

Oral Screening Lesion Identification Systems and Genetic Screening

Policy Number: AHS – G2113 – Oral Screening, Lesion Identification Systems and Genetic Screening	Prior Policy Name and Number, as applicable:
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I. Policy Description

Oral cancer is defined as cancer occurring in the oral cavity between the vermilion border of the lips and the junction of the hard and soft palates or the posterior one third of the tongue. Squamous cell carcinoma is the most common type of oral cancer (Gross, Lee, Okuno, & Rao, 2020).

Oral Screening and Lesion Identification Systems are adjunctive screening tests to identify malignancy in the lips, oral cavity or oropharynx (Fuller et al., 2015).

II. Related Policies

Policy Number	Policy Title

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. For individuals with oropharyngeal squamous cell carcinoma, high-risk HPV testing by one of the following methods **MEETS COVERAGE CRITERIA**:
 - a. HPV E6/E7 mRNA expression testing OR
 - b. Expression of p16 as detected by immunohistochemistry

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

2. Oral screening, lesion identification systems and genetic testing **DO NOT MEET COVERAGE CRITERIA** for all uses. This includes, but is not limited, to the following:

- a. OraRisk® HPV Complete Genotyping Test and OraRisk® HPV 16/18/HR Test (OralDNA labs, Brentwood, TN)
 - b. MOP™ testing
 - c. SaliMark OSCC® (PeriRx)
3. The use of salivary biomarkers to screen, detect, or diagnose oral cancer **DOES NOT MEET COVERAGE CRITERIA**. This includes, but is not limited to, the following:
- a. Salivary peptides and proteins, such as protein 14, Mac-2 binding protein, profilin 1, CD59, defensin-1, IL-1 β , IL-8, lactate dehydrogenase, and catalase
 - b. Salivary nucleic acids, such as methylated DNA testing, mRNAs, modified nucleotides (such as 8-OHdG), microRNA (miRNAs)
 - c. Salivary metabolites, such as valine, lactic acid, and phenylalanine

IV. Scientific Background

The American Cancer Society estimates the 2019 incidence of oral cancer to be 53,000 cases with approximately 10,860 deaths (Siegel, Miller, & Jemal, 2019). Estimates for 2020 from the American Cancer Society approximate that 53,260 people will be diagnosed with oral cavity and oropharyngeal cancers in the United States and 10,750 people will die from these cancers (ACS, 2020). The American Cancer Society estimates that in 2021, there will be approximate 54,0101 new cases of oral cavity or oropharyngeal cancer, and about 10,850 individuals will die from these cancers (ACS, 2021). Oral squamous cell carcinoma (OSCC) is the most common form of oral cavity cancer, which constitutes 94.08% of all epithelial tumors and 80.05% of all oral cancers (Dhanuthai et al., 2018; Scully & Porter, 2000). Many cases are preceded by a potentially malignant disorder (PMD), which is a heterogeneous group of conditions including erythroplakia, non-homogeneous leukoplakia, erosive lichen planus, oral submucous fibrosis and actinic keratosis (Warnakulasuriya, Johnson, & van der Waal, 2007). The early detection and excision of PMD can prevent malignant transformation (Paul Brocklehurst, 2017; van der Waal, 2009; Warnakulasuriya et al., 2007).

Human papillomavirus (HPV) is a common sexually transmitted infection that may lead to the development of warts or cancer in various parts of the body including the back of the throat, tonsils and base of the tongue. This type of cancer is known as oropharyngeal cancer. HPV is also a major contributor to the development of head and neck squamous cell carcinoma (HNSCC), which can develop in the mouth, nose and throat (Borsetto et al., 2018). According to the CDC (2021), there is no test to determine an individual's HPV status, and "there is no approved HPV test to find HPV in the mouth or throat."

Oral Screening Lesion Identification Systems and Genetic Screening

Diagnosing and treating dermatologic lesions of the mouth and gums is challenging for most clinicians because of the wide variety of disease processes that can present with similar appearing lesions and the fact that most clinicians receive inadequate training in mouth diseases (Lodi, 2020). Several index tests have been proposed as adjuncts to a conventional oral examination (COE) to improve diagnostic

test accuracy (Fedele, 2009; Lingen, Kalmar, Karrison, & Speight, 2008; Patton, Epstein, & Kerr, 2008; Rethman et al., 2010; Seoane Leston & Diz Dios, 2010). These tests include vital staining, brush cytology, light-based detection, and blood or saliva analysis. The COE is the standard visual and tactile exam of the mucosa under normal light. Although it is quick and minimally invasive, abnormalities may not be malignant or even visible (Macey et al., 2015). These screening tests are not only used for diagnostic purposes but can also be utilized as a tool to measure any changes that may be signs of future disease development (Speight et al., 2017).

Vital staining refers to a set of techniques where the oral mucosa tissues are stained for PMDs or malignancies. A dye such as toluidine blue is used to identify any tissues of interest. The sensitivity of the toluidine blue test for the detection of malignant lesions of the oral cavity and oropharynx has been identified at 92.6%, the specificity at 67.9% and the overall diagnostic accuracy at 80% (Vijayakumar, Reghunathan, Edacherian, & Mukundan, 2019). The vital staining procedure is as follows: pre-rinse with acetic acid, rinse with water, apply the dye, rinse again with acetic acid, rinse with water, then check the mucosa for staining. If the tissue is stained, it is considered a positive test. Advantages of this test include identifying invisible areas and how large a PMD is, while disadvantages include failure to stain the tissue and difficulty in differentiating benign from malignant lesions. Macey et al. (2015) evaluated 14 studies of 1248 patients (1338 lesions) and determined the sensitivity to be 0.84 and the specificity to be 0.70. The ViziLite® TBlue (Zila tolonium chloride) Annual Oral Cancer Screening System by DenMat helps to identify and monitor abnormal oral cells. This procedure takes two minutes to complete. The patient uses a specially formulated mouthwash which allows cell abnormalities to become visible to oral healthcare professionals (DenMat, 2020b). Zila tolonium chloride is a patented pharmaceutical-grade form of toluidine blue stain.

Brush cytology refers to the assessment of cells from suspicious areas. These cells are scraped off and evaluated microscopically. Cytopathologists classify the results. This technique allows the clinician to evaluate all three layers of the oral mucosa but may miss smaller lesions or areas with tissue problems such as necrosis. Macey et al. (2015) found 13 cytology studies encompassing 1554 patients (1622 lesions). After excluding one study reporting the results of multiple cytology tests, the sensitivity of brush cytology was calculated at 0.91 and the specificity was calculated at 0.91 (Macey et al., 2015).

Light-based detection (chemiluminescence) uses tissue reflectance to identify PMDs. An acetic acid pre-rinse is done, and then a blue-light source is used to evaluate the oral cavity. If the epithelium is bluish-white, the test is negative, but if the epithelium is distinctly white (“acetowhite”), the test is positive. This test is relatively easy to perform; however, visualization cannot be measured objectively, and no permanent records of the results can be obtained unless photographed. Macey et al. (2015) identified 11 studies with 1021 patients (1165 lesions) and found the sensitivity to be 0.91 and the specificity to be 0.58. The ViziLite PRO Oral Lesion screening system helps dentists to detect oral cancer via a simple light examination; this device utilizes five bright blue LEDs to detect oral cancer even in its earliest stages (DenMat, 2020a). The VELscope® Vx Enhanced Oral Assessment System also uses tissue fluorescence to identify abnormal oral cells that may not be apparent or visible to the naked eye (Apteryx, 2020). Finally, the Microlux™ DL Diagnostic System Kit also uses blue light to examine the oral mucosa and identify abnormalities; patients also rinse with a mild acetic acid solution (AdDent, 2020).

Finally, blood or saliva can be tested for biomarkers for cancer. The tests are non-invasive but have low standardization and are not widely used in clinical practice (Macey et al., 2015). Nonetheless,

saliva has been identified as an ideal diagnostic medium for the early detection of HNSCC activity because it is close to the tumor site and is an easy sample to obtain (Lim et al., 2016). Macey et al. (2015) concluded that none of the adjunctive biomarker tests can be recommended as a replacement for the currently used standard of COE followed by a scalpel biopsy and histological assessment. However, the NCCN has stated that that “Expression of p16 as detected by IHC [immunohistochemistry] is a widely available surrogate biomarker that has a very good agreement with HPV status as determined by the gold standard of HPV E6/E7 mRNA expression” (NCCN, 2021). The protein known as p16 slows cell division, therefore acting as a tumor suppressor. Researchers have identified p16^{INK4a}, RASSF1A, TIMP3, and PCQAP/MED15 as tumor suppressor genes that exhibited “excellent diagnostic accuracy in the early detection of OC [oral cancer] at 91.7% sensitivity and 92.3% specificity and of OPC [oropharyngeal cancer] at 99.8% sensitivity and 92.1% specificity from healthy controls” (Liyanage et al., 2019). A review by Kaur, Jacobs, Huang, Salvo, and Politis (2018) that researched salivary biomarkers for oral cancer and pre-cancer screening have identified a plethora of salivary biomarkers which showed an improvement in oral cancer diagnoses including mRNAs, salivary transcriptomes (IL-8, IL-1B, DUSP1, HA3, OAZ1, S100P, and SAT were highly specific (91%) and sensitive (91%) for oral cancer detection), and salivary biomarkers (M2BP, profilin, CD59, MRP14, and catalase had a sensitivity of 83% and a specificity of 90% for oral cancer detection) (Kaur et al., 2018).”

The OraRisk® HPV Complete Genotyping Test by OralDNA Labs is a salivary diagnostic test which can identify a total of 51 types of oral HPV including high-risk, low-risk and unknown-risk genotypes (OralDNA, 2020b). The OraRisk® HPV 16/18/HR Test, also developed by OralDNA Labs, is another salivary diagnostic test which identifies only high-risk types of oral HPV including HPV 16, HPV 18, and/or one or more of the following HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 (OralDNA, 2020a). The MOP™ Test by PCG Molecular is a salivary test which helps to identify early signs of oral cancer (PCG, 2014). Finally, the SaliMark™ OSCC, developed by PeriRx, is a commercial saliva test which helps to detect early signs of oral squamous cell carcinoma (PeriRx, 2020). Results from this test are available within three days.

Clinical Validity and Utility

Rashid and Warnakulasuriya (2015) studied the effectiveness of chemiluminescence (CL) and tissue auto-fluorescence (AF) devices as adjuncts in the detection of oral cancer (OC) and oral potentially malignant disorders (OPMD). The authors performed a systematic review of the published literature to evaluate the effectiveness of the Vizilite and Vizilite Plus with TB, MicroLux/DL and the VELscope as aids in the detection of OC and OPMDs. Twenty-five primary studies published between 2004 and 2013 satisfied the criteria for selection. A total of 13 studies utilized chemiluminescence and 12 utilized tissue autofluorescence. The investigators noted that “chemiluminescence shows good sensitivity at detecting any OPMDs and oral cancer. However, it preferentially detects leukoplakia and may fail to spot red patches.” Contrariwise, “tissue autofluorescence is sensitive at detecting white, red and white and red patches,” however, it may detect benign lesions at a high rate. The authors concluded that there is limited evidence for the use of these adjuncts in primary care, and these tools are better suited to specialist clinics in which there is a higher prevalence of disease and where experienced clinicians may better discriminate between benign and malignant lesions (Rashid & Warnakulasuriya, 2015).

Nagi, Reddy-Kantharaj, Rakesh, Janardhan-Reddy, and Sahu (2016) conducted a systematic review to evaluate the effectiveness of adjunctive devices that utilize the principles of chemiluminescence and tissue autofluorescence in the detection of oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD). Twenty primary studies published satisfied the criteria for selection. Ten used chemiluminescence and 10 used tissue autofluorescence. ViziLite was used for evaluation of chemiluminescence, and it was evaluated at a sensitivity of 0.771 to 1.00 and specificity of 0.00 to 0.278. Tissue autofluorescence was evaluated with VELscope. This technique was evaluated at a sensitivity of 0.22-1.00 and specificity of 0.16 to 1.00. The authors concluded that more clinical trials in the future should be conducted to establish optical imaging as an efficacious adjunct tool in early diagnosis of OSCC and OPMD (Nagi et al., 2016).

Lingen et al. (2017); Lingen et al. (2008) performed a meta-analysis of the screening adjuncts for oral cancer. The authors evaluated cytologic adjuncts as well as vital staining, tissue reflectance, autofluorescence, and salivary biomarkers. The vital staining cohort included 15 studies with 1453 lesions and was evaluated at a 0.87 sensitivity and 0.71 specificity. The tissue reflectance cohort (5 studies, 390 lesions) was assessed at a 0.72 sensitivity and 0.31 specificity. The autofluorescence segment (7 studies, 616 lesions) was computed at a 0.90 sensitivity and a 0.72 specificity. The authors stated, “most biomarkers showed a wide range of diagnostic test accuracy results, with sensitivity ranging from 0.5 to 0.9 and specificity ranging from 0.63 to 0.9.” Finally, cytology (15 studies, 2148 lesions) was assessed at a 0.92 sensitivity and 0.94 specificity. The authors concluded that cytology appeared to be most accurate adjunct (Lingen et al., 2017).

Another systematic review was completed that focused on the use of oral brush cytology for the early detection of oral cancer and OPMDs (Alsarraf, Kujan, & Farah, 2018). Thirty-six of the 343 abstracts and articles identified met the inclusion criteria, with publication dates ranging from 1994 to 2017. These articles led to the inclusion of 4302 total samples from OPMDs, oral squamous cell carcinoma, and healthy controls. The results were somewhat troubling. “Findings from this study indicate that meaningful evidence-based recommendations for the implementation of a minimally invasive technique to be utilized as an adjunctive tool for screening and early detection of oral cancer and OPMDs are complicated from the reported studies in the literature (Alsarraf et al., 2018).”

Kaur et al. (2018) completed a review which focused on salivary biomarkers for oral cancer and pre-cancer screening. A total of 270 articles published between 1995 and 2017 were identified for this review. The authors note that biomarkers may be arranged into four categories: normal health (IL-8, IL-1beta, etc.), general health (glycolytic enzyme lactate dehydrogenase, etc.), specific (S100P mRNA for cancer), and non-specific salivary (8-OHdG and MDA biomarkers of oral cancer and pre-cancer) (Kaur et al., 2018). Results from this study led to the conclusion that “Biomarkers such as methylation markers, IL-8, actin, myosin, and miRNAs are very speculative and remain without sufficient scientific evidence when it comes to oral cancer and pre-cancer detection using body fluids. Salivary peptides such as protein 14, Mac-2 binding protein, profilin 1, CD59, defensin-1, catalase proteins, etc. with sensitivity approximating 90% and specificity 80% for oral cancer diagnosis have been described”; “Furthermore, five salivary metabolites such as valine, lactic acid, and phenylalanine in combination yielded satisfactory accuracy (0.89), sensitivity (94.6%), and specificity (84.4%) in distinguishing oral cancer from controls or oral pre-cancer, respectively (Kaur et al., 2018).” Based on the results in this large group of studies, the researchers state that the “Combination approach of salivary biomarkers could be used as [a] screening tool to improve early detection and diagnostic precision of oral pre-cancer and cancer (Kaur et al., 2018).” The findings of this extensive review highlight that it is important for researchers to mitigate the current challenges involved with the use of salivary

biomarkers for oral cancer and pre-cancer screening as this technique has the potential to improve early detection and diagnostic methods.

Using “targeted proteomics, identified initially by relative quantification of salivary proteins on LC-MS [light chromatography-mass spectrometry],” Jain et al. (2021) identified a potential salivary biomarker panel having been motivated by the high prevalence, incidence, and mortality of oral cancer/oral squamous cell carcinoma among Indians. In a case-control cohort study, “Out of the twelve proteins validated, two proteins AHSG and KRT6C were significantly upregulated and four proteins, AZGP1, KLK1, BPIFB2 and LACRT were found to be significantly downregulated,” but when accounting for tobacco consumption habits, “AHSG and AZGP1 were dysregulated in cases compared to controls irrespective of their tobacco consumption habits. While KRT6C, KLK1 and BPIFB2 were significantly dysregulated only in the cases having tobacco consumption habits.” AZGP1 is important in insulin sensitivity and the cell cycle; KLK1 is a serine protease involved in “remodelling of the extracellular matrix, cellular proliferation and differentiation, angiogenesis, and apoptosis;” BPIFB2 is a lipid transfer/lipopopolysaccharide binding protein that is not well understood in cancer; KRT6C is a type II keratin subtype and is expressed in “filiform papillae of the tongue, stratified epithelial lining of the oesophagus, and oral mucosa and in glandular epithelia;” and AHSG is involved in “multiorgan expression during embryogenesis,” but is mostly in the liver and some osteoblasts in adults. In their risk prediction model, AZGP1, AHSG, and KRT6C had sensitivities of 82.4%, 78%, and 73.5%, respectively for all stages of OSCC, and 87.9%, 87.5%, and 73.5%, respectively for late stage OSCC. This could prove future benefits of utilizing salivary proteins in staging oral cancer and OSCC in certain patient populations.

Lim et al. (2016) completed a study to determine the diagnostic ability of four HNSCC biomarkers (RASSF1 α , p16^{INK4a}, TIMP3, PCQAP/MED15) isolated from saliva. The DNA methylation status of these biomarkers was measured via methylation-specific PCR (MSP). Data from a total of 88 HNSCC patients and 122 healthy controls was analyzed. The authors found that a “Salivary DNA tumour-suppressor methylation gene panel has the potential to detect early-stage tumours in HPV-negative HNSCC patients. HPV infection was found to deregulate the methylation levels in HPV-positive HNSCC patients”; biomarker analysis of HPV-negative HNSCC patients compared to healthy controls generated a sensitivity of 71% and specificity of 80%, while biomarker analysis of HPV-positive HNSCC patients compared to healthy controls generated a sensitivity of 80% and a specificity of 74% (Lim et al., 2016).

In their overview of non-invasive diagnostic devices in oral oncology, Mascitti et al. (2018) discussed and reviewed the Vizilite[®] chemiluminescence-based detected device for PMD and OSCC (Zila Pharmaceuticals), VELscope[®] non-magnifying device for visualization of oral mucosa autofluorescence (LED Medical Diagnostics), Identafi[®] device for multispectral screening of PMD (StarDental-DentalEZ), Microlux/DL[™] chemiluminescence-based device (AdDent Inc.), GOCCLES[®] device for autofluorescence abnormalities in the oral cavity (Pierrel S.p.A), Orasoptic DK[™] chemiluminescence-based device (Orasoptic), and other autofluorescence-based devices like those from Sapphire[®] PLUS LD (DenMat Holdings), DentLight DOE[™] Oral Exam System (DentLight), and ORalID[™] 2.0 (Forward Science Technologies). Ultimately, they concluded that there would be “great potential for screening and monitoring lesions. Unfortunately, to date several factors hinder an extensive use of these devices: (1) data do not demonstrate clear superiority of these methods compared to COE; (2) there remains the need for well-designed multicentre prospective studies; (3) these devices exhibit a not-negligible interobserver variability limiting their use to clinicians with

significant experience in oral pathology.” However, in terms of their benefits, “the current evidence suggests that these devices: (1) seem to be useful in assessing lesion margins that must be biopsied and, therefore, may be useful in surgical management; (2) can be used to investigate biological aspects of oral carcinogenesis, leading to more accurate methods for interpreting data from LBDS [light-based detection systems]; (3) can be enhanced with new approaches used to analyse optical imaging data, with the aim to quantify the results obtained; (4) lowering the costs of these devices could indirectly lead to greater attention for oral lesions among both patients and general dental practitioners, allowing in turn to promote a culture of oral cancer prevention; (5) finally, the possibility of implementing LBDS through the use of tissue-marking dyes can in principle allows to develop strategies for the use of nanoparticles. Indeed, nanoparticles can provide molecular targeted imaging, with higher image contrast and resolution” (Mascitti et al., 2018).

V. Guidelines and Recommendations

American Dental Association (ADA) (Lingen et al., 2017)

The ADA released an update to their 2010 guidelines in 2017. These guidelines were provided by an expert panel convened by the ADA Council on Scientific Affairs and the Center for Evidence-Based Dentistry. Their guidelines are as follows:

- “The panel does not recommend autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of PMDs among adult patients with clinically evident, seemingly innocuous, or suspicious lesions.”
- “The panel does not recommend commercially available salivary adjuncts for the evaluation of PMDs among adult patients with or without clinically evident, seemingly innocuous, or suspicious lesions, and their use should be considered only in the context of research.”
- “The panel does not recommend cytologic adjuncts for the evaluation of PMDs among adult patients with clinically evident, seemingly innocuous, or suspicious lesions. Should a patient decline the clinician’s recommendation for performing a biopsy of the lesion or referral to a specialist, the clinician can use a cytologic adjunct to provide additional lesion assessment.”
- “The panel suggests that for adult patients with a clinically evident oral mucosal lesion considered to be suspicious of a PMD or malignant disorder, or other symptoms, clinicians should perform a biopsy of the lesion or provide immediate referral to a specialist (Lingen et al., 2017).”

US Preventive Services Task Force (USPSTF) (Moyer, 2014)

In 2013, the USPSTF published final recommendations for screening of oral cancer. The recommendation stated that “the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults.” The USPSTF also noted that “additional tests proposed as adjuncts to the oral cancer screening examination include toluidine blue dye staining, chemiluminescent and autofluorescent lighting devices, and brush cytology. These

screening and adjunct tests have not been adequately tested in primary care nondental settings. Although there is interest in screening for oral HPV infection, medical and dental organizations do not recommend it (Moyer, 2014).”

National Comprehensive Cancer Network (NCCN) (NCCN, 2021)

NCCN clinical practice guidelines on head and neck cancers does not mention the use of adjunctive screening aids based on autofluorescence or tissue reflectance as a management tool (NCCN, 2021). Regarding biomarker testing, the NCCN states that “A few HPV testing options are available for use in the clinical setting. Expression of p16 as detected by IHC [immunohistochemistry] is a widely available surrogate biomarker that has a very good agreement with HPV status as determined by HPV E6/E7 mRNA expression.” They also state, “P16 expression is highly correlated with HPV status and prognosis and is widely available” (NCCN, 2021). HPV testing by p16 IHC is a required portion of the workup of the cancer of the oropharynx algorithm.

College of American Pathologists (CAP) (Lewis et al., 2018)

The CAP published guidelines on human papillomavirus testing in head and neck carcinomas. These guidelines state that “For oropharyngeal tissue specimens (ie, noncytology), pathologists should perform HR-HPV [high-risk HPV] testing by surrogate marker p16 IHC” (Lewis et al., 2018).

American Society of Clinical Oncology (ASCO) (Fakhry et al., 2018; Maghami et al., 2020)

An expert panel from the ASCO has “determined that the recommendations from the HPV Testing in Head and Neck Carcinomas guideline, published in 2018, are clear, thorough, and based upon the most relevant scientific evidence. ASCO endorsed the [CAP] guideline and added minor qualifying statements” (Fakhry et al., 2018).

The ASCO states that “It is recommended that HPV tumor status should be determined for newly diagnosed oropharyngeal squamous cell carcinomas. HPV tumor status testing may be performed by surrogate marker p16 immunohistochemistry either on the primary tumor or from cervical nodal metastases only if an oropharyngeal primary tumor is present” (Fakhry et al., 2018).

Regarding diagnosis and management of squamous cell carcinoma of unknown primary (SCCUP) in the head and neck, the ASCO states with a moderate strength recommendation, “High-risk (HR) human papillomavirus (HPV) testing should be done routinely on level II and III SCCUP nodes. Epstein-Barr virus (EBV) testing should be considered on HPV-negative metastases... HR-HPV testing may be done nonroutinely for SCC metastases at other nodal levels when the clinical suspicion is high” (Maghami et al., 2020).

European Head and Neck Society (EHNS)-European Society for Medical Oncology (ESMO)-European Society for Radiotherapy and Oncology (ESTRO) (Machiels et al., 2020)

In 2020, the EHNS, ESMO, and ESTRO released joint clinical practice guidelines for squamous cell carcinoma of the oral cavity, larynx, oropharynx, and hypopharynx. For HPV testing, they recommended that “for SCCHN [squamous cell carcinoma of the head and neck] of unknown primary, p16 and EBER [Epstein-Barr-encoded RNA] are recommended. If p16 staining is positive, another

specific HPV test should be carried out to confirm the HPV status [III, A].” p16 measured by immunohistochemistry is validated in use as a surrogate marker for HPV-induced oropharyngeal cancer and prognostic factor for oropharyngeal cancer [I, A] (Machiels et al., 2020)

VI. State and Federal Regulations, as applicable

No FDA-approved tests for the assessment of oral cancer were found as of April 8, 2021. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81599	Unlisted multianalyte assay with algorithmic analysis
82397	Chemiluminescent assay
87623	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (eg, 6, 11, 42, 43, 44)
87624	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
87625	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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