

The Importance of

ORAL HPV SCREENING

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White Paper



Executive Summary

Human papillomavirus (HPV) is a double-stranded DNA virus classified into high and low-risk genotypes based on oncogenic potential. High-risk HPV types, particularly HPV-16, have emerged as the dominant etiologic factor in a subset of oropharyngeal squamous cell carcinoma (HPV-OPSCC), an increasingly prevalent subset of head and neck cancers, distinct from cancers traditionally associated with tobacco and alcohol use. HPV-OPSCC typically affects younger, non-smoking adults, carries a distinct molecular profile, and responds differently to therapy. This white paper reviews the natural course of HPV oral infection, quantifies cancer risk, and evaluates saliva-based molecular assays as a non-invasive tool for population screening, early detection, management, and post treatment surveillance of HPV-OPSCC. In addition, this paper suggests testing guidelines, in the absence of approved testing strategies.

Pathogenesis of HPV

HPV infects basal epithelial cells through micro-abrasions, primarily targeting tonsillar crypts, the base of the tongue, and other oropharyngeal tissues. High-risk HPV types integrate their genomes into host cells, producing viral oncoproteins E6 and E7.

Natural Course of Oral HPV Infection

- **Initial Infection:** Most oral HPV infections are asymptomatic and resolve without treatment
 - Median clearance time for oral HPV 16 is approximately 12 months
 - Infected individuals can transmit infection even if the infection is asymptomatic
- **Viral Clearance:** >90% clear within 12–24 months
- **Persistence:** Associated with 8.6-fold increased risk of HPV-OPSCC within 10 years, especially in males, smokers, and immunocompromised individuals
- **Cancer Progression:**
 - Average interval from persistent infection to cancer diagnosis is 4–6 years creating a window of opportunity for screening and prevention
 - HPV-OPSCC is generally associated with better prognosis than HPV-negative OPSCC
 - HPV-OPSCC has a higher response to chemotherapy, improved 5-year survival (85% vs 50% for HPV-negative OPSCC)

Transmission

- Oral-Genital Contact: Primary mode; increased risk with multiple partners
- Deep Kissing: Salivary transfer; less common
- Autoinoculation: Self-transfer from infected sites
- Perinatal Transmission: Rarely during vaginal delivery

Prevalence

HPV Prevalence: General U.S. Adult Population (Ages 18–69, N=95,000)*

Group	Genital High Risk	Oral High Risk
Men	25.10%	6.80%
Women	20.40%	1.20%

*Centers for Disease Control and Prevention, National Center for Health Statistics. (2014). National Health Nutrition Examination Survey 2013–2014 data documentation, codebook, and frequencies. U.S. Department of Health and Human Services. <https://www.cdc.gov/nchs/nhanes/continuousnhanes.htm>

Highest prevalence occurs in two age peaks: 30–34 and 55–60

- Older men, individuals with high numbers of sexual partners, current smokers, people living with HIV, and the unvaccinated, are at highest risk for oral HPV infection, with risk modulated by behavioral and demographic factors

Incidence: HPV Head and Neck Cancers

High Risk Oral HPV and Cancer Progression in Adult Population Ages 18-69

High Risk Oral HPV Prevalence*	Annual HPV-Attributable OPSCC**	Percent Infected Developing Cancer	Annual Number of Cases
Men	10.10%	0.19%	12000
Women	3.60%	0.24%	3000

*Gillison ML, et al. Prevalence of Oral HPV in the United States, 2019-2020. JAMA

Otolaryngol Head Neck Surg. 2022

** CDC Annual Cancer Report

- Annual percent change in HPV-OPSCC between 2010 and 2024 is +5.4%
- OPSCC incidence has been rising steadily, particularly among men aged 40–60.
 - HPV now accounts for >70% of OPSCC cases in the U.S., surpassing cervical cancer as the most common HPV-associated malignancy
- Risk Factors include multiple oral sex partners, tobacco and alcohol use (synergistic with HPV), immunosuppression, and male sex
- HPV-16 is responsible for approximately 90% of HPV-positive oropharyngeal cancers
- The long-term effect of HPV vaccination on oral HPV prevalence and OPSCC incidence is under investigation, with early data suggesting reductions in oral HPV prevalence in vaccinated populations

Clinical Presentation and Asymptomatic Nature of HPV Infections

Most oral HPV infections resolve spontaneously; persistent HPV-16 markedly increases OPSCC risk (8.6-fold within 10 years). Symptomatic presentations include

- Oral warts
- Persistent sore throat
- Unilateral tonsillar swelling
- Neck mass

Problem Statement

There is a need to identify who is infected, is the infection persistent, and if so, is the persistence associated with hyperplasia

- Persistent infection with high-risk HPV, particularly HPV-16, is a well-established etiologic factor in the development of HPV-OPSCC
- HPV-positive OPSCC frequently presents at advanced stages due to asymptomatic progression, despite having better prognosis and treatment responsiveness than HPV-negative cancers
- At the present time, there are no guidelines for testing

Problem Solution

Routine screening may facilitate early cancer detection, risk stratification, and optimized clinical management

- High salivary HPV-16 sensitivity (81%) and specificity (94%) in preclinical OPSCC detection
- High viral load and persistent E6/E7 mRNA predict malignancy
- Post-therapy HPV clearance predicts survival
- Salivary HPV surveillance useful in immunocompromised or high-risk populations

Salivary Diagnostics

Saliva bathes the oropharyngeal mucosa providing an ideal, non-invasive matrix for HPV screening and detection

- Captures exfoliated cells from oral mucosa
- Highly acceptable to patients
- Collection is painless
- Repeatable and suitable for longitudinal monitoring
- High diagnostic sensitivity (>80%) and genotype specificity
- Effective in laboratory-developed tests (LDTs)

Clinical Utility of Salivary Diagnostics

- A 2023 meta-analysis (n+22k) reported pooled sensitivity of 81% and specificity of 94% for salivary HPV-16 in detecting pre-clinical HPV-OPSCC
- High viral load (>103 copies/mL) and/or E6/E7 mRNA persistence >6 months predicts malignant transformation
- Salivary HPV clearance at 12 weeks post-treatment correlates with 97% disease-free survival
- Salivary prevalence data show a 37% reduction of high-risk oral HPV among fully vaccinated cohorts

Spectrum SDNA-1000 Saliva Collection Device Validation

- Validated by Alimetric for high sensitivity, precision, and accuracy
- Capable of detecting multiple analytes
- Non-invasive, cost-effective, and highly compliant for patient use
- Facilitates differentiation of HPV-related OPSCC from tobacco/alcohol-associated OPSCC

Conclusion: Importance of HPV Screening in Oral Cavity

Routine screening has the potential to identify individuals at risk for HPV-related malignancy, resulting in early management with improved outcomes.

Global HPV-attributable cancer burden:

HPV is responsible for 4.5% of global cancer cases (8.8% women, 0.9% men), Approximately 690,000 cases annually. HPV-OPSCC represents a significant and growing subset, distinct clinically and prognostically from tobacco/alcohol-associated cancers*

Proportion of OPSCC cases that are HPV-positive:

Globally, **30.8–42.7%** of oropharyngeal squamous cell carcinoma (OPSCC) cases are HPV-positive, with a **meta-analysis reporting 45.8% positivity****

Temporal trends in HPV-OPSCC burden:

HPV-attributable OPSCC cases increased from approximately **22,000 cases in 2008 to 29,000 in 2012**, with the **HPV-attributable fraction rising from 26% to 31%** during that time.***

*de Martel, C., et al. (2020). Int J Cancer, 147(4), 1111–1120. <https://doi.org/10.1002/ijc.30716>

** Mes, S., et al. (2023). Mol Oral Microbiol, 38(4), 259–274.

<https://pubmed.ncbi.nlm.nih.gov/38158517/>

Fakhry, C., et al. (2023). JCO Global Oncology, 9, e2300464.

<https://ascopubs.org/doi/full/10.1200/GO.23.00464>

*** Gillison, M. L., et al. (2015). Oral Oncology, 50(6), 369–374.

<https://doi.org/10.1016/j.oraloncology.2014.12.00>

Problem Statement

The Lack of Consensus Guidelines for Oral HPV testing and Management of OPSCC Risk

Problem Solution

Development of Evidence Based Consensus Guidelines Defining Why, Who, How, When To Test

- Defining risk clearly in patients who test positive for HPV
- Managing transient infections versus persistent oncogenic infection
 - Protocols for determining transient versus persistent oncogenic infection are needed
 - Protocols for Identifying appropriate retesting intervals for HPV positive, asymptomatic individuals are needed
- Validation of screening tests, especially saliva-based diagnostics, and establishing clinical protocols for managing positive test results

Suggested Testing Protocol for Who and When To Test

1. Population: Adults 30-65 who practice oral sex, deep kissing with more than 2 lifetime partners; smokers, immunocompromised individuals
2. Testing Interval: Baseline followed by repeat testing every 12 months if not high risk, or every 6 months if high risk (longitudinal testing improves PPV)
3. Reflex Pathway: Individuals who are persistently positive should undergo fiber-optic exam, imaging, and if necessary, tissue biopsy
4. Patients should be encouraged to get vaccinated

Conclusion:

Salivary diagnostics offer significant potential in addressing challenges, enabling timely intervention, improving prognosis, and enhancing patient outcomes in HPV-associated head and neck cancers. Routine saliva-based molecular testing for HPV positivity and persistence offers a practical, scalable avenue for early identification of high-risk oral HPV infections. Integration of salivary diagnostics into head and neck cancer prevention pathways could enable timely intervention when treating head and neck cancers.

References:

Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst.* 2000;92(9):709-720

- Robust epidemiological and molecular evidence supporting a causal relationship between high-risk HPV (especially HPV16) and a subset of head and neck cancers, particularly oropharyngeal squamous cell carcinomas
- First major study to establish a causal link between HPV and a subset of HNSCC
- A strong association between HPV DNA presence, transcriptional activity of HPV oncogenes (E6/E7), and distinct clinical-pathologic profiles, including younger age at diagnosis, lower tobacco exposure, and improved prognosis relative to HPV-negative cases described

- Retrospective molecular pathology study
 - 253 head and neck squamous cell carcinoma (HNSCC) specimens analyzed for HPV DNA using PCR, Southern blot, and in situ hybridization
 - HPV DNA detected in 25% of tumors; 90% of HPV-positive tumors were HPV16
 - HPV-positive tumors were more likely in the oropharynx, had squamous cell basaloid histology, fewer TP53 mutations, and better prognosis
 - Foundational evidence for HPV-positive oropharyngeal cancer as a distinct clinical entity

Münger K, Baldwin A, Edwards KM, et al. Mechanisms of human papillomavirus-induced oncogenesis. *Virology.* 2004;324(1):17-27

- Review of the molecular mechanisms by which HPV induces oncogenesis
- Authors emphasize HPV's E6 and E7 oncogenes play critical roles by disrupting tumor suppressor pathways
 - E7 binds to and inactivates retinoblastoma (Rb) proteins, leading to dysregulated cell cycle progression and genomic instability—hallmarks of HPV-driven cancers
 - High-risk HPV types (e.g., HPV16, 18) encode E6 and E7 oncoproteins that inactivate tumor suppressors p53 and Rb
 - These interactions promote genomic instability and malignant transformation

Pickard RK Xiao W, Broutian T, He X, Gillison ML. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. *Sex Transm Dis.* 2012;39(7):559–566. doi:10.1097/OLQ.0b013e31824f1c65

- Study of 1,626 men from Brazil, Mexico, and the U.S. followed for oral HPV incidence and clearance
- Key data on natural history of oral HPV in men
- In the HIM cohort study examining oral HPV infection dynamics in men (1,626 men from Brazil, Mexico, and the U.S.), the authors reported a notable annual incidence rate of oral HPV infection (~4.4%), with HPV16 as the most prevalent genotype
 - High clearance rates (~45% Prospective cohort study (HIM Study) within 6 months; ~80% by 12 months), suggesting that while oral HPV infections are common, and the majority resolve spontaneously are described
- Risk factors: smoking, number of sexual partners, and new oral sex partners

Reuschenbach M, Rühling T, et al. Transmission and clearance of human papillomavirus infection in women: Oral HPV transmission pathways. *Rev Med Virol.* 2021;31(1):e2337. doi:10.1002/rmv.2337

- Narrative review of HPV transmission and clearance pathways in women
- This systematic review analyzes oral HPV transmission in women, highlighting sexual behaviors (especially oral sex) as significant risk factors
- Rapid clearance of oral HPV infections in women (similar to men), reinforcing the transient nature of most oral HPV infections but underscoring their potential to persist in a minority, increasing oncogenic risk are described

- Oral HPV likely transmitted via sexual contact (oral-genital, oral-oral)
- Autoinoculation and perinatal transmission possible but less significant
- Clearance influenced by immune status, age, and viral load

D'Souza G, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *JAMA*. 2007;298(7):743-749

- This pivotal case-control study solidified the epidemiologic link between oral HPV and oropharyngeal cancer
 - Oral HPV16 infection significantly increased oropharyngeal cancer risk by a factor of over 14-fold
 - The strongest risk factors identified included oral sexual behaviors and multiple sexual partners, confirming sexual transmission as key
 - Case-control study (100 oropharyngeal cancer cases, 200 controls)
 - Strong association between oral HPV16 infection and oropharyngeal cancer (OR ~14.6)
 - Sexual behavior (oral sex, number of partners) significantly associated with cancer risk
 - HPV-positive tumors had better prognosis than HPV-negative ones

Chaturvedi AK et al. Natural History of Oral HPV Infection. *N Engl J Med* 2021

- In this comprehensive review on the natural history of oral HPV infection, the authors emphasized that most oral HPV infections clear spontaneously, typically within one year,
 - Persistence (particularly of HPV16) is relatively rare but significantly associated with progression to oropharyngeal cancer
 - Persistent HPV16 infections emerged as a crucial marker for cancer risk
- Oral HPV infection is dynamic, with most infections clearing naturally
- High-risk HPV types, especially HPV16, had the lowest clearance rates

Kreimer AR, et al. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Lancet Infect Dis*. 2010;10(8):563-570

- This global systematic review highlighted HPV16 as the predominant genotype in head and neck cancers worldwide, detected in approximately 85% of HPV-positive oropharyngeal tumors
- Noted is significant geographical variability in HPV prevalence in head and neck cancers
 - Higher in developed regions compared to developing countries, suggesting behavioral or demographic influences
- HPV16 most prevalent in oropharyngeal cancers globally
 - Other high-risk types (e.g., HPV18, 31, 33) present at much lower rates
 - Highest HPV prevalence in North America and Europe than Asia

Gillison ML, et al. Tobacco use and oral HPV16 infection. *JAMA Oncol*. 2017;3(2):169-177

- This study examined the relationship between tobacco use and oral HPV16 infection, reporting a positive association
 - Tobacco users showed significantly increased oral HPV16 prevalence compared to non-smokers, suggesting tobacco may either enhance susceptibility to infection or reduce viral clearance, compounding the carcinogenic risk
 - Tobacco use associated with higher prevalence of oral HPV16 infection
 - Effects seen for both current and former smokers
 - Synergistic risk with sexual behavior factors

Gillison ML, et al. Prevalence of Oral HPV in the United States, 2019–2020. *JAMA Otolaryngol Head Neck Surg*. 2022

- In an update on U.S. national prevalence of oral HPV (2019–2020), Gillison reported stable oral HPV prevalence compared to earlier surveys (~7% overall)
 - The highest prevalence was seen in men, individuals aged 50–60, and those reporting multiple oral sexual partners, emphasizing continued demographic-specific risk patterns
 - 7.5% of U.S. adults had oral HPV infection; HPV16 prevalence ~1%
 - Men had higher infection rates than women
 - Declines in prevalence likely related to changes in behavior and vaccination

Chaturvedi AK, et al. Human papillomavirus and rising oropharyngeal cancer incidence United States. *J Clin Oncol*. 2011;29(32):4294–4301

- This study documented rising incidence rates of HPV-associated oropharyngeal cancers in the U.S. from 1988 to 2004, particularly among men under age 60
- Increase primarily due to higher oral HPV exposure through changing sexual behaviors
 - Strong correlation with HPV-positive disease
 - OPC incidence increased despite declines in tobacco and alcohol use

Giuliano AR, Felsher M, Waterboer T, et al. Oral human papillomavirus prevalence and genotyping among a healthy adult population in the US. *JAMA otolaryngol Head Neck Surg*. 2023;149(9):783–795. Doi:10.1001/jamaoto.2023-1573

- This large U.S. study assessed oral HPV prevalence and genotype distribution among healthy adults
 - Approximately 6.9% tested positive, predominantly with HPV16
 - Prevalence was higher among males and correlated significantly with sexual behavior, indicating the ongoing need for targeted preventive measures
- Cross-sectional study of 3,196 healthy U.S. adults aged 18–60
- Conducted across 43 dental clinics in 21 states
- Overall oral HPV prevalence: 6.6%; high-risk HPV: 2.0%; HPV16: 0.7%
 - Men had higher prevalence than women

- Vaccinated individuals had significantly lower prevalence of vaccine-type HPV

CDC Annual Report to the Nation on the Status of Cancer, 2024 Annual epidemiological surveillance report by CDC, NCI, ACS, and NAACCR

- Includes incidence and mortality trends from national cancer registries
- Overall cancer mortality continues to decline in the U.S.
- HPV-associated oropharyngeal cancers remain a growing concern, especially among men
- COVID-19 pandemic caused a temporary dip in cancer diagnoses in 2020, rebounding by 2021
- This comprehensive annual report highlighted a continued upward trend in HPV-associated oropharyngeal cancers, with HPV-positive cases constituting a significant proportion of head and neck cancers
- The CDC emphasized vaccination and early detection strategies as critical preventive measures

Mehanna H, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer—systematic review and meta-analysis of trends by time and region. *BMJ*. 2010;340:c14

- Systematic review and meta-analysis of HPV prevalence in head and neck cancers by region and time
- Meta-analysis revealed increasing prevalence of HPV in oropharyngeal cancers over several decades, with marked regional differences (highest in North America and Europe)
- HPV prevalence in oropharyngeal cancer (OPC) rose from 40.5% pre-2000 to 72.2% by 2005–2009
- No significant increase in HPV prevalence in non-oropharyngeal head and neck cancers
- North America and Europe now show similar HPV-OPC prevalence

Fakhry C, et al. Prognostic significance of oral HPV16 DNA detection after treatment for oropharyngeal cancer. *JAMA Otolaryngol Head Neck Surg*. 2014;140(12):1131-1138

- Prospective cohort study of 124 patients with HPV-positive oropharyngeal cancer
- Oral rinse samples collected at diagnosis and post-treatment
- This study demonstrated that detecting oral HPV16 DNA post-treatment for oropharyngeal cancer served as a robust prognostic biomarker
- Patients with persistent HPV16 DNA post-treatment showed significantly higher recurrence and mortality rates compared to those clearing the infection, emphasizing the potential clinical utility of HPV testing in surveillance
 - All patients with persistent HPV16 DNA experienced recurrence
 - Median time to recurrence: ~7 months after first positive post-treatment sample

Li H, et al. Diagnostic Accuracy of Salivary HPV Testing: Meta analysis. *Clin Cancer Res* 2023

- This meta-analysis confirmed high diagnostic accuracy of salivary HPV DNA testing for detecting HPV-positive oropharyngeal cancers
- Saliva-based detection showed strong sensitivity and specificity, highlighting its potential as a non-invasive diagnostic and screening tool
- Diagnostic odds ratio and area under the curve indicated acceptable accuracy

Chera BS, et al. Salivary HPV DNA Clearance as a Prognostic Biomarker. *JAMA Oncol* 2024

- The study revealed that clearance of salivary HPV DNA following treatment strongly correlated with favorable prognosis in HPV-positive oropharyngeal cancer patients
- Lack of clearance indicated higher recurrence risk, underscoring the potential of salivary HPV testing in clinical follow-up

Tota JE, et al. Impact of Vaccination on Oral HPV Prevalence. *Cancer Epidemiol Biomarkers Prev* 2025

- Examining the impact of HPV vaccination, the authors reported a substantial reduction in oral HPV prevalence among vaccinated cohorts, underscoring vaccination's critical role in primary prevention of HPV-associated oropharyngeal cancers
- HPV vaccination expected to significantly reduce oral HPV prevalence in younger cohorts
 - Impact on overall OPC incidence will be delayed due to older unvaccinated populations
 - Most benefit seen in individuals under 55 by 2045

Wang MB, et al. HPV-positive oropharyngeal carcinoma: a review of biologic and clinical characteristics. *Otolaryngol Head Neck Surg*. 2016;154(6):1040-1047

- The review characterized HPV-positive oropharyngeal carcinomas as biologically and clinically distinct from HPV-negative tumors
 - Tailored therapeutic approaches feasible
 - HPV-positive OPC is biologically distinct: younger patients, better prognosis, and improved treatment response
 - E6/E7 oncoproteins drive carcinogenesis via p53 and Rb inactivation
 - ◊ Treatment de-intensification is under investigation for this subgroup

Weems D, et al. Development and validation of a salivary HPV DNA test for oropharyngeal cancer detection. *Cancer Prev Res (Phila)*. 2015;8(3):221-227

- The authors successfully developed and validated a highly sensitive salivary HPV DNA test capable of detecting HPV-positive oropharyngeal carcinoma
 - They demonstrated its feasibility for potential clinical use as an early detection tool in at-risk populations
 - Salivary HPV DNA testing showed high specificity and moderate sensitivity for HPV16-positive OPC
 - ◊ 72% of OPC patients had detectable HPV DNA in saliva
 - Potential for early detection and recurrence monitoring

Ngoc Ha Tran et. al. Advances in Human Papilloma Virus Detection and Molecular Understanding in Head and Neck Cancers: Implications for Clinical Management. *Journal of Medical Virology*. June 24. doi: org/10.1002/jmv.29746

- Review of advances in HPV detection and molecular understanding in head and neck cancers
- This review summarized significant advancements in molecular detection technologies (such as next-generation sequencing and digital PCR) for HPV in head and neck cancers, and discussed how these innovations might enhance clinical management through precise diagnostics, treatment monitoring, and personalized medicine strategies
 - Liquid biopsy (saliva-based RT-qPCR) is emerging as a promising diagnostic tool
- Molecular profiling can guide treatment decisions and improve outcomes

Oljak M, Cuschieri K, Alemany L, Vorsters A. 2023. Testing for Human Papillomaviruses in Urine, Blood, and Oral Specimens: An Update for the Laboratory. *J Clin Microbiol* doi: 10.1128/jcm.01403-22

- The authors provided an updated overview of laboratory testing methods for HPV detection in various specimen types, including oral, urine, and blood samples
- They emphasized recent advances in sensitivity, specificity, and feasibility of non-invasive testing strategies, highlighting their practical application for routine HPV screening and cancer diagnostics
- Laboratory-focused review on HPV testing in urine, blood, and oral specimens
- Oral specimens (saliva, oral rinse) are increasingly viable for HPV detection
- ddPCR and RT-qPCR are the most sensitive methods for detecting high-risk HPV types
 - Standardization and validation across labs remain challenges



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