Clinical Policy Bulletin: Oral Screening and Lesion Identification Systems

Number: 0760

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers the following experimental and investigational for early detection of oral cancer and other indications because their effectiveness has not been established: (not an all-inclusive list)

- MOP genetic testing
- Oral lesion identification systems (e.g., the Dentlight Oral Exam Light Kit, Microlux DL, Orascoptic DK, Sapphire Plus, TRIMIRA Identafi 3000, and ViziLite-Blue and VELscope)
- Wide-field and high-resolution in-vivo imaging

Aetna considers oral human papillomavirus (HPV) testing (e.g., the OraRisk HPV Salivary DNA Test) experimental and investigational for all indications because its effectiveness has not been established.

Aetna considers the use of microRNAs for screening of oral squamous cell carcinomas experimental and investigational because the effectiveness of this approach has not been established.

See also CPB 0686 - Oral and Esophageal Brush Biopsy.

Background

Head and neck cancers account for 5 % of all tumors, and about 50 % of head and neck tumors occur specifically in the oral cavity. In 2000, 300,000 of the 615,000 new cases of oral cavity tumors reported worldwide were primary oral cavity squamous cell carcinomas (SCC). Recent data from the Surveillance, Epidemiology, and End Results Program suggested that 28,900 new cases of oral cancer will be identified and 7,400 deaths attributed to oral cancer each year in the United States. The 6th leading cause of cancer-related mortality, oral cancer accounts for 1 death every hour in the United States (Kademani, 2007). Since oral cancers are often detected in later stages, it is thought that early detection may lower the morbidity and mortality of oral cavity tumors.

ViziLite-Blue:

The United States Food and Drug Administration (FDA) cleared ViziLite as an adjunct to visual examination of the oral cavity in November 2001. This chemiluminescent light technology has been used since 1995 for the identification of abnormalities in stratified squamous epithelium. The ViziLite-Blue oral examination kit, an oral lesion identification and marking system, is designed to be used as
an adjunct to the conventional head and neck examination in patients at increased risk for oral cancer. It is comprised of a chemiluminescent light source (ViziLite) to improve the identification of lesions and a blue phenothiazine dye to mark those lesions identified by ViziLite. The ViziLite-Blue oral examination kit was cleared by the FDA through the 510(k) process in November 2004.

Ram and Siar (2005) examined the use of ViziLite as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions (PMELs) by comparing it against 1% tolonium chloride mouth rinse. A total of 46 clinically identified lesions (14 primary SCC, 26 PMELs and 6 benign lesions) and 5 cases of normal oral mucosa from 40 subjects (including 10 previously treated SCC cases) were examined with ViziLite and tolonium chloride. Biopsy and histological verification of 31 lesions disclosed 14 SCC (45.2%), 10 epithelial dysplasias (32.3%), 5 lichen planus (16.1%) and 2 benign lesions (6.4%). For the remaining 15 lesions, a biopsy was not performed owing to patient’s lack of consent or ill-health. The 5 cases of normal oral mucosa which tested negative for both tools were also not biopsied for ethical reasons. Sensitivity for ViziLite and tolonium chloride was 100% and 70.3%, respectively; and specificity was 14.2% for ViziLite and 25% for tolonium chloride. Their accuracy was 80.6% and 64.5%, respectively. The authors concluded that the present findings suggested that ViziLite is a more reliable diagnostic tool than tolonium chloride in the detection of oral cancer and PMELs, and for follow-up of patients treated for the same.

Kerr and associates (2006) examined the use of ViziLite as an adjunct to standard visual examination (SVE) to enhance visualization of mucosal lesions, particularly those "clinically suspicious" for oral pre-cancer or cancer. Individuals were considered at risk for oral cancer or pre-cancer if they have no a priori knowledge of the presence or absence of an oral lesion at the time of examination. A total of 501 consecutive consenting subjects, over 40 years of age and with a positive tobacco history, received a standard visual examination with conventional incandescent lighting, followed by chemiluminescent lighting. All lesions were recorded, and for lesions detected by both screening modalities, comparisons were made of the subjective parameters of lesion brightness, sharpness, surface texture, and relative size. A total of 410 epithelial lesions were detected in 270 subjects by SVE, of which 127 were clinically "suspicious" for oral cancer and pre-cancer. Ninety-eight lesions were also visualized by chemiluminescent lighting as "aceto-white" (CL+), in addition to 6 lesions not previously seen by SVE. Seventy-seven of the CL+ lesions (78.5%) were clinically suspicious; all "suspicious" lesions with an ulcerative component and ulcerated lesions consistent with trauma were CL+. Leukoplakias were significantly more likely to be CL+ than erythroplakias (p < 0.01). Overall, those lesions illuminated by ViziLite appeared brighter, sharper, and smaller compared to incandescent illumination. The authors concluded that these findings suggested that oral chemiluminescent lighting, when used as a screening adjunct following SVE, provides additional visual information. Leukoplakias may be more readily visualized by chemiluminescence. Studies are underway to explore the clinical significance and predictive value of oral chemiluminescent lighting.

Epstein et al (2006) stated that early diagnosis of oral mucosal lesions has been advocated as a means of improving outcomes of cancer therapy. Improved visualization of mucosal lesions may aid in diagnosis by guiding tissue sampling or referral. This multi-center study reported the effect of chemiluminescent light (ViziLite) upon visualization of mucosal lesions. The chemiluminescent light did not appear to improve visualization of red lesions, but white lesions and lesions that were both red and white showed enhanced brightness and sharpness.

Farah and McCullough (2007) noted that conventional screening practice for oral lesions involves visual scrutiny of the oral tissues with the naked eye under projected incandescent or halogen illumination. Visualization is the principal strategy used to assess patients’ lesions at risk for malignant transformation; hence, any procedure which highlights such lesions should aid the clinician. The aim of this pilot study was to examine the efficacy of acetic acid wash and chemiluminescent light (ViziLite) in enhancing visualization of oral mucosal white lesions, and its ability to highlight malignant and potentially malignant lesions. Fifty-five patients referred for assessment of an oral white lesion, were prospectively screened with ViziLite, and an incisional scalpel biopsy performed for a definitive diagnosis. The size, location, ease of visibility, border distinctness, and presence of satellite lesions
were recorded. The ViziLite tool enhanced intra-oral visualization of 26 white lesions. Indeed, all lesions appeared "aceto-white", regardless of the definitive diagnosis. Examination of the oral tissues with ViziLite illumination did not change the provisional diagnosis, nor alter the biopsy site. ViziLite illumination does not discriminate between keratotic, inflammatory, malignant or potentially malignant oral mucosal white lesions and thus, a high index of suspicion, expert clinical judgment, and scalpel biopsy are still essential for proper patient care.

Oh and Laskin (2007) stated that early detection of oral cancer is crucial in improving survival rate. To improve early detection, the use of a dilute acetic acid rinse and observation under a chemiluminescent light (ViziLite; Zila Pharmaceuticals, Phoenix, AZ) has been recommended. However, to date, the contributions of the individual components of the system have not been studied. The present study was done to investigate the efficacy of the individual components of the ViziLite system in providing improved visualization of early oral mucosal lesions. A total of 100 patients, 39 males and 61 females, aged 18 to 93 years (mean age of 44 years), who presented to the Virginia Commonwealth University School of Dentistry for dental screening were examined. There were 58 Caucasians, 29 African-Americans, 5 Hispanics, 6 Asians, and 2 of mixed ethnicity. Thirty-five patients smoked, 53 used alcohol, and 25 both smoked and drank. After written consent, the oral cavity was examined under incandescent light for soft tissue abnormalities. After 1-min rinse with 1 % acetic acid, the mouth was re-examined for additional mucosal abnormalities. Then, the mouth was examined once again using the ViziLite system's chemiluminescent light. Any lesions detected by these 3 examinations that were clinically undiagnosable were brush biopsied (Oral CDx) for determination of cellular representation. In the original examination of the 100 patients, 57 clinically diagnosable benign lesions (e.g., linea alba, leukoedema) and 29 clinically undiagnosable lesions were detected. After the rinse, 6 additional diagnosable lesions (linea alba) and 3 undiagnosable lesions were found. No additional lesions were detected with the chemiluminescent light. Of the 32 undiagnosable lesions that were brush biopsied, 2 were positive for atypical cellular characterization and warranted further investigation with a scalpel biopsy. Neither of these lesions was found to be pre-malignant or malignant. The authors concluded that although the acid rinse accentuated some lesions, the overall detection rate was not significantly improved. The chemiluminescent light produced reflections that made visualization more difficult and thus was not beneficial.

Epstein et al (2008) examined the adjunctive value of ViziLite(R) and application of pharmaceutical grade toluidine blue to further evaluate lesions identified during the conventional oral soft tissue examination. Lesions deemed clinically suspicious by visual examination under incandescent light were further assessed under chemiluminescence and then application of toluidine blue stain. Differences between the conventional visual examination and chemiluminescent examination were noted on 4 characteristics that may aid in lesion identification. Tissue retention of toluidine blue stain was documented. Each suspicious lesion was biopsied and diagnosed based upon routine histopathology. Both adjunctive examinations were evaluated by comparing the histological diagnosis. The additive value of toluidine blue stain retention was assessed in lesions diagnosed as "serious pathology" defined as severe dysplasia, carcinoma in-situ and SCC. A total of 97 clinically suspicious lesions in 84 patients were identified. The chemiluminescent examination improved the brightness and/or sharpness of margin in 61.8 % of identified lesions. Biopsied lesions with toluidine blue stain retention reduced the false-positive rate by 55.26 % while maintaining a 100 % negative-predictive value (NPV). Vizilite was shown to increase the brightness and margins of mucosal lesions in a majority of cases and therefore may assist in identification of mucosal lesions not considered under traditional visual examination. Toluidine blue stain retention was associated with a large reduction in biopsies showing benign histology (false-positive biopsy results), while maintaining a 100 % NPV for the presence of severe dysplasia or cancer. The authors noted that practitioners may consider use of these adjuncts in practice, however the results presented are based upon experienced providers in referral centers for mucosal disease or cancer centers. Thus, positive findings may be an indication for referral to experienced providers.

McIntosh and colleagues (2009) evaluated the effectiveness of acetic acid mouthwash and diffused light illumination (Microlux/DL) as a diagnostic aid in the visualization of oral mucosal lesions and its
ability to highlight malignant and potentially malignant lesions. A total of 50 patients referred for assessment of an oral white lesion were initially examined under routine incandescent operatory light. The location, size, ease of visibility, border distinctness and presence of satellite lesions were recorded. Clinical examination was repeated using the Microlux/DL diffused light illumination kit. An incisional biopsy was performed to provide a definitive histopathological diagnosis. Microlux/DL examination enhanced the visibility of 34 lesions, however, it did not help uncover any clinically undetected lesions, change the provisional diagnosis, or alter the biopsy site. Microlux/DL showed a sensitivity of 77.8 % and a specificity of 70.7 %, with a positive predictive value (PPV) of 36.8 %. The authors concluded that although Microlux/DL appears useful at enhancing lesion visibility, it is a poor discriminator for inflammatory, traumatic and malignant lesions.

VELscope:

VELscope received 510(k) market clearance in April 2006. It was deemed to be substantially equivalent to ViziLite. VELscope is intended to be used by dentists or health-care providers as an adjunct to traditional oral examination by incandescent light to enhance the visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer or pre-malignant dysplasia. It is further intended to be used by surgeons to help identify diseased tissue around a clinically apparent lesion and thus aid in determining the appropriate margin for surgical excision. VELscope uses visible light in the 430 nm wavelength in order to cause fluorescent excitation of certain compounds in the tissues.

Lane and associates (2006) described a simple hand-held device that facilitates the direct visualization of oral-cavity fluorescence for the detection of high-risk pre-cancerous and early cancerous lesions. Blue excitation light (400 to 460 nm) was employed to excite green-red fluorescence from fluorophores in the oral tissues. Tissue fluorescence was viewed directly along an optical axis collinear with the axis of excitation to reduce inter- and intra-operator variability. This device enables the direct visualization of fluorescence in the context of surrounding normal tissue. Results from a pilot study of 44 patients were presented. Using histology as the gold standard, the device achieves a sensitivity of 98 % and specificity of 100 % when discriminating normal mucosa from severe dysplasia/carcinoma in-situ (CIS) or invasive carcinoma.

In an article on a new technique for detecting oral cancer, Kois and Truelove (2006) stated that the VELscope can aid in patient assessment, and when added to a well-thought out clinical assessment process that takes into consideration the age of the patient and risk factors that include tobacco, alcohol, and immunological status, it increases the clinician’s ability to detect oral changes that may represent pre-malignant or malignant cellular transformation. False-positive findings are possible in the presence of highly inflamed lesions, and it is possible that use of the scope alone may result in failure to detect regions of dysplasia, but it has been the authors’ experience that use of the VELscope improves clinical decision-making about the nature of oral lesions and aids in decisions to biopsy regions of concern. Where tissue changes are generalized or cover significant areas of the mouth, use of the scope has allowed practitioners to identify the best region for biopsy. As with all clinical diagnostic activities, no single system or process is enough, and all clinicians are advised to use good clinical practice to assess patients and to recall and biopsy lesions that do not resolve within a predetermined time frame. Lesions that are VELscope-positive and absorb light need to be followed with particular caution, and if they do not resolve within a 2-week period, then further assessment and biopsy are generally advised. It is much better to occasionally sample tissue that turns out to be benign than to fail to diagnose dysplastic or malignant lesions. It is unclear if the use of the VELscope would improve early detection and result in fewer deaths from oral cancer.

Poh and colleagues (2006) used a simple hand-held device in the operating room to directly visualize sub-clinical field changes around oral cancers, documenting alteration to fluorescence. A total of 122 oral mucosa biopsies were obtained from 20 surgical specimens with each biopsy being assessed for location, fluorescence visualization (FV) status, histology, and loss of heterozygosity (LOH; 10 markers on 3 regions: 3p14, 9p21, and 17p13). All tumors showed FV loss (FVL). For 19 of the 20 tumors, the
loss extended in at least one direction beyond the clinically visible tumor, with the extension varying from 4 to 25 mm. Thirty-two of 36 FVL biopsies showed histological change (including 7 squamous cell carcinoma/CIS, 10 severe dysplasias, and 15 mild/moderate dysplasias) compared with 1 of the 66 FV retained (FVR) biopsies. Molecular analysis on margins with low-grade or no dysplasia showed a significant association of LOH in FVL biopsies, with LOH at 3p and/or 9p (previously associated with local tumor recurrence) present in 12 of 19 FVL biopsies compared with 3 of 13 FVR biopsies (p = 0.04). The authors concluded that these findings showed that direct FV can identify sub-clinical high-risk fields with cancerous and pre-cancerous changes in the operating room setting. These findings have little bearing in the primary care setting.

Poh et al (2007) presented 3 representative cases in which occult lesions were identified with fluorescence visualization during longitudinal follow-up, resulting in the diagnosis of a primary dysplasia in case 1, a second primary cancer in case 2, and cancer recurrence in case 3. The authors concluded that this was the first report of the diagnosis of occult oral disease using a simple non-invasive device. These early examples indicate the potential value of this technology to guide the management of patients with oral lesions, facilitating the detection of high-risk changes not apparent with white-light visualization.

The United States Preventive Services Task Force (2004) stated that the evidence is insufficient to recommend for or against routinely screening adults for oral cancer. In a Cochrane review, Kujan and colleagues (2006) evaluated the effectiveness of current screening methods in decreasing oral cancer mortality. The authors concluded that given the limitation of evidence (only 1 included randomized controlled trial) and the potential methodological weakness of the included study, it is valid to say that there is insufficient evidence to support or refute the use of a visual examination as a method of screening for oral cancer using a visual examination in the general population. Furthermore, no robust evidence exists to suggest that other methods of screening (e.g., toluidine blue, fluorescence imaging, and brush biopsy) are either beneficial or harmful. Future high quality studies to evaluate the effectiveness and costs of screening are needed for the best use of public health resources. In addition, studies to elucidate the natural history of oral cancer, prevention methods, and the effectiveness of opportunistic screening in high risk groups are needed.

In a systematic review, Patton et al (2008) evaluated the effectiveness of toluidine blue (TB), ViziLite Plus with TBlue, ViziLite, Microlux DL, Orascoptic DK, VELscope, and OralCDx brush biopsy for the early detection of oral premalignant and malignant lesions (OPML). These researchers abstracted data relating to study design, sampling and characteristics of the study group, interventions, reported outcomes and diagnostic accuracy of adjunctive aids from 23 articles meeting inclusion and exclusion criteria, including availability of histologic outcomes. The largest evidence base was for TB. A limited number of studies was available for ViziLite, ViziLite Plus with TBlue and OralCDx. Studies of VELscope have been conducted primarily to assess the margins of lesions in known OPML. The authors identified no studies of Microlux DL or Orascoptic DK. Study designs had various limitations in applicability to the general practice setting, including use of higher-risk populations and expert examiners. The authors concluded that there is evidence that TB is effective as a diagnostic adjunct for use in high-risk populations and suspicious mucosal lesions. OralCDx is useful in assessment of dysplastic changes in clinically suspicious lesions; however, there are insufficient data meeting the inclusion criteria to assess usefulness in innocuous mucosal lesions. Overall, there is insufficient evidence to support or refute the use of visually based examination adjuncts. These investigators noted that given the lack of data on the effectiveness of adjunctive cancer detection techniques in general dental practice settings, clinicians must rely on a thorough oral mucosal examination supported by specialty referral and/or tissue biopsy for OPML diagnosis.

Trullenque-Eriksson et al (2009) analysed publications that are related to examination techniques that might improve the visualization of suspicious lesions of the oral mucosa (ViziLite system and VELscope system) or that might facilitate the cytological identification of suspicious lesions (OralCDx). A literature search was performed, using the PubMed database and the key words "brush biopsy", "OralCDx", "ViziLite" and "Velscope", limiting the search to papers in English or Spanish published
from 2002 to 2008. According to the results of studies identified, the ViziLite system has a sensitivity of 100% and specificity ranging from 0 to 14.2%, the VELscope system has a sensitivity of 98 to 100% and specificity of 94 to 100%, and the Oral CDx system has a sensitivity of 71.4 to 100% and specificity of 32 to 100%. The authors concluded that clinical examination and histopathological confirmation with biopsy remain the gold standard for the detection of oral cancer. They stated that more randomized controlled studies are needed to confirm the positive cost-benefit relationship and the true usefulness of these "new diagnostic methods" in oral mucosal pathology.

Matsumoto (2011) examined if objective discrimination criteria can be set for the VELscope system when observing oral mucosal lesions. This investigator examined 74 cases with biopsy-confirmed oral mucosal lesions; 37 SCC lesions, 14 moderate-to-severe epithelial dysplasia lesions, 13 mild epithelial dysplasia lesions and 10 lichen planus lesions. Lesions were examined macroscopically under the conventional overhead light, and then, examined by this device. Each examination was recorded with a digital camera. The researcher contrasted findings with histopathological manifestation, and calculated the attenuation score. It is found that several conditions and sites, such as keratinization and the degree of inflammatory cell infiltration, were associated with detection sensitivity using this device. Based on the attenuation scores, a significant difference was seen between SCC and epithelial dysplasia. The author concluded that these findings suggested that the VELscope system might be a valuable adjunct in the early detection of potentially malignant and malignant lesions of the oral cavity.

Awan et al (2011) evaluated the accuracy of autofluorescence against conventional oral examination and surgical biopsy. A total of 126 patients, 70 males and 56 females (mean age of 58.5 +/- 11.9 years) who presented to the Oral Medicine Clinics at King's and Guy's Hospitals, London with oral white and red patches suspicious of oral potentially malignant disorders (OPMD) were enrolled. Following a complete visual and autofluorescence examination, all underwent an incisional biopsy for histopathological assessment. Seventy patients had oral leukoplakia/erythroplakia, 32 had oral lichen planus, 9 chronic hyperplastic candidiasis and rest frictional keratosis (13) or oral submucous fibrosis (2). Of 126 lesions, 105 (83%) showed loss of fluorescence. Following biopsy, 44 had oral epithelial dysplasia (29 mild, 8 moderate and 7 severe). The sensitivity and specificity of autofluorescence for the detection of a dysplastic lesion was 84.1% and 15.3%, respectively. While VELscope was useful in confirming the presence of oral leukoplakia and erythroplakia and other oral mucosal disorders, the device was unable to discriminate high-risk from low-risk lesions.

Koch et al (2011) evaluated the sensitivity and specificity of the autofluorescence examination. A total of 78 patients were examined in this study. All of them suffered from suspicious oral mucosal lesions. Two different investigation methods were applied:

1. the standard examination by white light, and
2. an examination by a novel light source of 400 nm that evoked a green light emission (greater than 500 nm) in normal mucosa.

It was proposed that malignant oral mucosal lesions show different autofluorescence characteristics than the green autofluorescence of healthy mucosa. Red autofluorescence indicated SCC with a sensitivity of 20% and a specificity of 98%. The results showed that dysplasia and carcinoma could be identified with a sensitivity of 96% and a specificity of 18% by using the autofluorescence method. The sensitivity decreased according to the grade of mucosal keratosis and was influenced by the localization of the lesion. The authors concluded that benign as well as malignant oral lesions could not be distinguished by a diminished autofluorescence signal. A red autofluorescence signal, however, could indicate cancerous processes of the oral mucosa.

Lopez-Jornet and De la Mano-Espinosa (2011) reviewed papers published on autofluorescence imaging, a non-invasive technique that is used to identify neoplastic oral cavity lesions. A literature search was performed, using the PubMed database and the key words "autofluorescence" and "Velscope", limiting the search to papers in English or Spanish published from 2002 to June 2009. The
The Velscope system has a sensitivity of 98 to 100 % and specificity of 94 to 100 %. Autofluorescence is a supplementary tool used in the diagnosis of oral cancer, although other more reliable and robust studies are needed for confirmation. The authors concluded that there is insufficient evidence to demonstrate that its use as an adjunct to conventional oral screening provides additional benefit to conventional oral cancer screening alone.

The American Dental Association (ADA)'s evidence-based guideline on “Screening for oral squamous cell carcinomas” (Rethman et al, 2010) concluded that screening by means of visual and tactile examination to detect potentially malignant and malignant lesions may result in detection of oral cancers at earlier stages, but there is insufficient evidence to determine if screening alters disease-specific mortality in asymptomatic people seeking dental care. The guideline evaluated adjunctive screening aids based on tissue reflectance (i.e., ViziLite Plus, MicroLux/DL, Orascoptic DK), autofluorescence (i.e., VELscope), and autofluorescence and tissue reflectance (i.e., TRIMIRA Identafi). The ADA guideline concluded that there is insufficient evidence that use of commercial devices for lesion detection that are based on autofluorescence or tissue reflectance enhance visual detection of potentially malignant lesions beyond a conventional visual and tactile examination. Moreover, the ADA guideline noted that additional research is needed for oral cancer screening and the use of adjuncts.

In a prospective clinical study, Marzouki et al (2012) examined the usefulness of the VELscope in detecting malignant and premalignant oral cavity lesions. A total of 85 patients with a history of smoking, alcohol use, and/or head and neck cancer were recruited into the study. The VELscope was used to examine patients' oral cavities after a clinical examination. Biopsies were then taken from suspicious areas. Of the 85 patients included in the study, 33 underwent biopsies prompted by a clinical examination, the VELscope, or both. Biopsy results that showed invasive malignancy or dysplasias were considered positive. Five positive biopsies for pre-malignant lesions were detected only by the VELscope and were not visible on clinical examination. On the other hand, only 1 positive biopsy for a pre-malignant lesion was detected by the clinical examination only and not seen on the VELscope. Seven positive biopsies were detected by both methods. This indicated that the diagnostic yield from a regular examination was 47 % (95 % confidence intervals [CI]: 23 to 72) and that the diagnostic yield from the addition of the VELscope was an additional 31 % (95 % CI: 11 to 59). Sensitivity and specificity for the VELscope were 92 % and 77 %, respectively. The authors concluded that the VELscope may add sensitivity to the clinical examination and be a useful adjunct in high-risk patients.

Lane et al (2012) stated that optical spectroscopy devices are being developed and tested for the screening and diagnosis of cancer and pre-cancer in multiple organ sites. The studies reported here used a prototype of a device that uses white light, green-amber light at 545 nm, and violet light at 405 nm. Given that oral neoplasia is rare, the need for a device that increases the sensitivity of comprehensive white light oral screening is evident. Such a device, in the hands of dentists, family practitioners, otorhinolaryngologists, general surgeons, obstetrician gynecologists, and internists, could greatly increase the number of patients who have lesions detected in the pre-cancerous phase. These researchers presented a case series of oral pre-cancers and cancers that have been photographed during larger ongoing clinical trials. Over 300 patients were measured at 2 clinical sites that are comprehensive cancer centers and a faculty practice associated with a major dental school. Each site was conducting independent research on the sensitivity and specificity of several optical technologies for the diagnosis of oral neoplasia. The cases presented in this case series were taken from the larger database of images from the clinical trials using the afore-mentioned device. Optical spectroscopy was performed and biopsies obtained from all sites measured, representing abnormal and normal areas on comprehensive white light examination and after use of the fluorescence and reflectance spectroscopy device. The gold standard of test accuracy was the histologic report of biopsies read by the study histopathologists at each of the 3 study sites. Comprehensive white light examination showed some lesions; however, the addition of a fluorescence image and a selected reflectance wavelength was helpful in identifying other characteristics of the lesions. The addition of the violet light-induced fluorescence excited at 405 nm provided an additional view of both the stromal neovasculature of the
lesions and the stromal changes associated with lesion growth that were biologically indicative of stromal breakdown. The addition of 545 nm green-amber light reflectance increased the view of the keratinized image and allowed the abnormal surface vasculature to be more prominent. The authors concluded that optical spectroscopy is a promising technology for the diagnosis of oral neoplasia. The conclusion of several ongoing clinical trials and an eventual randomized phase III clinical trial will provide definitive findings that sensitivity is or is not increased over comprehensive white light examination.

Farah et al (2012) evaluated the effectiveness of VELscope in the detection of oral mucosal lesions. A total of 112 patients referred with a potentially malignant oral mucosal lesion were examined under routine incandescent light, and then with VELscope, noting loss of autofluorescence and presence of blanching. Incisional biopsies were performed to provide definitive histopathological diagnoses. VELscope enhanced the visibility of 41 lesions and helped uncover 5 clinically undetected lesions. VELscope examination alone showed a sensitivity of 30 % and a specificity of 63 %. Its accuracy at identifying dysplasia was 55 %. The authors concluded that VELscope examination cannot provide a definitive diagnosis regarding the presence of epithelial dysplasia. Loss of autofluorescence is not useful in diagnosing epithelial dysplasia in its own right without relevant clinical interpretation.

McNamara et al (2012) noted that direct visual fluorescent examination (DVFE) is a proposed adjunct to conventional oral examination (COE). These investigators evaluated the benefit of DVFE in screening for potentially malignant mucosal lesions in a general population of patients presenting for dental care. A total of 130 patients were evaluated by COE followed by DVFE. Areas clinically suspicious by COE or with positive DVFE (visual fluorescence loss [VFL]) underwent surgical biopsy. Association between COE and DVFE was assessed and compared with histopathology. A total of 42 subjects had 1 or more areas of VFL, yet histologic evidence of pre-malignancy/malignancy was only identified in a single individual. Furthermore, 1 lesion negative by DVFE exhibited epithelial dysplasia. Direct visual fluorescent examination was statistically different from scalpel biopsy (p = 0.0001). No difference was found between COE and scalpel biopsy (p = 1.0). The authors concluded that these findings suggested that COE is more valid than DVFE at discriminating benign mucosal alterations from pre-malignancy and do not support use of DVFE as an oral cancer screening adjunct.

Huber (2012) stated that during the past decade, several adjunctive aids have been introduced to the marketplace with the promoted goal of improving the dental practitioner's ability to screen for and identify oral pre-malignant and malignant lesions (OPMLs). These products include the OralCDx Brush Test, ViziLite Plus with TBlue, Microlux, VELscope Vx, Sapphire Plus, Identafi, and the DOE Oral Exam System. They are all marketed as aids for the clinician to use in addition to, not in lieu of, the accomplishment of a COE. Studies addressing the effectiveness of these products when used in the general practice setting to screen for OPMLs are limited and conflicting. The ability to discriminate between truly dangerous OPML against the milieu of benign mucosal lesions remains a concern and further research is necessary to determine the true value of these products as marketed to the general practitioner.

The OraRisk HPV Test:

Human papillomavirus (HPV) infection is a significant risk factor for uterine cervical carcinoma. Moreover, there is increasing evidence that oral infection with HPV, particularly with high-risk genotypes, is a significant independent risk factor for oral SCC (OSCC). The OraRisk HPV is a salivary diagnostic test for oral cancer. It can be used in the dental office by the dental hygienist. Patients rinse with a saline solution and expectorate into a test vial that is sent to a laboratory for evaluation of the presence of HPV. However, there is insufficient evidence regarding the clinical value of the OraRisk test in detecting oral cancer.

Lee and Wong (2009) stated that saliva, a multi-constituent oral fluid, has high potential for the surveillance of general health and disease. To reach the above goal through saliva-based diagnostics, two prerequisites must be fulfilled:
I. discovering biomarker(s) for different diseases among the complicated components of saliva, and
II. advancing sensitivity and specificity of biomarker(s) through persistent development of technologies.

Under the support and research blueprint initiated by the National Institute of Dental and Craniofacial Research, salivary diagnostics has not only steadily progressed with respect to accuracy and availability, but has also bridged up-to-date nanotechnology to expand the areas of application. With collective efforts over several years, saliva has been demonstrated to be a promising bodily fluid for early detection of diseases, and salivary diagnostics has exhibited tremendous potential in clinical applications.

Pink et al (2009) noted that oral fluid is now systematically being researched and oral fluid analysis is being compared with the analysis of other diagnostic media such as blood and urine. A number of recent studies have focused on oncogenic marker detection and its monitoring in saliva. The latest clinical and laboratory findings on diagnostic markers of oropharyngeal carcinoma in oral fluid could be the beginning of their wider use as a diagnostic medium. The authors concluded that the diagnostic value of saliva, aided by current technological development will increase rapidly in the near future.

Saheb Jamee et al (2009) evaluated the presence of HPV in saliva rinses of patients with OSCC and analyzed the possibility of using saliva as a diagnostic method for screening high-risk patients. The saliva sample of 22 patients with OSCC and 20 age-and sex-matched healthy controls were obtained. The presence of HPV 6, 11, 16, 18, 31, and 33 was evaluated by polymerase chain reaction. In 40.9% of the patients and in 25% of the controls, the saliva was shown to be positive for HPV. In 27.3% of the patients and in 20% of the controls, the saliva was shown to be positive for HPV16; and none of the controls, except 1 patient was shown to be positive for HPV 18. Neither patients nor controls were positive for HPV 31 and 33. These differences were not statistically significant. The authors concluded that these findings were unable to support the detection of HPV in saliva rinses as a diagnostic method for OSCC.

Syrianen et al (2011) calculated pooled risk estimates for the association of HPV with OSCC and OPMD when compared with healthy oral mucosa as controls. They also examined the effects of sampling techniques on HPV detection rates. Systematic review was performed using PubMed (January 1966 to September 2010) and Embase (January 1990 to September 2010). Eligible studies included randomized controlled, cohort and cross-sectional studies. Pooled data were analyzed by calculating odds ratios, using a random effects model. Risk of bias was based on characteristics of study group, appropriateness of the control group and prospective design. Of the 1,121 publications identified, 39 cross-sectional studies met the inclusion criteria. Collectively, 1,885 cases and 2,248 controls of OSCC and 956 cases and 675 controls of OPMD were available for analysis. Significant association was found between pooled HPV-DNA detection and OSCC (odds ratio [OR] = 3.98; 95% CI: 2.62 to 6.02) and even for HPV16 only (OR = 3.86; 95% CI: 2.16 to 6.86). HPV was also associated with OPMD (OR = 3.87; 95% CI: 2.87 to 5.21). In a subgroup analysis of OPMD, HPV was also associated with oral leukoplakia (OR = 4.03; 95% CI: 2.34 to 6.92), oral lichen planus (OR = 5.12; 95% CI: 2.40 to 10.93), and epithelial dysplasia (OR = 5.10; 95% CI: 2.03 to 12.80). The authors concluded that these findings suggest a potentially important causal association between HPV and OSCC and OPMD.

**General Information:**

In a Cochrane review, Brocklehurst et al (2013) evaluated the effectiveness of current screening methods in decreasing oral cancer mortality. These investigators searched the following electronic databases: the Cochrane Oral Health Group's Trials Register (to July 22, 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 6), MEDLINE via OVID (1946 to July 22, 2013), EMBASE via OVID (1980 to July 22, 2013) and CANCERLIT via PubMed
(1950 to July 22, 2013). There were no restrictions on language in the search of the electronic databases. Randomized controlled trials (RCTs) of screening for oral cancer or potentially malignant disorders using visual examination, toluidine blue, fluorescence imaging or brush biopsy were selected for analysis. Two review authors screened the results of the searches against inclusion criteria, extracted data and assessed risk of bias independently and in duplicate. They used mean differences (MDs) and 95% CIs for continuous data and risk ratios (RRs) with 95% CIs for dichotomous data. Meta-analyses would have been undertaken using a random-effects model if the number of studies had exceeded a minimum of 3. Study authors were contacted where possible and where deemed necessary for missing information. A total of 3,239 citations were identified through the searches. Only 1 RCT, with 15-year follow-up met the inclusion criteria (n = 13 clusters: 191,873 participants). There was no statistically significant difference in the oral cancer mortality rates for the screened group (15.4/100,000 person-years) and the control group (17.1/100,000 person-years), with a RR of 0.88 (95% CI: 0.69 to 1.12). A 24% reduction in mortality was reported between the screening group (30/100,000 person-years) and the control group (39.0/100,000) for high-risk individuals who used tobacco or alcohol or both, which was statistically significant (RR 0.76; 95% CI: 0.60 to 0.97). No statistically significant differences were found for incidence rates. A statistically significant reduction in the number of individuals diagnosed with stage III or worse oral cancer was found for those in the screening group (RR 0.81; 95% CI: 0.70 to 0.93). No harms were reported. The study was assessed as at high risk of bias. The authors concluded that there is evidence that a visual examination as part of a population-based screening program reduces the mortality rate of oral cancer in high-risk individuals. In addition, there is a stage shift and improvement in survival rates across the population as a whole. However, the evidence is limited to 1 study, which has a high risk of bias and did not account for the effect of cluster randomization in the analysis. They stated that there was no evidence to support the use of adjunctive technologies like toluidine blue, brush biopsy or fluorescence imaging as a screening tool to reduce oral cancer mortality. Moreover, they stated that further RCTs are recommended to assess the efficacy and cost-effectiveness of a visual examination as part of a population-based screening program in low, middle and high-income countries.

The U.S. Preventive Services Task Force (USPSTF)'s recommendation statement on “Screening for oral cancer” (USPSTF, 2014) stated that “The primary screening test for oral cancer is a systematic clinical examination of the oral cavity. According to the World Health Organization and the National Institute of Dental and Craniofacial Research, an oral cancer screening examination should include a visual inspection of the face, neck, lips, labial mucosa, buccal mucosa, gingiva, floor of the mouth, tongue, and palate. Mouth mirrors can help visualize all surfaces. The examination also includes palpating the regional lymph nodes, tongue, and floor of the mouth. Any abnormality that lasts for more than 2 weeks should be reevaluated and considered for biopsy …. Additional tests proposed as adjuncts to the oral cancer screening examination include toluidine blue dye staining, chemiluminescent and autofluorescent lighting devices, and brush cytopathology. These screening and adjunct tests have not been adequately tested in primary care non dental settings. Although there is interest in screening for oral HPV infection, medical and dental organizations do not recommend it. Currently, no screening test for oral HPV infection has been approved by the U.S. Food and Drug Administration (FDA). Evaluating the accuracy of tests that detect oral HPV infection is a potentially promising area of research”.

Fuller and colleagues (2015) reviewed the published evidence concerning adjunctive diagnostic techniques in the diagnosis of oral lesions of unknown malignant potential. These investigators conducted a systematic literature review with meta-analysis using PubMed to search for articles published from June 1993 through June 2013 to identify prospective studies evaluating any diagnostic method, with tissue biopsy confirmation, in clinically evident oral lesions of unknown malignant potential. Aggregate weighted totals and SEs for true, false-positive, false-negative, and inadequate results were calculated and compared among subgroups. A total of 48 articles satisfying inclusion criteria were identified; 25 were included in quantitative synthesis. The authors concluded that oral cytology holds higher diagnostic value than specialist's oral examination, which holds higher value than in-vivo toluidine blue staining. Moreover, they stated that this study does not support the use of
computer-aided or liquid-based cytology. They noted that future studies should be designed to test multiple methods in the same patient population to allow direct comparison among various techniques.

Rashid and Warnakulasuriya (2015) evaluated the effectiveness of devices that utilize the principles of chemi-luminescence (CL) and tissue auto-fluorescence (AF) as adjuncts in the detection of oral cancer (OC) and OPMDs. These researchers 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. A total of 25 primary studies published between 2004 and 2013 satisfied selection criteria — 13 utilized CL and 12 tissue AF. Some had utilized both study methods on the same population. Chemi-luminescence showed good sensitivity at detecting any OPMDs and oral cancer. However, it preferentially detected leukoplakia and may fail to spot red patches. The additive use of TL may improve specificity. Tissue AF was sensitive at detecting white, red and white and red patches, and the area of FVL often extended beyond the clinically visible lesion. However, in addition to OPMDs, VELScope may detect erythematous lesions of benign inflammation resulting in false-positive test results. The authors concluded that there is limited evidence for their use 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.

Omar (2015) examined the validity of using advanced non-invasive technologies in diagnosis of OSCC by identifying and evaluating relevant published reports. Medline, Embase, and CINAHL were searched to identify clinical trials and other information published between 1990 and June 10, 2014; the searches of Medline and Embase were updated to November 2014. Studies of non-invasive methods of diagnosing OSCC, including oral brush biopsy, optical biopsy, saliva-based oral cancer diagnosis, and others were included. Data were abstracted and evaluated in duplicate for possible relevance on 2 occasions at an interval of 2 months before being included or excluded. This study identified 163 studies of non-invasive methods for diagnosing OSCC that met the inclusion criteria. These included 6 studies of oral brush biopsy, 42 of saliva-based oral diagnosis, and 115 of optical biopsy; 69 of these studies were assessed by the modified version of the QUADAS instrument. Saliva-based oral cancer diagnosis and optical biopsy were found to be promising non-invasive methods for diagnosing OSCC. The strength of evidence was rated low for accuracy outcomes because the studies did not report important details needed to evaluate the risk for bias. The authors concluded that screening for and early detection of cancer and pre-cancerous lesions have the potential to reduce the morbidity and mortality of this disease. They stated that advances in technologies for saliva-based oral diagnosis and optical biopsy are promising pathways for the future development of more effective non-invasive methods for diagnosing OSCC that are easy to perform clinically in primary care settings.

In a Cochrane review, Macey and colleagues (2015) estimated the DA of index tests for the detection of OC and PMD of the lip and oral cavity, in people presenting with clinically evident lesions. These researchers also estimated the relative accuracy of the different index tests. The electronic databases were searched on April 30, 2013. They searched Medline (OVID) (1946 to April 2013) and 4 other electronic databases (the Cochrane Diagnostic Test Accuracy Studies Register, the Cochrane Oral Health Group’s Trials Register, Embase (OVID) and Medion (Ovid)). There were no restrictions on language in the searches of the electronic databases. These investigators conducted citation searches and screened reference lists of included studies for additional references. They selected studies that reported the DA of the following index tests when used as an adjunct to conventional oral examination in detecting PMD or oral squamous cell carcinoma of the lip or oral cavity: Vital staining, oral cytology, light-based detection and oral spectroscopy, blood or saliva analysis (which test for the presence of biomarkers in blood or saliva). Two review authors independently screened titles and abstracts for relevance. Eligibility, data extraction and quality assessment were carried out by at least 2 authors, independently and in duplicate. Studies were assessed for methodological quality using QUADAS-2. Meta-analysis was used to combine the results of studies for each index test using the bivariate approach to estimate the expected values of sensitivity and specificity. These researchers included 41 studies, recruiting 4,002 participants, in this review. These studies evaluated the DA of conventional oral examination with: Vital staining (14 studies), oral cytology (13 studies), light-based detection or
oral spectroscopy (13 studies); 6 studies assessed 2 combined index tests. There were no eligible DA studies evaluating blood or salivary sample analysis. The summary estimates for vital staining obtained from the meta-analysis were sensitivity of 0.84 (95% CI: 0.74 to 0.90) with specificity of 0.70 (0.59 to 0.79), with 14 studies were included in the meta-analysis. For cytology, sensitivity was 0.91 (0.81 to 0.96) and specificity was 0.91 (0.81 to 0.95) with 12 studies included in the meta-analysis. For light-based detection, sensitivity was 0.91 (0.77 to 0.97) and specificity was 0.58 (0.22 to 0.87) with 11 studies included in the meta-analysis. The relative test accuracy was assessed by adding covariates to the bivariate analysis, no difference in model fit was observed. The authors concluded that the overall quality of the included studies was poor; none of the adjunctive tests could be recommended as a replacement for the currently used standard of a scalpel biopsy and histological assessment. They stated that given the relatively high values of the summary estimates of sensitivity and specificity for cytology, this would appear to offer the most potential; and combined adjunctive tests involving cytology warrant further investigation.

Giovannacci and associates (2016) performed a systematic review on non-invasive tools for diagnosis of oral dysplasia (OD) and early OSCC. Medline, Scopus, Web of Knowledge databases were searched, using as entry terms "oral dysplasia and diagnosis" / "oral cancer and diagnosis". Data extracted from each study included number of lesions evaluated, histopathological diagnosis, SE, statistical power (SP), PPV, NPV, diagnostic accuracy (DA) and the main conclusions. After title and abstract scanning of 11,080 records, these researchers selected 35 articles for full text evaluation. Most evaluated tools were AF, CL, TB, and CL-associated with TB (CLTB). The authors concluded that there is a great inhomogeneity of the reported values and there is no significant evidence of superiority of one tool over the other. They stated that further clinical trials with a higher level of evidence are needed to evaluate the real usefulness visual diagnostic tools.

In a systematic review, Nagi and colleagues (2016) evaluated the effectiveness of devices that utilize the principles of CL and tissue AF as adjuncts in the detection of OSCC and OPMD. The electronic retrieval systems and databases searched for relevant articles were PubMed [Medline] and Science direct. The search was for limited articles published in English or with an English abstract and articles published during the period from January 2005 to April 2014. Clinical trials utilized ViziLite, Microlux TM/DL and Visual Enhanced Light scope (VELscope) for early detection of OPMD and OSCC were selected for analysis. A total of 20 primary studies published satisfied selection criteria -- 10 utilized CL and 10 tissue AF. Sensitivity of Vizilite for detecting OSCC and OPMD ranged from 77.1% to 100% and specificity was low that ranged from 0% to 27.8%. Most have shown that CL increased the brightness and margins of oral mucosal white lesions and thus assisted in identification of mucosal lesions not considered under conventional visual examination. However, it preferentially detected leukoplakia and may fail to spot red patches. Clinical trials demonstrated that sensitivity of VELscope in detecting malignancy and OPMD ranged from 22% to 100% and specificity ranged from 16% to 100%. Most studies concluded that VELscope could help the experienced clinician to find oral precursor malignant lesions. But it could not differentiate between dysplasia and benign inflammatory conditions. The authors concluded that both devices are simple, non-invasive tests of the oral mucosa, but are only suited for clinicians with sufficient experience and training. They stated that more clinical trials should be conducted to establish optical imaging as an effective adjunct tool in early diagnosis of OSCC and OPMD.

**Wide-Field and High-Resolution In-Vivo Imaging:**

Shin and colleagues (2010) stated that early detection is an essential component of cancer management. Unfortunately, visual examination can often be unreliable, and many settings lack the financial capital and infrastructure to operate PET, CT, and MRI systems. Moreover, the infra-structure and expense associated with surgical biopsy and microscopy are a challenge to establishing cancer screening/early detection programs in low-resource settings. Improvements in performance and declining costs have led to the availability of optoelectronic components, which can be used to develop low-cost diagnostic imaging devices for use at the point-of-care. These investigators demonstrated a fiber-optic fluorescence microscope using a consumer-grade camera for in-vivo cellular imaging. The
fber-optic fluorescence microscope includes an LED light, an objective lens, a fiber-optic bundle, and a consumer-grade digital camera. The system was used to image an oral cancer cell line labeled with 1.1% proflavine. A human tissue specimen was imaged following surgical resection, enabling dysplastic and cancerous regions to be evaluated. The oral mucosa of a healthy human subject was imaged in-vivo, following topical application of 0.01% proflavine. The fiber-optic microscope resolved individual nuclei in all specimens and tissues imaged. This capability allowed qualitative and quantitative differences between normal and pre-cancerous or cancerous tissues to be identified. The optical efficiency of the system permitted imaging of the human oral mucosa in real time. The authors concluded that these findings indicated this device as a useful tool to assist in the identification of early neoplastic changes in epithelial tissues. This portable, inexpensive unit may be particularly appropriate for use at the point-of-care in low-resource settings.

Shao et al (2012) presented a new integrated micro-endoscopy system combining label-free, fiber-based, real-time C-scan optical-resolution photo-acoustic microscopy (F-OR-PAM) and a high-resolution fluorescence micro-endoscopy system for visualizing fluorescently labeled cellular components and optically absorbing microvasculature simultaneously. With a diode-pumped 532-nm fiber laser, the F-OR-PAM sub-system is able to reach a resolution of approximately 7 μm. The fluorescence subsystem, which does not require any mechanical scanning, consists of a 447.5-nm-centered diode laser as the light source, an objective lens, and a CCD camera. Proflavine was used as the fluorescent contrast agent by topical application. The scanning laser and the diode laser light source shared the same light path within an optical fiber bundle containing 30,000 individual single-mode fibers. The absorption of proflavine at 532 nm was low, which mitigated absorption bleaching of the contrast agent by the photo-acoustic excitation source. These researchers demonstrated imaging in live murine models. The authors concluded that the system is able to provide cellular morphology with cellular resolution co-registered with the structural information given by F-OR-PAM. They stated that the system has the potential to serve as a virtual biopsy technique, helping visualize angiogenesis and the effects of anti-cancer drugs on both cells and the microcirculation, as well as aid in the study of other diseases.

In a review on “Discrimination of benign and neoplastic mucosa with a high-resolution microendoscope (HRME) in head and neck cancer”, Vila et al (2012) stated that “Although HRME is a promising tool, there are several limitations which highlight areas for further development. One issue is the strong affinity of the contrast agent, proflavine, for keratin …. Because HRME imaging is limited to the superficial mucosa with a depth of penetration of roughly 50 micrometers, images may be wrongly classified as normal, when in fact tumor extends into the submucosa underneath normal superficial mucosa on histopathologic analysis …. High-resolution microendoscopic imaging provides non-invasive visualization of squamous epithelium in the upper aerodigestive tract in real time, and permits accurate discrimination of benign mucosa and invasive cancer. Keratinization and submucosal tumor spread are diagnostic challenges, which may be addressed by development of strategies for submucosal delivery of the HRME probe. With further refinement, HRME and other optical imaging methods have the potential to enhance the rational selection of initial margins, and decrease operative time and expense by limiting the use of frozen section analysis”.

Furthermore, NCCN’s clinical practice guideline on “Head and neck cancers” (Version 1.2015) does not mention the use of proflavine/fluorescence imaging as a management tool.

**MOP Genetic Test:**

According to the Pleasant Family Dentistry, MOP is a genetic test for oral cancer; and it has 3 components:

- **Cell abnormalities**

  Cell abnormalities - Changes to one’s cells could mean a pre-cancerous condition or infection exists.
HPV (Human Papilloma Virus)

HPV (Human Papilloma Virus) - While HPV can lead to some cases of oral cancer, HPV infection may clear up on its own. In either case, we would monitor you to find out, and test you more frequently if an infection tends to linger.

DNA damage

DNA damage - People with certain DNA damage seem to be at a higher risk for oral cancer. These abnormalities don’t mean you have oral cancer or that you are destined to get it, but we recommend more frequent monitoring just to be safe.

Towle et al (2013) stated that earlier studies involving a priori gene selection have identified promoter regions deregulated by DNA methylation changes in oral squamous cell cancers (OSCCs) and precancers. Interrogation of global DNA methylation patterns for such specimens has not been reported, though such analyses are needed to uncover novel molecular factors driving disease. These researchers evaluated global DNA methylation patterns for 30 biopsies obtained from 10 patients undergoing surgical removal of an OSCC or carcinoma in-situ (CIS). From a disease field in each patient, these investigators collected

- I. dysplastic,
- II. CIS or OSCC, and
- III. adjacent normal biopsies.

DNA isolated from each biopsy was profiled for methylation status using the Illumina HumanMethylation27K platform. These data demonstrated that aberrant methylation of promoter CpG islands exists across oral pre-cancer and OSCC genomes. Non-hierarchical clustering of all methylation data revealed distinct methylation patterns between the normal and the CIS/OSCC tissues (with results for dysplastic biopsies split between groups). Multiple genes exhibiting recurrent aberrant DNA methylation were found for both dysplastic and CIS/OSCC groups, and included enrichment for genes found in the WNT and MAPK signaling pathways. The authors concluded that in identifying aberrant DNA methylation at the earliest stages of oral pre-cancer and finding recurring epigenetic disruption of specific genes/pathways across this analyzed cohort, the authors saw evidence that CpG methylation changes may play a role in oral cancer progression and that global DNA methylation analyses may have significant utility in wider studies that seek to derive biomarkers or potentially druggable targets to improve oral cancer outcomes.

Furthermore, NCCN’s clinical practice guideline on “Head and neck cancers” (Version 1.2015) does not mention genetic testing as a screening/management tool.

Oral Human Papillomavirus Testing:

In a prospective cohort study, Woelber and colleagues (2017) examined the co-prevalence of cervical and oropharyngeal HPV infection in patients with HPV-related high-grade disease of the uterine cervix (high-grade squamous intraepithelial lesion [HSIL]). Women with abnormal cervical cytology admitted to the authors’ colposcopy units received HPV testing of the uterine cervix and the oropharynx via smear. From a subset of patients, oral lavage was collected to compare detection rates of HPV DNA between lavage and swab. Patients with confirmed high-risk HPV (HR-HPV)-positive HSIL of the cervix were further investigated. Sexual behavior and lifestyle factors were documented with a standardized questionnaire. A total of 235 women were included in the study; 135 (57.5 %) were cervically HR-HPV positive with histologically confirmed high-grade cervical intraepithelial lesion (median [range] age of 30 [21 to 45] years). Of these, only 6 (4.4 %) also had a positive oral specimen. In 3 (50 %) of the 6 cases, the same HPV type was detected in oral and cervical samples (HPV 16, 35, and 45). Oral HPV detection was not higher when combining swab and lavage compared
with swab alone. A relation between sexual behavior and oral HPV detection could not be
demonstrated. The authors concluded that oral HPV prevalence in women with cervical HPV infection
and HSIL was low. They stated that simultaneous testing of oropharyngeal and cervical HPV infection
does not appear promising as future screening strategy.

Zafereo and associates (2016) stated that HPV is a causal and prognostic factor for oropharyngeal
cancer, but its role in squamous cell carcinoma of the oral cavity (SCCOC) is unclear. These
researchers sought to clarify HPV's role in SCCOC. Patients with newly diagnosed SCCOC (n = 460)
were prospectively recruited, treated, and followed at 1 institution; p16/HPV status was determined by
p16 immunohistochemistry (IHC) (n = 210), PCR-based HPV 16/18 E6/7 DNA testing (n = 403), and/or
HPV in-situ hybridization (ISH) (n = 178). Kaplan-Meier curves and log-rank tests were used to
compare survival by p16/HPV status. p16 expression was detected in 30 % of tumors (62/210) and
HPV 16/18 E6/7 DNA in 28 % (114/403), although correlation between these 2 assays was poor (r =
-0.01). Patients with p16-positive tumors were more likely to be younger and have primary tumors of
the tongue. Only 4 % of tumors (7/171) were positive for HPV by ISH. Comparisons of patients with
p16-positive and p16-negative tumors, patients with HPV-positive and HPV-negative tumors by PCR,
and patients with HPV-positive and HPV-negative tumors by ISH showed no significant differences in
disease-specific or disease-free survival by p16/HPV status. When these investigators applied a more
stringent definition of HPV positivity based on a combination of assay results, only 10 of 166 tumors
were HPV-positive, and there were no significant differences in demographic, exposure, clinical, or
survival characteristics between these patients and the 156 HPV-negative patients. The authors
concluded that very few patients with SCCOC have HPV-driven tumors; SCCOC that over-expressed
p16 may be a unique subset deserving of further study.

Uken and co-workers (2016) noted that the incidence of HPV associated oropharyngeal squamous cell
cancer (OSCC) is on the rise. With the HPV-positive uterine cervix as a reservoir, HPV-positive OSCC
is discussed as a sexually transmitted disease. Mechanisms of HPV transmission to the oral cavity are
poorly understood. To gain more insight into HPV-transmission routes, cervically HPV-positive women
and their sexual partners were screened for oral HPV infection. Women with cervical dysplasia
underwent HPV testing of the uterine cervix and tonsillar region via brush test. In addition, sexual
partners received oral HPV testing. Tonsillar brush tests of patients admitted for routine surgery served
as the control group. The HPV-PCR (Roche Linear Array Kit) was used to differentiate 37 HPV types.
All participants completed a risk-factor questionnaire focusing on sexual habits. A total of 101 women
were tested HPV-positive at the cervix. Only 3/101 (3 %) were tested HPV-positive in the oropharynx.
In 60/101 (60 %) women the sexual partner could be tested for oral HPV infection: testing was
positive in 3/60 (5 %). No oral HPV was detected in the control group. The risk-factor questionnaire
revealed significant differences between the female study group and control group in terms
of age at first sexual intercourse and smoking habits. The authors concluded that the limited data
suggested that among sexual partners in Germany, HPV transmission to the oropharynx by oral-
genital sex or by auto-inoculation is a rare and unlikely event with low HPV concordance. They stated
that another explanation for the low oral prevalence could be an independent clearance of HPV from
the oropharyngeal site compared to cervix uteri or at different time intervals.

Maatouk and Abdo (2016) noted that HPV infection is the most common sexually transmissible viral
infection worldwide; HPV is highly prevalent in sexually active men who have sex with men (MSM).
These investigators examined HPV prevalence in the oral cavity of MSM from Beirut, Lebanon. From
November 2015 to January 2016, a total of 42 MSM were recruited using respondent-driven sampling
and provided oral samples for HPV DNA and for linear array testing to detect HPV type. In total, 28
(66.67 %) HIV-negative and 14 (33.33 %) HIV-positive MSM were included. Overall, HPV prevalence
in the oral cavity was 10 % (95 % CI: 0.93 to 19.07) among all participants, but there was no statistical
difference according to HIV status. The HPV type was exclusively HPV-6. The authors concluded that
these findings did not find an urgent need for routine HPV prevalence and screening for cancers in the
oral cavity of a MSM group in Lebanon; however, they confirmed previous findings regarding
geographic variations in HPV prevalence.
MiRNA in Oral Squamous Cell Carcinoma:

Tian and colleagues (2015) noted that OSCC is one of the most leading causes of cancers worldwide. Due to a low 5-year survival rate, highly effective methods for the early detection of OSCC are needed. MicroRNAs (miRNAs), as promising biomarkers, can bring insights into tumorigenesis of oral cancers. However, studies on the accuracy of miRNAs detection in OSCC have inconsistent conclusions. These investigators conducted a meta-analysis to review the articles investigating the diagnostic value of miRNAs in OSCC. The PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), Web of Science were searched (updated to June 11, 2015) to identify all articles evaluating the diagnostic yield of miRNAs for OSCC. The pooled sensitivity, specificity, and other diagnostic parameters were used to assess the performance of miRNAs assays on OSCC detection. Statistical analysis was conducted by employing the R software. The present meta-analysis comprised 23 studies from 10 articles, including 598 OSCC patients and 320 healthy individuals, available for analysis. The summary receiver operator characteristic (SROC) curve was plotted. Meanwhile, the pooled diagnostic parameters and the area under curve (AUC) were calculated based on all included studies. The pooled diagnostic parameters calculated from all 23 studies were as follows: pooled sensitivity of 0.759 (95 % CI: 0.701 to 0.809), pooled specificity of 0.773 (95 % CI: 0.713 to 0.823) and AUC of 0.832, which indicated a relatively high DA of miRNAs in differentiating OSCC patients from healthy controls. In addition, subgroup analyses were conducted to access the heterogeneity between studies, which was based on specimen (serum/plasma/blood/saliva/ tissue) and ethnicity (Asian/Caucasian).

The authors concluded that the findings of this meta-analysis suggested that miRNAs might be used in non-invasive screening tests for OSCC, however, this approach needs to be validated by large-scale studies.

In a meta-analysis, Lin and co-workers (2016) summarized the global DA of miRNAs for patients with OC. A systematic review of multiple databases was performed to obtain original studies fulfilling search criteria and the quality of studies was assessed by the QUADAS tool. The bivariate meta-analysis model was employed to plot the SROC curve. Influence analysis, meta-regression, and publication bias assay were all conducted using Stata 12.0 software. The trim-fill adjustment method was used to further assess the possible effect of publication bias. A total of 8 studies were included. The SROC analysis showed that miRNA profiling allowed for the discrimination between patients with high-risk oral lesions (OC or pre-cancer) and healthy donors, with a sensitivity of 0.84 (95 % CI: 0.78 to 0.88) and specificity of 0.83 (95 % CI: 0.78 to 0.87), corresponding to an AUC of 0.90. Subgroup analyses suggested that miRNA signature harbored higher DA for OSCC than pre-cancer lesions (AUC, sensitivity, and specificity of 0.90, 0.83, or 0.82, respectively). Moreover, stratified analyses revealed that parallel miRNA profiling, plasma- and Caucasian-based analyses all conferred promising accuracies for OC detection. The funnel plot assay manifested evidence of a publication bias. After the adjustment by the trim and fill method, the pooled adjusted efforts were slightly attenuated. The authors concluded that miRNA profiles indicated a potential diagnostic value for detection of OC and potentially malignant disorders. They stated that further studies should be performed to rigorously evaluate the DA of miRNA profiling for OC.

Philipone and associates (2016) noted that leukoplakia is the most common precursor lesion of OSCC. Currently, the risk of progression to OSCC is assessed based on histopathologic examination alone. However, this method fails to identify the subset of microscopically innocuous leukoplakia that ultimately transforms to OSCC. These investigators examined if miRNAs can be utilized to identify non- and low-grade dysplastic oral lesions at risk for cancer progression. A retrospective study of genome-wide miRNA expression level analyses was performed in the training cohort (n = 20) using deep sequencing formalin-fixed paraffin embedded incisional biopsy tissues from patients with oral leukoplakic lesions diagnosed with non- or low-grade dysplasia and known clinical outcome. The promising miRNA candidates were then evaluated in the validation cohort (n = 80) using quantitative real-time PCR (qRT-PCR); 4 promising miRNAs-208b-3p, 204-5p, 129-2-3p and 3065-5p were identified. Combining these 4 miRNAs as a panel with age and histologic diagnosis (p < 0.004), the
The final model had a predictive value for the area under the receiver operating characteristic (ROC) curve (AUC) of 0.792, sensitivity of 76.9 % and specificity of 73.7 % to accurately identify non- and low-grade dysplastic lesions at risk of cancer progression, which is a significant improvement over histopathologic examination alone (AUC of 0.645). The authors concluded that while further investigation is needed, discovery of predictive markers that can accurately identify histologically innocuous oral lesions at high risk for progression to OSSC will significantly improve clinical outcome by means of early intervention.

Yan and colleagues (2017) stated that miRNAs have been used as diagnostic and prognostic biomarkers for many cancers including OSCC. Several studies have been shown that miRNA play important roles during the progression of OSCC. However, the results vary largely in different studies due to different platforms and sample sizes. These researchers systematically evaluated a large scale of miRNA profiles from current qualified OSCC samples, and further examined the functions of genes regulated by these key miRNAs as well as the signaling pathways through which these miRNA effect carcinogenesis. A total of 7 key miRNAs were identified, and of which 3 were significantly up-regulated, including hsa-miR-21, hsa-miR-31, hsa-miR-338, and 4 were down-regulated, namely hsa-miR-125b, hsa-miR-133a, hsa-miR-133b, and hsa-miR-139. The function enrichment analysis revealed that target genes of up-regulated miRNAs were associated with cellular protein metabolic process, macromolecule metabolic process, and TGF-beta pathway, while the targets of down-regulated were enriched in negative regulation of macromolecule biosynthetic process and gene expression, and p53, long-term potentiation and adherens junction pathways. Transcription factor analysis revealed that there were 67 (51.1 %) transcription factors influenced by both up- and down-regulated miRNAs. The authors concluded that 7 key miRNAs were found to play essential role in progression of OSCC, as well as the target genes and transcription factors of these miRNAs. They stated that the potential functions of these target genes identified in this study may be profitable to diagnosis and prognostic prediction of OSCC as biomarkers.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</strong></td>
</tr>
<tr>
<td><strong>micro RNAs</strong> - No specific code:</td>
</tr>
<tr>
<td><strong>CPT codes not covered for indications listed in the CPB:</strong></td>
</tr>
<tr>
<td>40899</td>
</tr>
<tr>
<td>41599</td>
</tr>
<tr>
<td>41899</td>
</tr>
<tr>
<td>82397</td>
</tr>
<tr>
<td>87623</td>
</tr>
<tr>
<td>87624</td>
</tr>
<tr>
<td>87625</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0431</td>
<td>Adjunctive pre-diagnostic test that aids in detection of mucosal abnormalities including premalignant and malignant lesions, not to include cytology or biopsy procedures</td>
</tr>
<tr>
<td>G0476</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); human papillomavirus (HPV), high-risk types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) for cervical cancer screening, must be performed in addition to pap test</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

- **A69.0**, **K00.0** - K14.9: Disease of oral cavity, salivary glands, and jaws
- **C00.0** - **C10.9**: Malignant neoplasm of lip and oral cavity
- **D00.00** - **D00.08**: Carcinoma in situ of lip, oral cavity, and pharynx
- **D37.01** - **D37.02**
  - **D37.04** - **D37.09**: Neoplasm of uncertain behavior of lip, oral cavity, and pharynx
- **Z12.81**: Screening for encounter for malignant neoplasms of oral cavity

The above policy is based on the following references:

15. Poh CF, Ng SP, Williams PM, et al. Direct fluorescence visualization of clinically occult high-risk...
oral premalignant disease using a simple hand-held device. Head Neck. 2007;29(1):71-76.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0760 Oral Screening and Lesion Identification Systems

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania  updated 11/22/2017