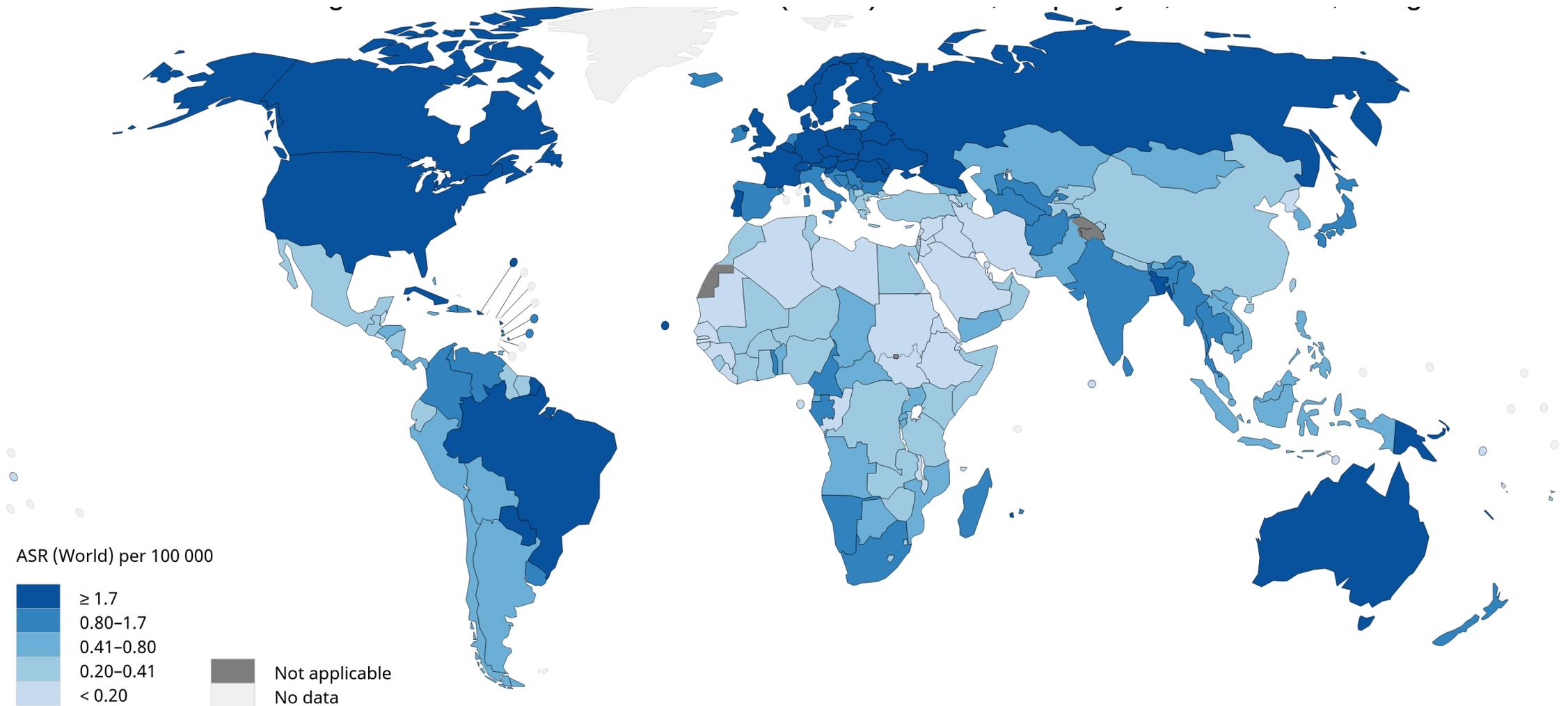
Oropharyngeal cancer

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

(ICD-O-3) codes: C01.9, C02.4, C05.1, C05.2, C05.8, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2, C10.3, C10.8, C10.9, C14.0 and C14.2



Age-standardized incidence of Oropharyngeal Cancer in 2020, all sexes and ages

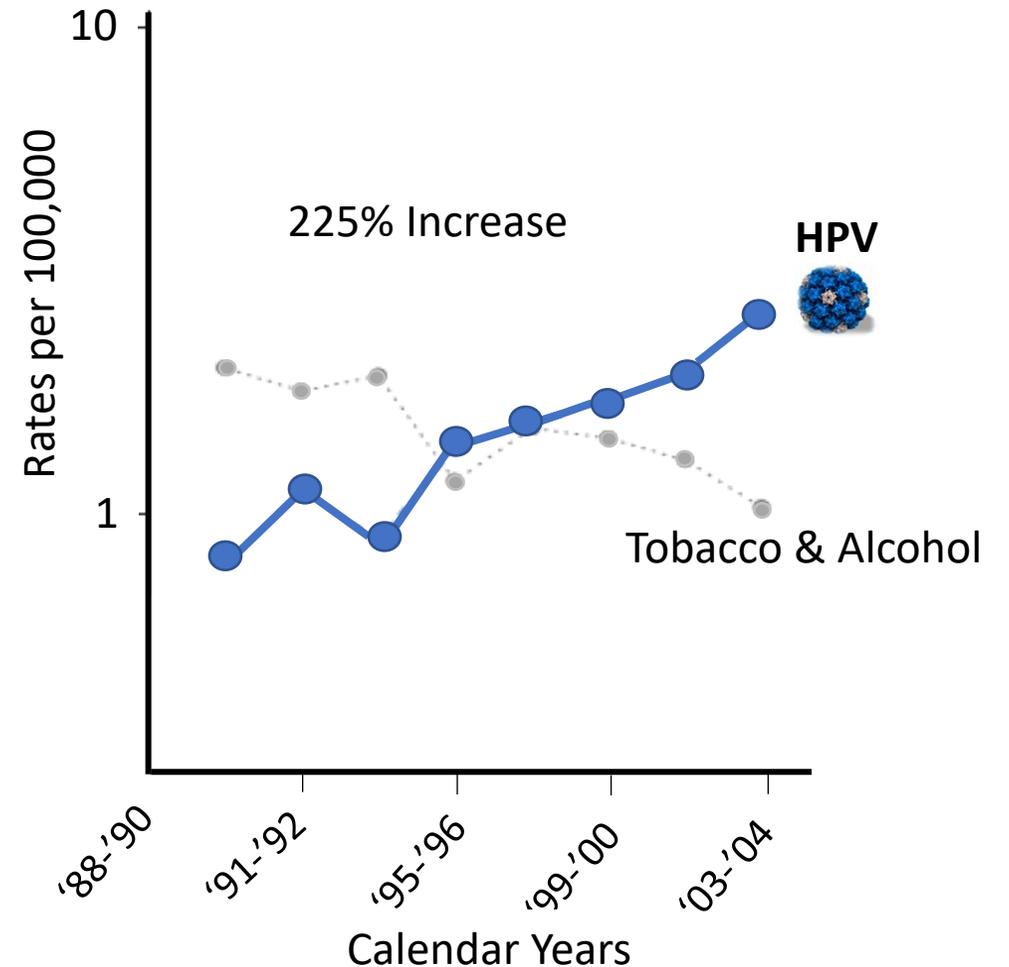


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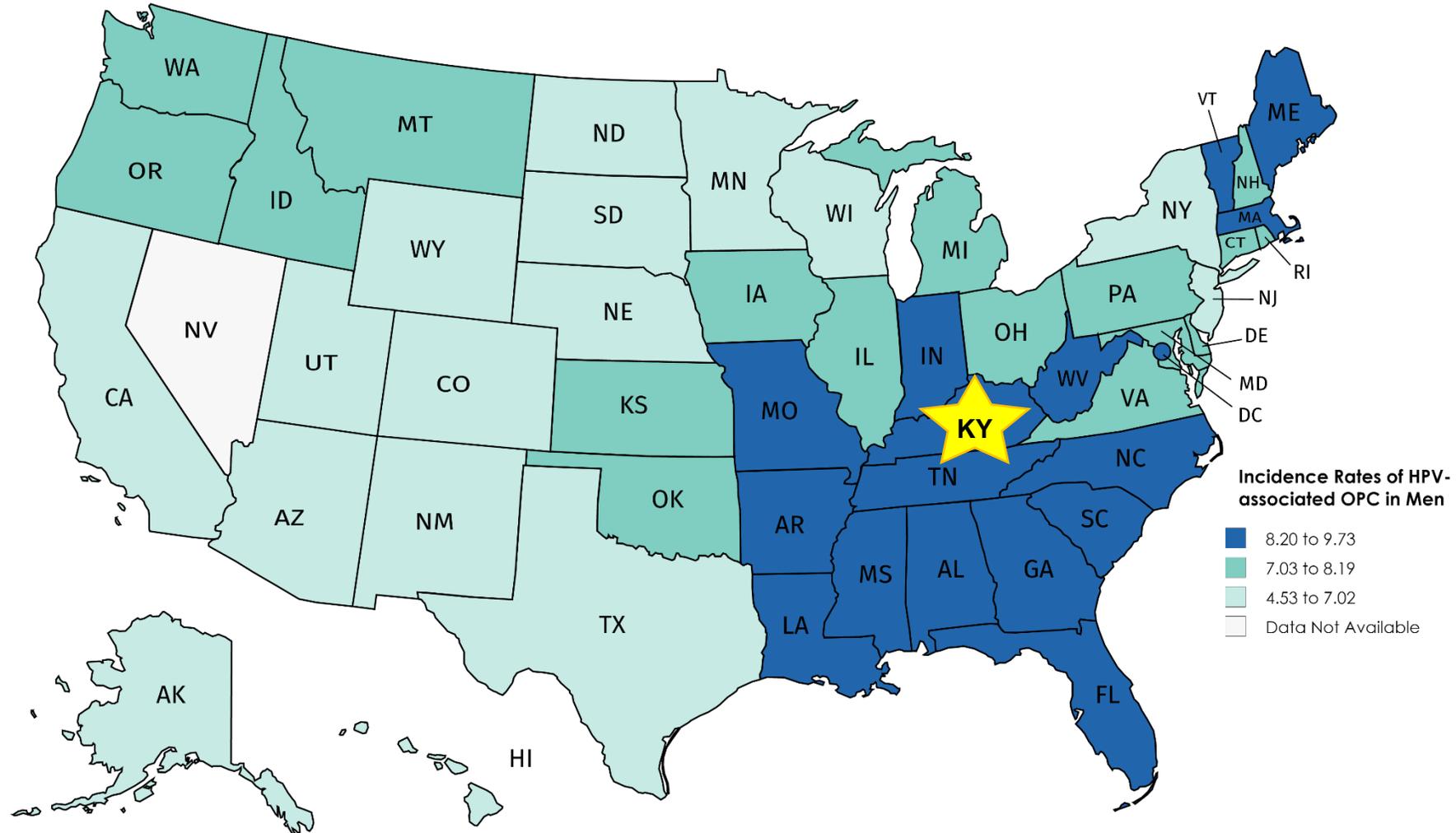
Data source: GLOBOCAN 2020
Graph production: IARC
(<http://gco.iarc.fr/today>)
World Health Organization

HPV-driven Oropharyngeal Cancer (HPV-OPC)

- Incidence is rapidly increasing in the US
- ~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 screening



Southeast has the highest incidence of OPC in the country



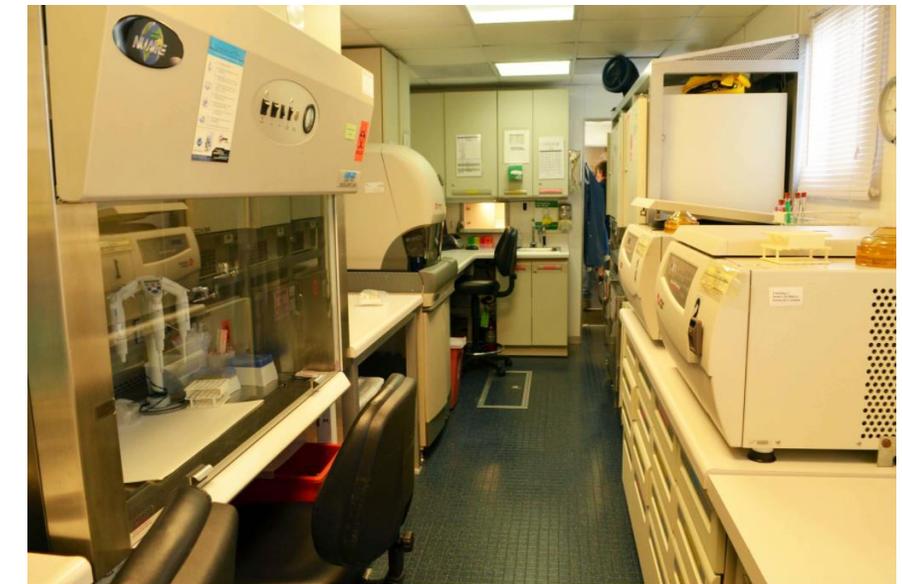
Source: <https://www.cdc.gov/cancer/hpv/statistics/state/oropharyngeal.htm>
Rates are per 100,000 and age-adjusted to the 2000 US Std. Population

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

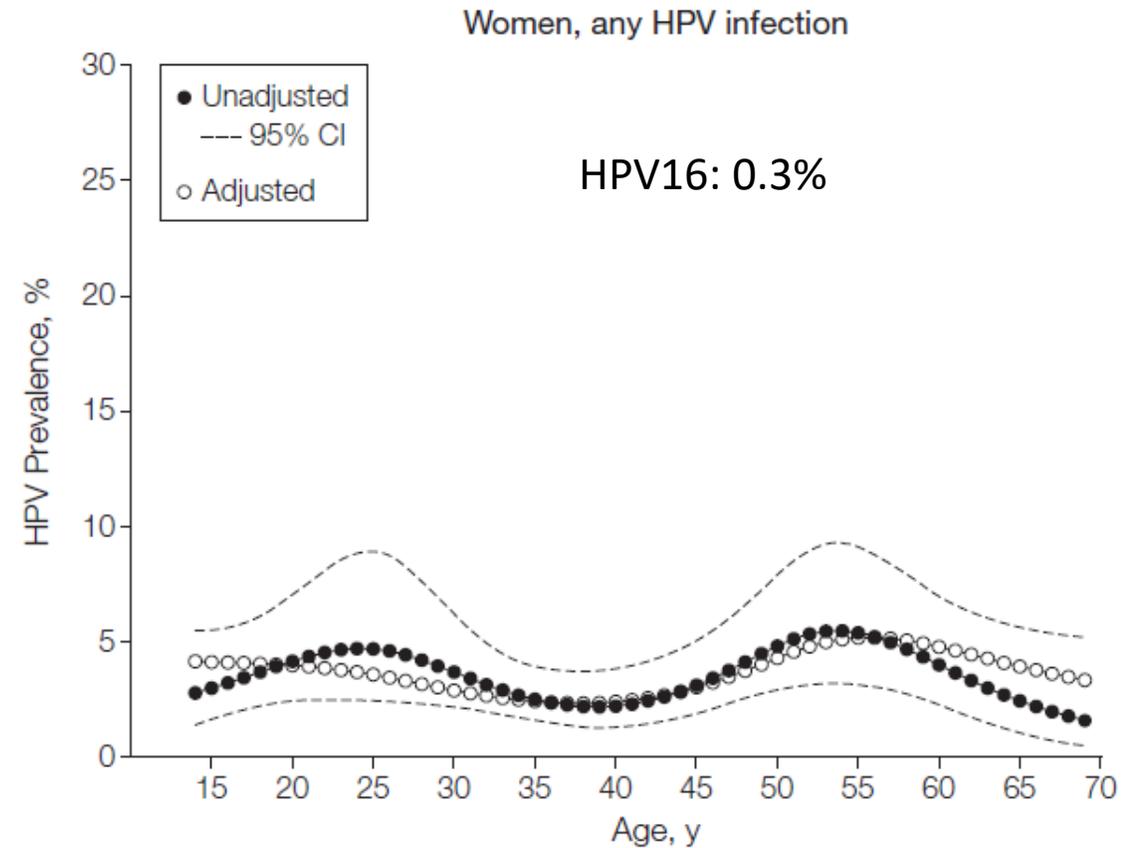
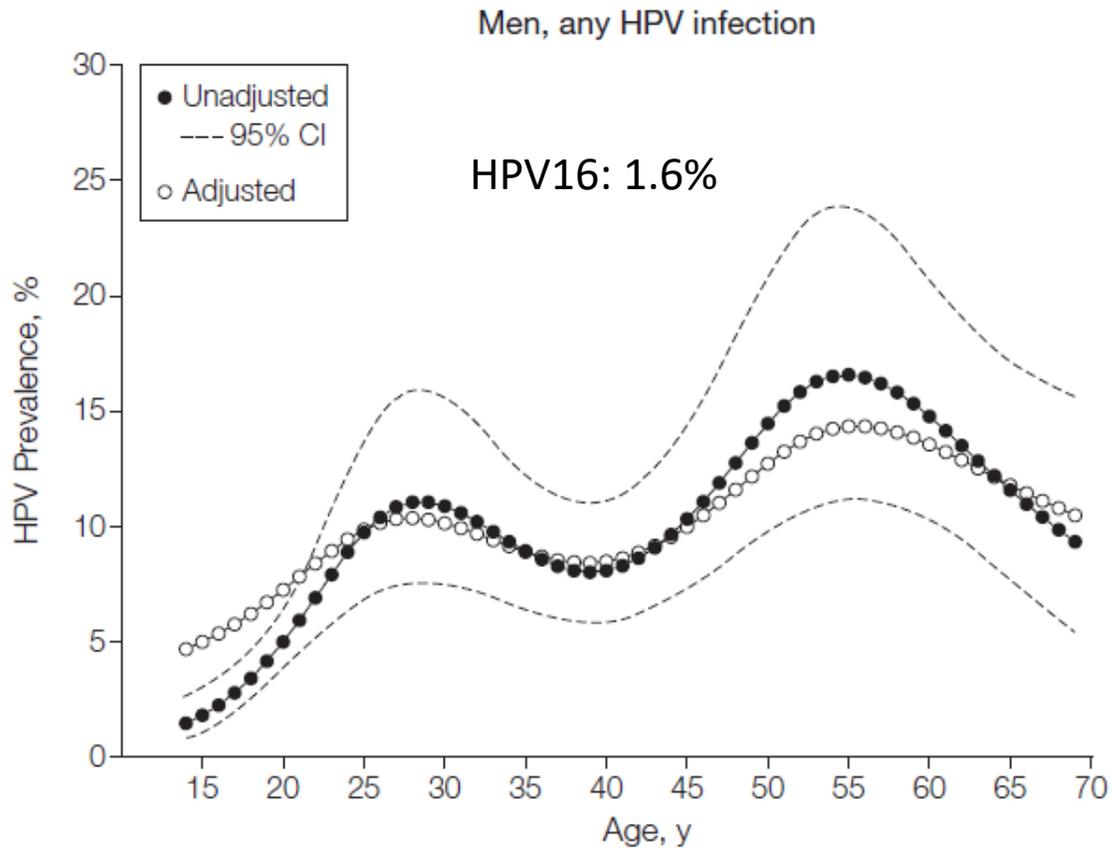
NHANES – Studying the US population



National Health and Nutrition Examination Survey



Prevalence of Oral HPV infection in the US (NHANES)

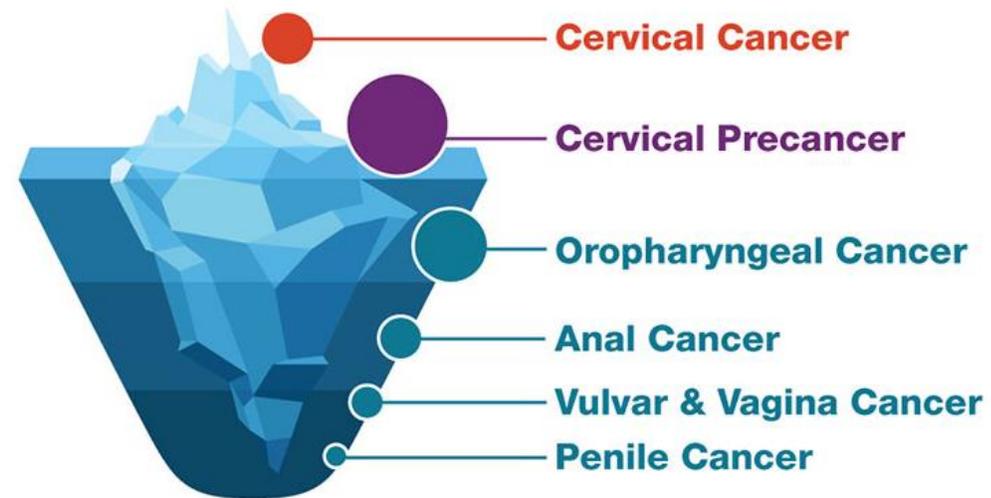


Risk Factors for Oral HPV: Age, sex, number of sexual partners and current number of cigarettes smoked per day

Prevention

HPV Vaccines for Prevention of HPV-driven Cancers

Screening Won't Protect Your Patients from Most HPV 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

Vaccine Efficacy Results from the Costa Rica Vaccine Trial

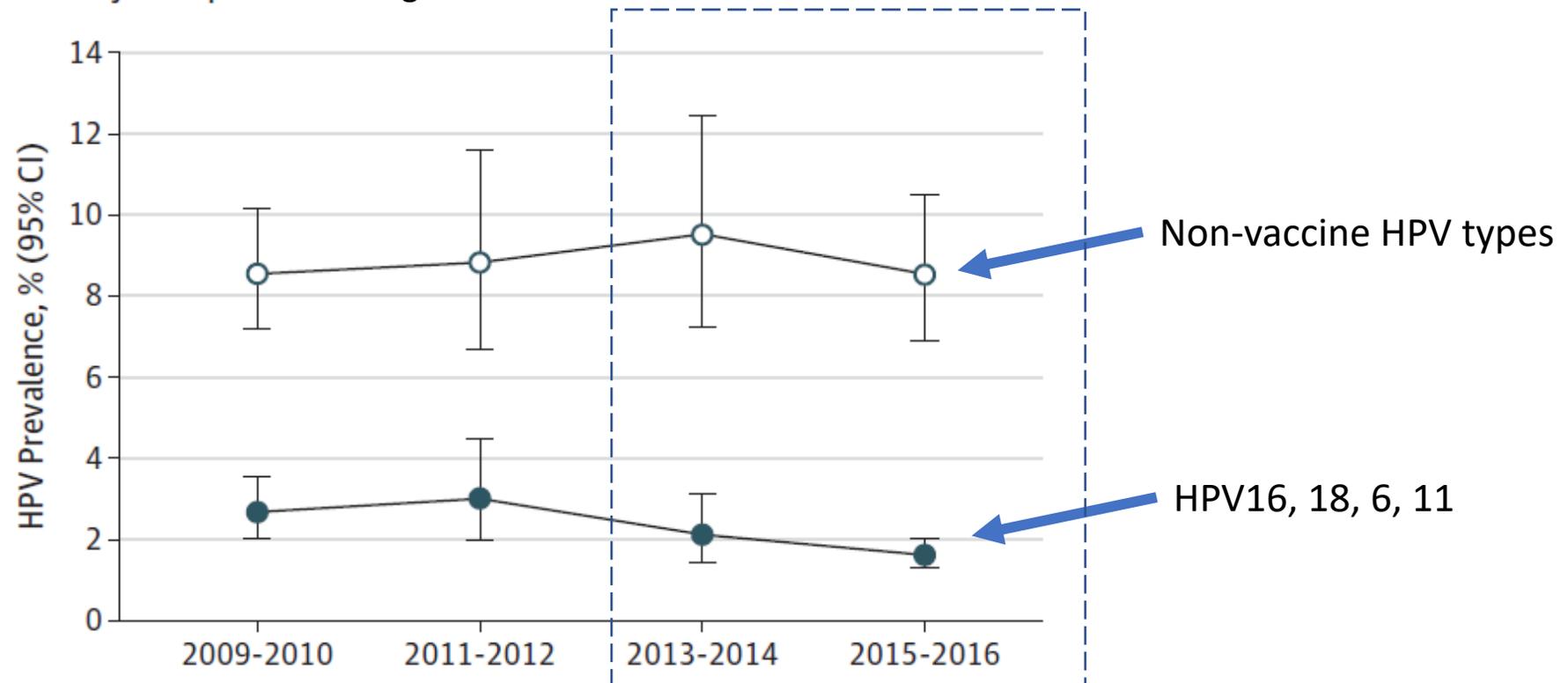


Aimee Kreimer, NCI

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%		

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

A Men: unadjusted prevalence Age 18-59



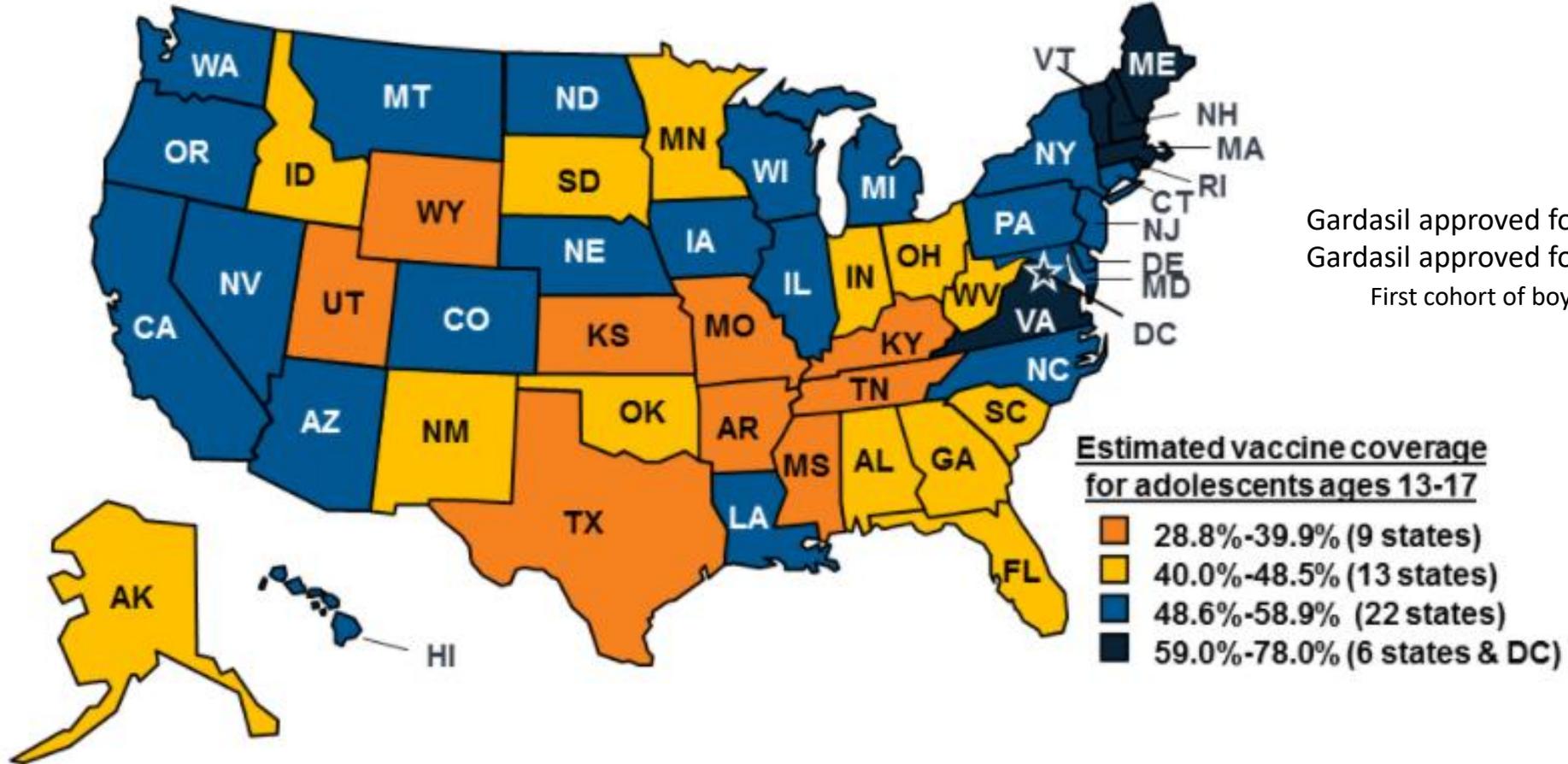
≥1 Dose of HPV Vaccine

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

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).

Diagnosis, Treatment and Survival

Diagnosing HPV-OPC

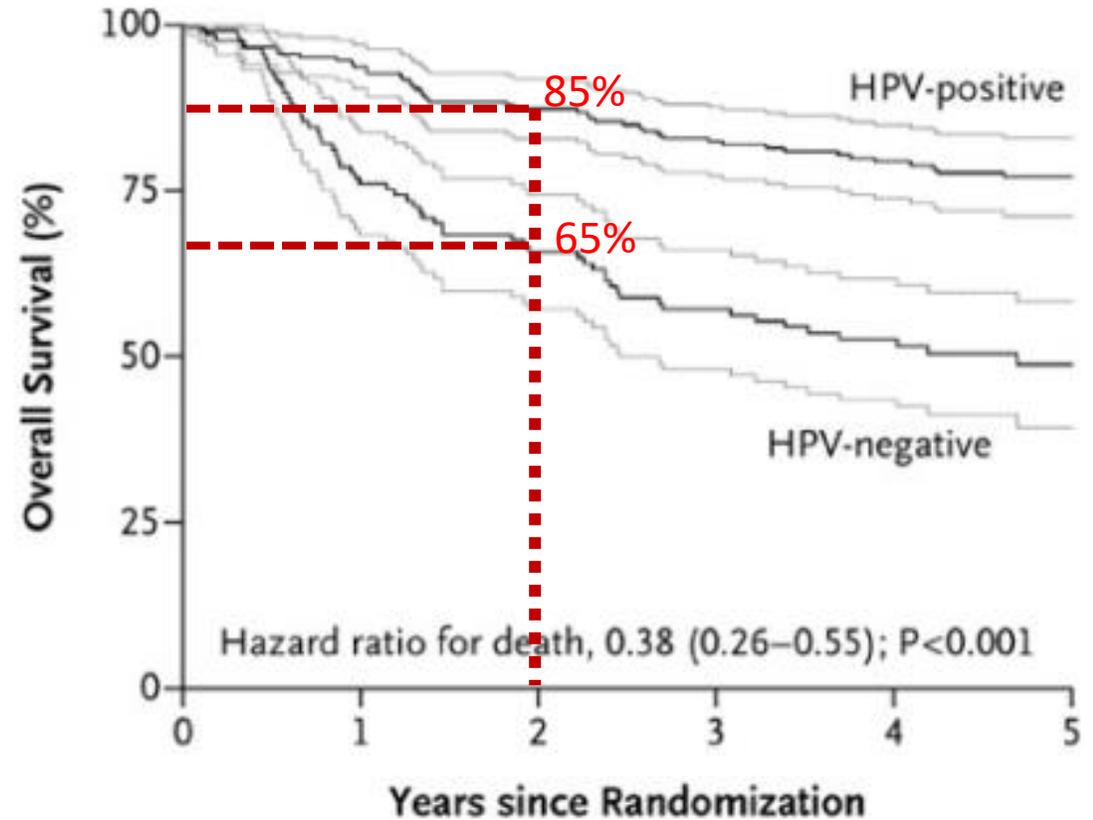
- Often begins with an enlarged node in the neck
- Referred to ENT if node does not resolve with antibiotics
- Fine needle aspiration
 - Look for squamous cell carcinoma
 - Test for p16 if enough cells present (more later)
- Imaging to find primary tumor
 - CT, MRI, PET
 - Up to 5% of cases remain unknown primaries and are assumed HPV-OPC



Treatment and Survival

- Surgery with adjuvant therapy – transoral robotic surgery (TORS)
- Definitive chemoradiation (CRT)
- HPV-positive OPC has superior survival compared to HPV-negative OPC

Overall Survival According to Tumor HPV Status



No. at Risk	0	1	2	3	4	5
HPV-positive	206	193	179	165	151	73
HPV-negative	117	89	76	65	51	22

Big Changes in the Field

- HPV testing
- Treatment De-escalation
- Staging – AJCC 8th Edition Staging

Official Guidelines for HPV Testing

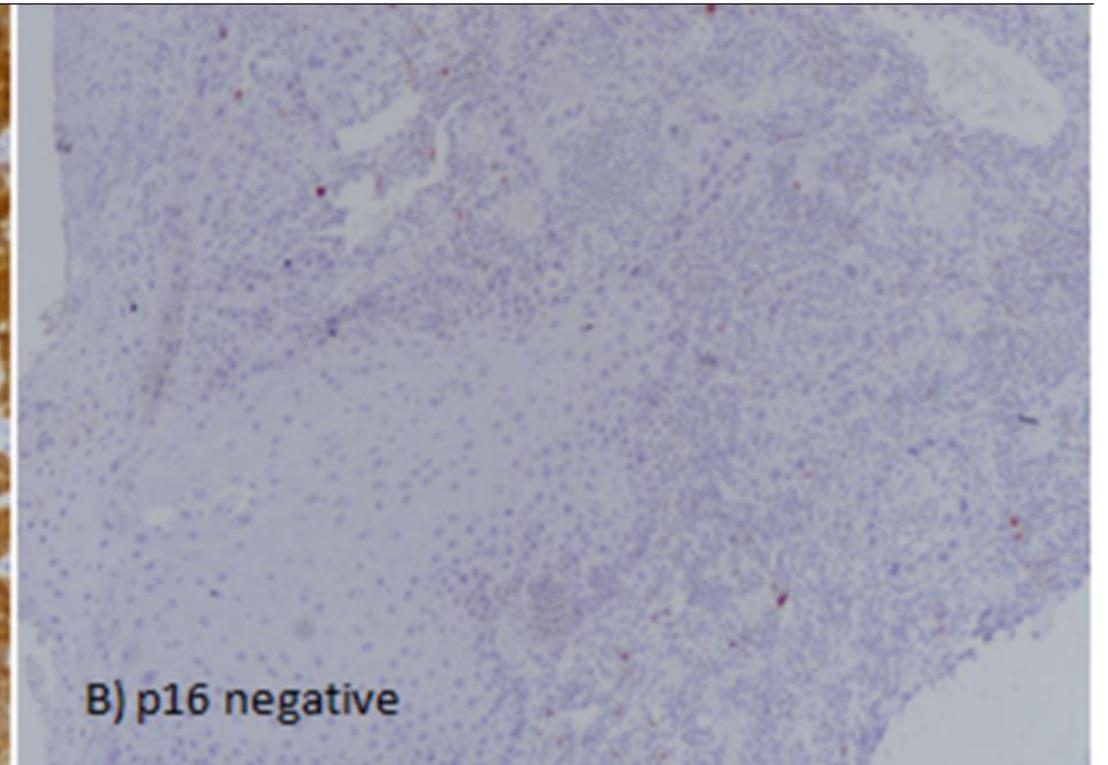
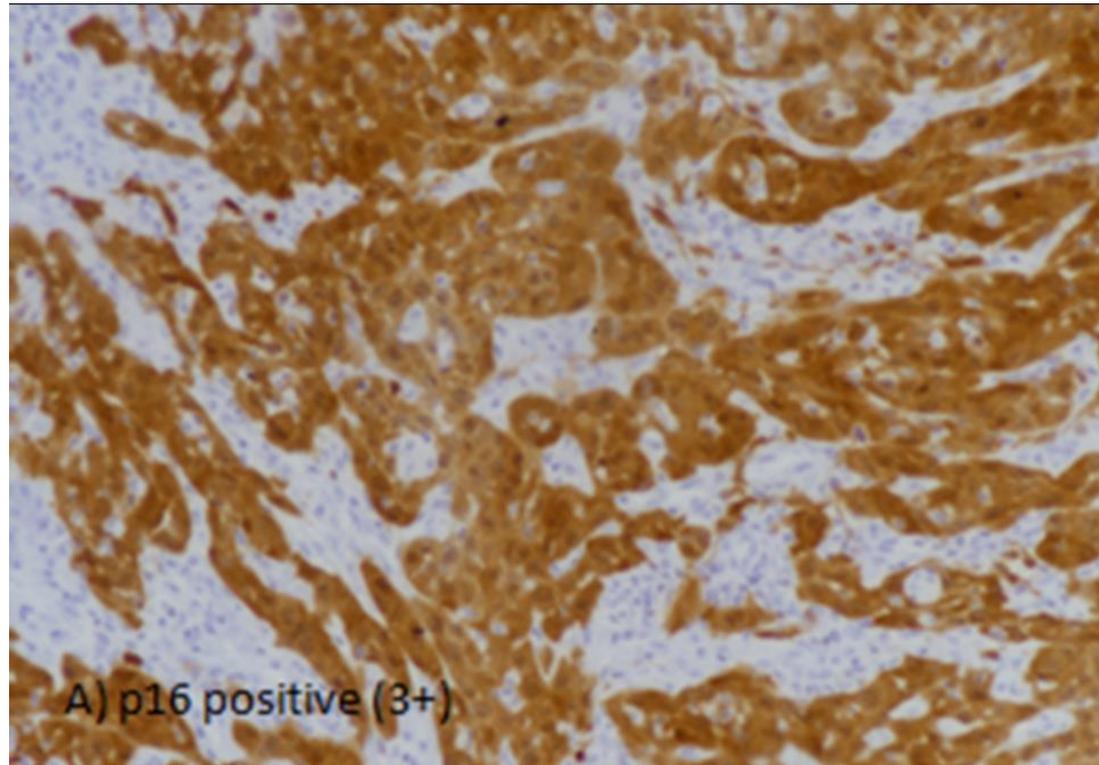
- Sporadic HPV testing began in around 2012 – confusion
 - P16 testing – variable definitions of positivity
 - HPV DNA testing
 - Lack of guidance on what anatomic subsites should be tested

- College of American Pathologists Guidelines 2017
 - P16 testing on all OPCs (SCC) with 70% nuclear staining considered positive
 - Recommended against routine testing for non-SCC and/or non-OPC head and neck cancers



James Lewis

P16 Immunohistochemical Analysis



Devastating Effects of Cancer Treatment

- Good News:

- Most patients survive HPV-OPC



- Bad News:

- Yet, treatment is associated with debilitating and often permanent side effects
- Feeding tubes, chronic pain, wooden neck, lymphedema, mucositis
- Side effects are most commonly associated with chemoradiation

Can we de-escalate treatment for HPV-OPC patients?

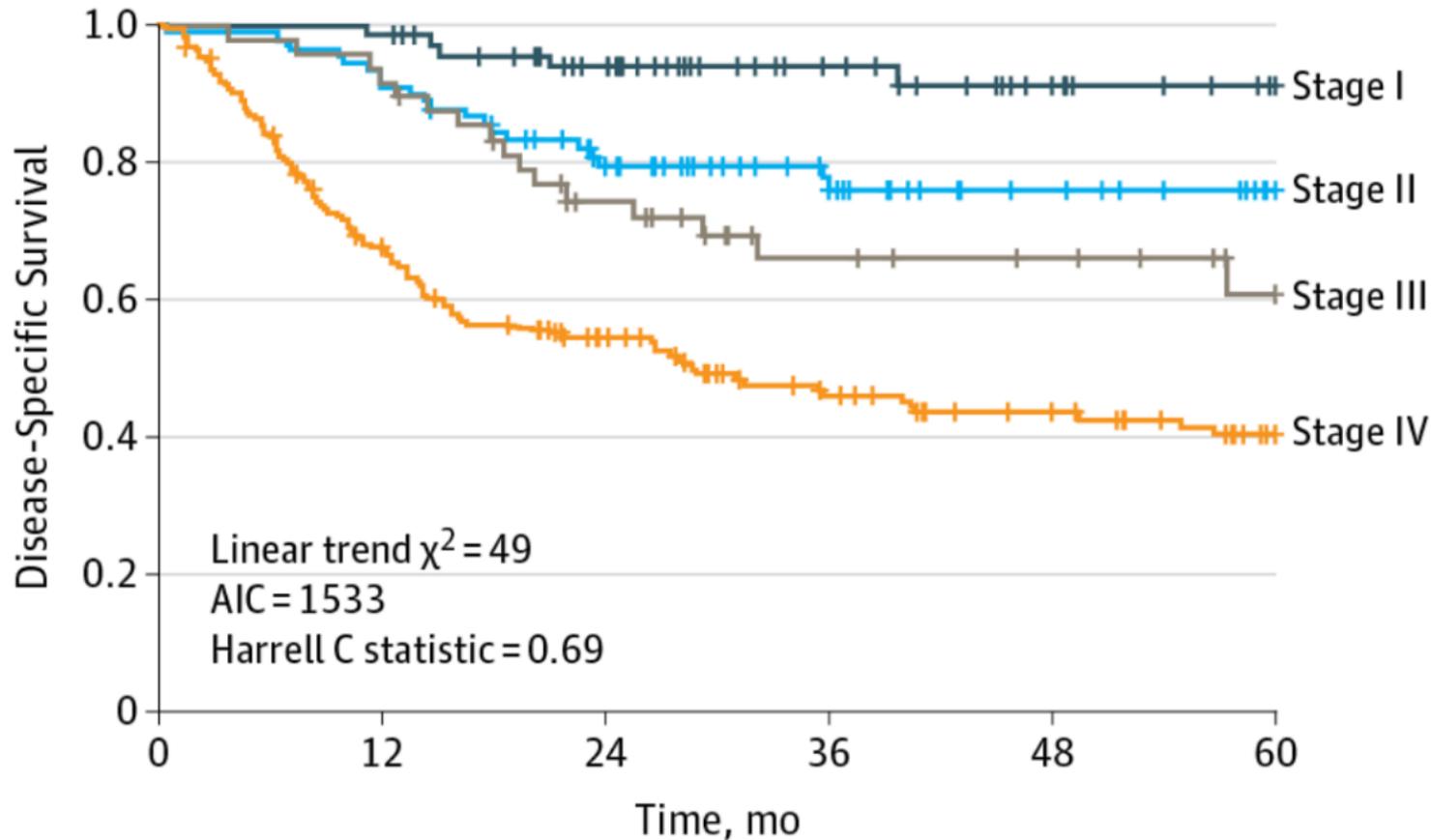
Clinical Challenges of HPV-OPC Treatment

- HPV-OPC has higher overall survival
- Yet, not all HPV-OPC patients respond well to treatment
- Up to 25% of patients who initially respond to treatment will recur in 3 years
- Few clinical and molecular markers to identify these “high-risk” HPV-OPC patients prior to treatment

AJCC 7th Edition Staging was non-prognostic for HPV-OPC

Traditional Staging Principles

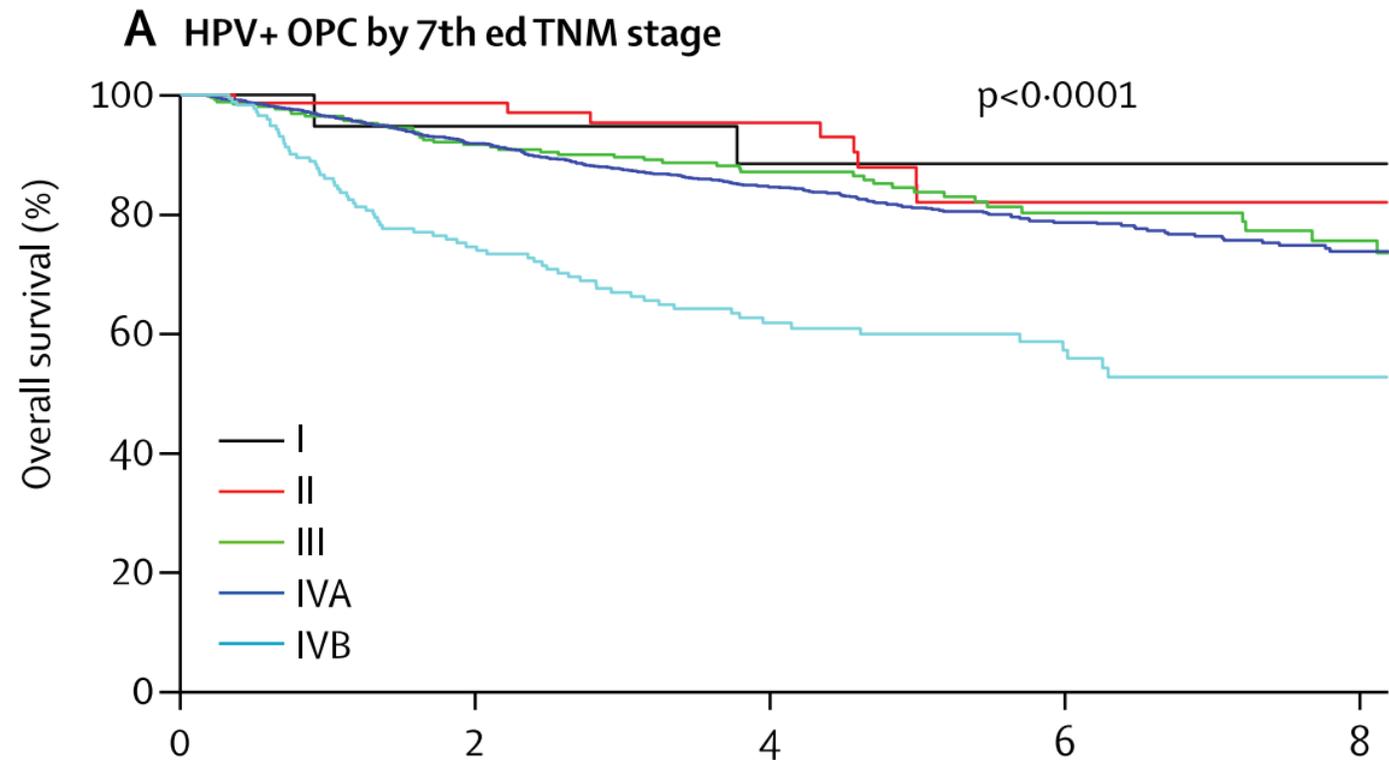
AJCC staging system



Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

AJCC 7th Edition Staging for HPV-OPC was Non-Prognostic

- HPV-OPC tumors metastasize to the neck very early in cancer development
- Most HPV-OPC patients were then being diagnosed as having Stage 4 cancer despite having very survival
- Stage was not reflective of patients' actual survival



AJCC 8th Edition Staging for HPV-OPC (2018)

Separate staging for P16+ vs. P16- OPC

Table 5. AJCC (8th Edition) Prognostic Stage Groups for Non-HPV-Associated (p16-) OPSCC

T Category	N Category	M Category	Stage Group
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

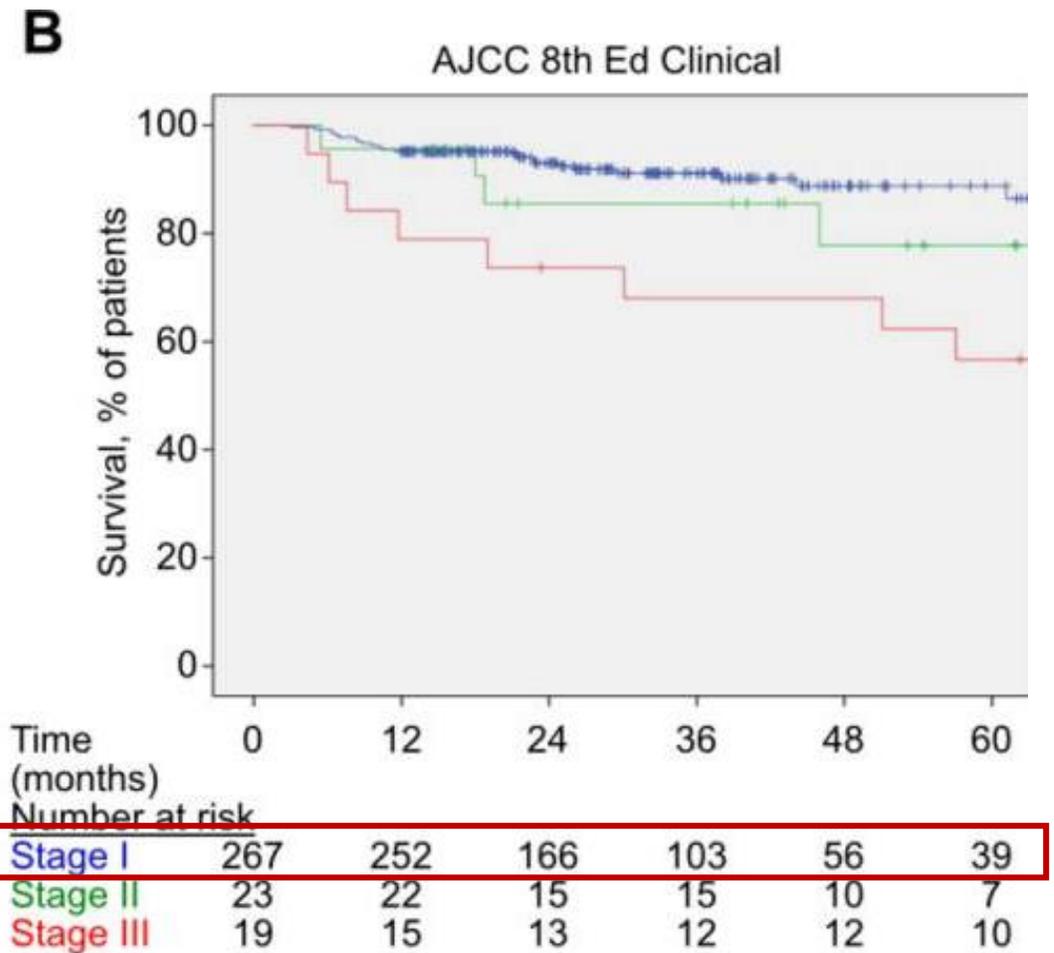
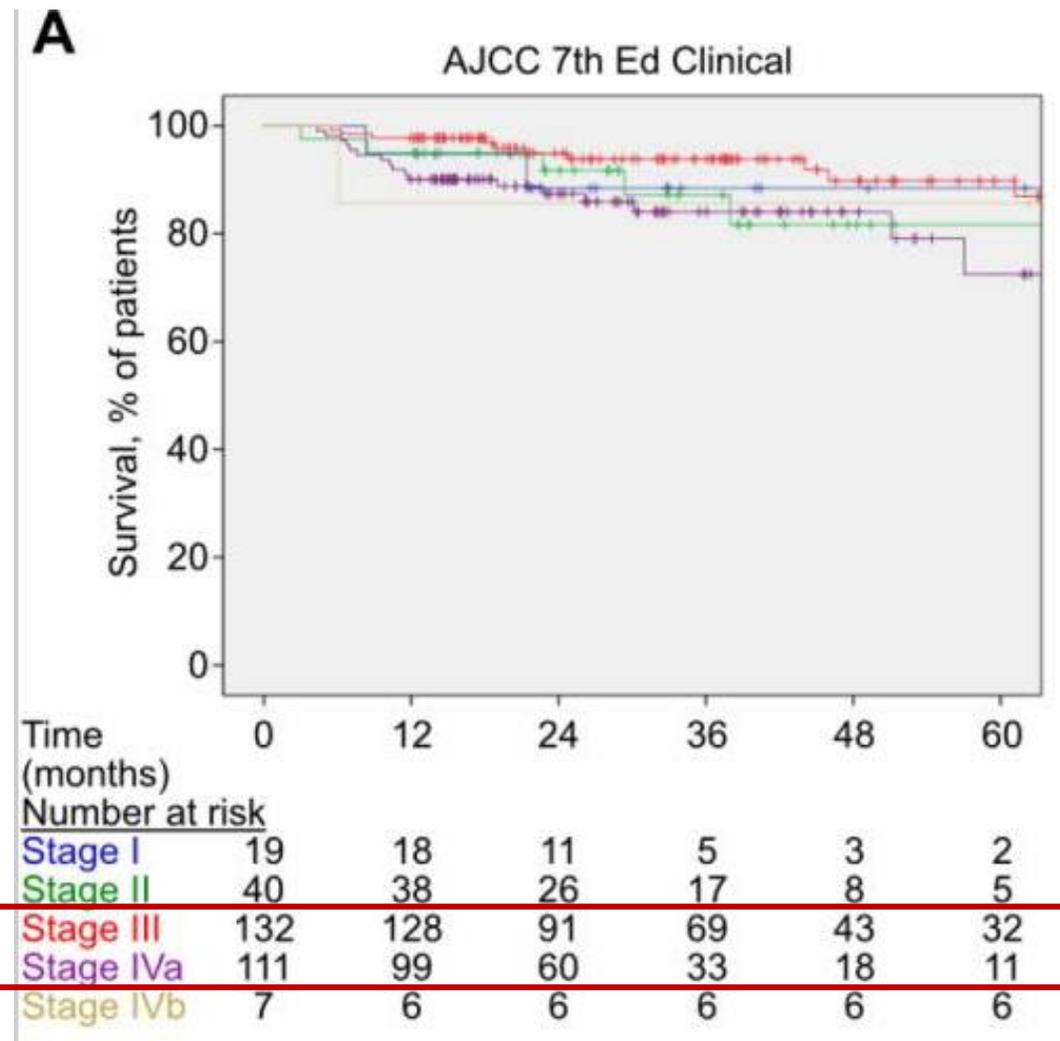
AJCC = American Joint Committee on Cancer; HPV = human papillomavirus; OPSCC = oropharyngeal squamous cell carcinoma.

Table 2. AJCC (8th Edition) Prognostic Stage Groups for HPV-Associated (p16+) OPSCC (Clinical)

T Category	N Category	M Category	Stage Group
T0, T1, or T2	N0 or N1	M0	I
T0, T1, or T2	N2	M0	II
T3	N0, N1, or N2	M0	II
T0, T1, T2, T3, or T4	N3	M0	III
T4	N0, N1, N2, or N3	M0	III
Any T	Any N	M1	IV

AJCC = American Joint Committee on Cancer; HPV = human papillomavirus; OPSCC = oropharyngeal squamous cell carcinoma.

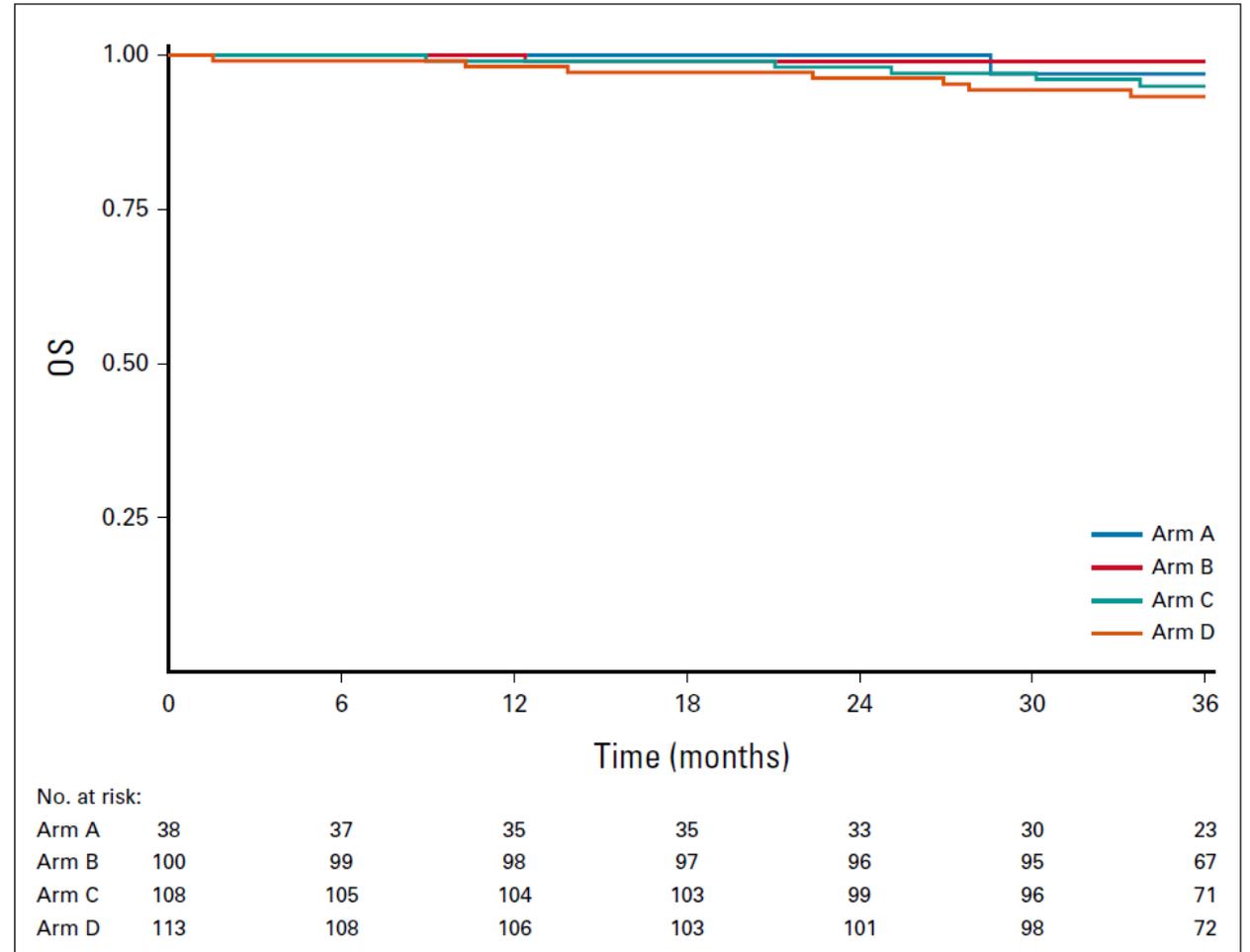
Comparison of 7th and 8th AJCC Editions



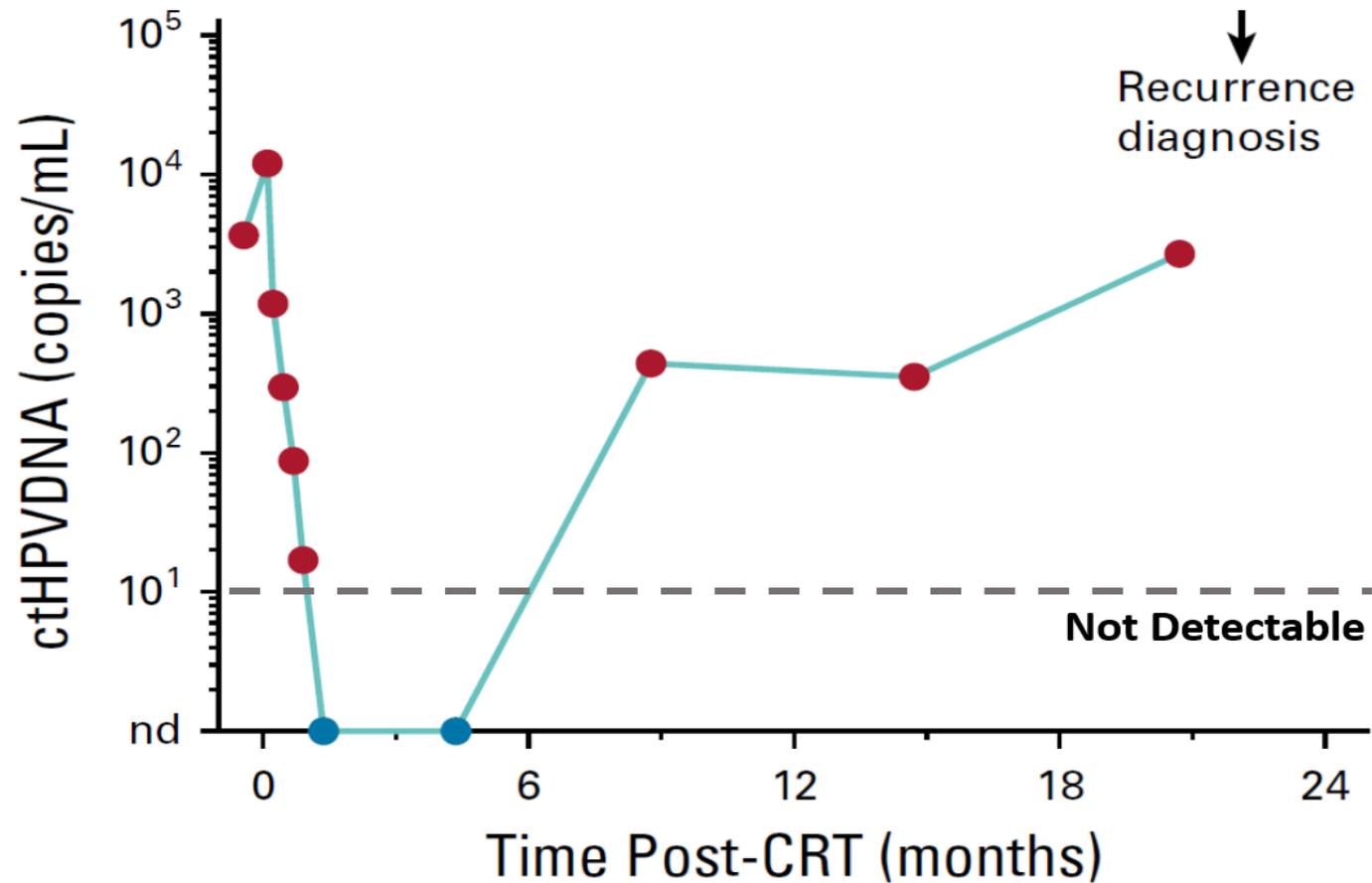
We made a lot of progress, but
there is still much to do:
Up and Coming Advances

Treatment De-escalation

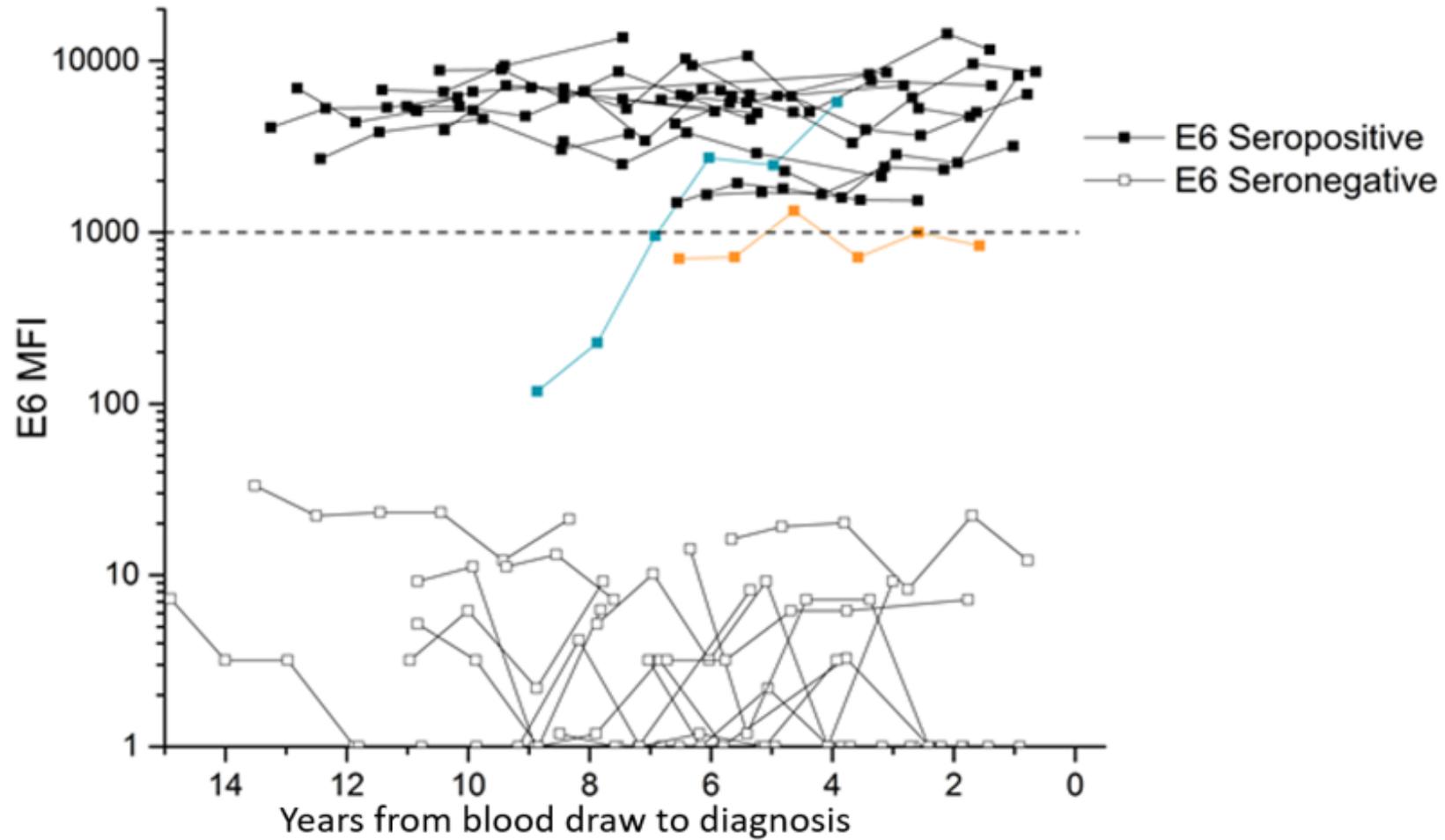
- Many studies on going
- ECOG 3311 – TORs reduced radiation with or without chemotherapy
- No differences in survival for those who were de-escalated



Circulating HPV Tumor DNA



Biomarkers for Early Detection



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 are due to HPV16
- HPV vaccination is highly effective at preventing oral HPV infection, but vaccine uptake is still low.
- HPV-OPC is often diagnosed with a lump in the neck and p16-testing
- HPV-OPC patients have superior survival compared to HPV-negative patients; yet, treatment is highly morbid
- Field is now focused on de-escalated treatment – but there is more work to be done to find the correct method
- Ongoing research on early detection

Questions?

