# Medical Coverage Policy

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# Oral Cancer Screening Systems

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## Related Coverage Resources

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## Overview

This Coverage Policy addresses various types of oral cancer screening systems which have been proposed as adjunctive tests for the detection of oral cancer. The current evidence does not support the use of these adjunctive screening systems. A thorough conventional visual and tactile examination with normal incandescent lighting, followed by a scalpel biopsy and microscopic evaluation is the established standard of care for determining a final diagnosis and treatment plan for oral cancer.

## Coverage Policy

**Adjunctive oral cancer screening systems, including, but not limited to any of the following, are considered experimental, investigational or unproven:**

- ViziLite™ (Zila Inc., Phoenix, AZ)
- Vizilite® Plus Oral Cancer Screening System (Den-Mat Holdings, LLC, Lompoc, CA)
- VELscope® (LED Medical Diagnostics, White Rock, BC, Canada)
- Microlux™/DL (AdDent, Inc., Danbury, CT)
- Bio/Screen Oral Exam Light (AdDent, Inc., Danbury, CT)
- OraBlu Lesion Marking System (AdDent, Inc., Danbury, CT)
- OralID™ 2.0 (Forward Science Technologies, LLC, Stafford, TX)
- Orascoptic™ DK™ (Sybron Dental Specialties, Inc., Orange, CA)
- Sapphire O/E Oral Examination System/Sapphire Plus Lesion Detection (Den-Mat Holdings LLC, Lompoc, CA)
- TRIMIRA™ Identafi™ 3000 (TRIMIRA, LLC, Houston, TX)
- Dentlight Oral Exam Light Kit (DentLight, Inc., Richardson, TX)

## General Background

According to the National Cancer institute (NCI) (2022), new cases of oral cavity and oropharynx cancers in the United States are estimated to be 54,000. The incidence rate is highest in individuals ages 75 to 84 years of male gender (NCI, 2022; Howlander, et al., 2020). The highest incidence occurs in males of any race with white males (rate of 18.6 per 100,000) having highest rates, followed by American Indian/Alaska Native (14.6/100,000), Black (13.1/100,000), Asian/Pacific Islander (12.9/100,000), and Hispanic (10.9/100,000) (NCI, 2021). Globally, estimated annual incidents of oral/oralpharyngeal cancers are approximately 275,000 with disproportionately higher numbers (approximately 20-fold) seen in South and Southeast Asia (India, Sri Lanka, Pakistan, and Bangladesh), France, and Brazil. In most countries, men have higher rates of oral cavity cancer than women (secondary to tobacco use) and higher rates of lip cancer (due to sunlight exposure from outdoor occupations) (NCI, 2022).

Oral carcinomas may occur anywhere in the oral cavity, including the posterolateral margin of the tongue and floor of the mouth. In more than 50% of cases, there is evidence of spreading to regional lymph nodes and metastases at the time of diagnosis. Early detection of potentially malignant oral lesions can improve clinical outcomes and quality of life. However, screening for oral cancer has not demonstrated a reduction in mortality from cancer of the oral cavity. Visual

detection of oral cancer at an early stage is difficult since premalignant and malignant lesions cannot be easily differentiated from benign lesions. Clinical characteristics such as induration, elevation, bleeding and cervical adenopathy are associated with advanced oral cancers but are typically absent in early-stage lesions. After the detection of a potential oral cancer lesion via a conventional visual and tactile examination, diagnosis is typically based on histopathological evaluation of a full-thickness incisional scalpel biopsy of the lesion which is considered the gold standard for final diagnosis and treatment planning. In an effort to improve evaluation of oral mucosal abnormalities, a number of light-based visualization adjuncts have been developed. These tests include: chemilluminescence, blue-white LED, and autofluorescence are used as light sources in light-based systems, including: ViziLite™ (Zila Inc., Phoenix, AZ)**;** VELscope® (LED Medical Diagnostics, White Rock, BC, Canada); MicroLux™/DL (AdDent, Inc., Danbury, CT); Bio/Screen (AdDent, Inc., Danbury, CT); Orascoptic DK™ (Sybron Dental Specialties, Inc., Orange, CA); TRIMIRA™ Identafi™ 3000 (TRIMIRA, LLC, Houston, TX); Dentlight Oral Exam Light Kit (DentLight, Inc., Richardson, TX); and Sapphire O/E Oral Examination System/Sapphire Plus Lesion Detection, Vizilite® Plus Oral Cancer Screening System (Den-Mat Holdings, LLC, Lompoc, CA).

Human papillomavirus (HPV) are a group of more than 200 related viruses. Persistent HPV infections have been recognized as the cause of essentially all cervical cancers, 70% of oropharyngeal cancers, as well as 90% of anal cancer (NCI, 2021). At least 14 high-risk HPV types have been identified, including HPV types 16 and 18. Recent data indicate that HPV, specifically HPV-16, is also an independent risk factor for oropharyngeal cancer. HPV may modulate the malignancy process in some tobacco and alcohol induced tumors of the oropharynx and may also be associated with development of oropharyngeal cancer in some non-smokers.

There is insufficient evidence in the published medical literature to demonstrate that the use of light-based visualization adjuncts, or the use of the MOP Test provide additional benefit compared to conventional visual and tactile oral cancer screening. It has not been proven that the use of these tools results in improved health outcomes.

**U.S. Food and Drug Administration (FDA)**
**ViziLite™:** The ViziLite Comprehensive Exam Tray (Zila Inc., Phoenix, AZ) received U.S. Food and Drug Administration (FDA) approval through the 510(k) process in November 2001. ViziLite (OralLite) was approved for use in combination with conventional visual oral mucosal examination by healthcare providers to improve identification, evaluation and monitoring of oral mucosal abnormalities in a patient population at increased risk of oral cancer. ViziLite is a single-use product that consists of an acetic acid rinse, retractor, and light stick. The patient rinses with the ViziLite acetic acid solution and expectorates. The ViziLite light stick is activated by bending until the inner capsule breaks. The examiner shakes the stick until it glows, then inserts the light stick into the hollow end of the retractor. After dimming the lights, the oral cavity is examined using the ViziLite device. The technology used in this device is based on similar technology utilizing chemiluminescent light to evaluate dysplastic and malignant squamous cell lesions in the cervix. The light is reported to impart a blue hue to normal tissue, while lesions become clinically discernible and take on an "acetowhite" appearance.

In November 2004, the FDA approved the ViziLite Blue Oral Lesion Identification and Marking System, a three-component swab system used as an adjunct to the ViziLite Test. This system consists of three swab components: two swabs of 1% acetic acid rinse, including a post-dye decolorizer and one swab with a metachromatic vital tissue dye, tolonium chloride (also called toluidine blue). The dye is applied to ViziLite-identified white lesions to allow the healthcare provider to visualize the lesions with incandescent light.
**VELscope®:** VELscope (LED Medical Diagnostics, White Rock, BC, Canada) received approval through the 510(k) process on April 7, 2006. According to the 510(k) summary, the device was

determined to be substantially equivalent to the predicate device, ViziLite. VELscope is intended to be used by a dentist or health-care provider 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 premalignant dysplasia. VELscope is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion and thus aid in determining the appropriate margin for surgical excision. The summary also states that VELscope is complementary to, and is intended to be used in combination with, a traditional oral mucosal examination with white light. The difference between VELscope system and the predicate device is that VELscope uses filters to block the reflected blue light to allow the visualization of the natural tissue fluorescence. The VELscope VX was FDA approved in 2010. The main technological differences between the VEI-scope Vx and the predicate VELscope system are: The light source has now been integrated into the handpiece which is cordless and operates on a lithium ion battery.

**MicroLux™/DL (AdDent, Inc., Danbury, CT):** Microlux/DL received FDA 510(k) clearance on March 28, 2005. It was considered to be substantially equivalent to ViziLite. According to the FDA summary, the only difference between the MicroLux DL and ViziLite is that the former uses a blue-white LED as a light source and the latter uses a blue-white chemical luminescent light source. The associated 1% acetic rinse and diagnostic procedures are identical. The device is used as an aid to improve the visualization of oral lesions. It is designed to be used by a dentist or health care provider, in combination with a traditional examination by incandescent light.

The ORABLU Oral Lesion Marking System, FDA 510(k) approved in 2012, is a three component swab system intended to be used by a dentist as an adjunct to traditional oral examination by incandescent light, combined with further examination with one of three oral examination lights manufactured by AdDent, Inc.: The Microlux DIL, Microlux BLU, and Blo/Screen. The ORABLU Oral Lesion Marking System is used as an aid to enhance the visualization of oral mucosal irregularities by physically marking areas of oral mucosa that may warrant further investigation.

**Bio/Screen (AdDent, Inc., Danbury, CT):** The Bio/Screen Oral Exam Light is a handheld device proposed for use as an adjunct to oral examination to enhance the visualization of the oral mucosal. The light uses five violet LEDS and is proposed to improve visualization of dysplastic lesions and squamous cell carcinoma. OraBlu is proposed to be used as a companion product for marking mucosal irregularities for additional verification of abnormalities and to help determine the need for biopsy. Bio/Screen was FDA 510(k) approved "to be used by a dentist or healthcare provider as an adjunct to traditional oral examination by incandescent light to enhance the visualization of oral mucosal abnormalities and aid in defining lesion borders" The OraBlu Oral Lesion Marking System was 510(k) approved "to be used by a dentist as an adjunct to traditional oral examination by incandescent light, combined with further examination with one of three oral examination lights manufactured by AdDent, Inc." including the MicroluxDL, Microlux BLUE and Bio/Screen systems (AdDent, 2021; FDA, 2012; FDA, 2009).

**OralID™ 2.0 (Forward Science Technologies LLC, Stafford, TX):** OralID is a hand-held oral illumination and examination light proposed for use as an adjunctive tool for fluorescence visualization of oral mucosal tissue. The device is FDA 510(k) approved "to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer". In November 2016, OralID was upgraded to the Oral ID 2.0. The 2.0 is proposed to have upgraded electronics (enhanced power switch and rechargeable batteries) making it an oral cancer screening kit without consumables (Dentistry IQ, 2016, FDA, 2013).

**Orascoptic DK™ (Sybron Dental Specialties, Inc., Orange, CA):** The Orascoptic DK is a 510(K) exempt Class I device intended for various purposes, including oral lesion screening. It is a

battery operated hand-held LED instrument with an oral lesion screening attachment and is used in conjunction with a 1% acetic acid solution. The examination process is similar to that used with ViziLite and MicroLux, above.

**TRIMIRA™ Identafi™ 3000 (TRIMIRA, LLC, Houston, TX):** The TRIMIRA Identafi 3000 received FDA 510(k) clearance on February 17, 2009. The device is a battery operated, hand-held multispectral oral examination light used in conventional and specialized oral examination. It is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer or premalignant dysplasia.

**Dentlight Oral Exam Light Kit (DentLight, Inc., Richardson, TX):** The Dentlight Oral Exam Light Kit received FDA 510(k) clearance on July 15, 2010. The device is a rechargeable-battery-powered cordless unit with interchangeable light head (white and violet) and accessories. It is indicated for providing illumination to aid visualization during oral procedures and as an adjunct to enhance the visualization for oral examination of mucosal abnormalities and oral lesions.

**Sapphire™ O/E Oral Examination System/Sapphire Plus Lesion Detection (Den-Mat Holdings, LLC, Lompoc, CA):** The Sapphire O/E oral examination light received FDA 510(k) clearance on April 3, 2008, and is intended for use by a dentist or qualified health-care provider as an adjunct to traditional oral examination by white 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 dysphasia. The device is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion and thus aid in determining the appropriate margin for surgical excision.

**Literature Review**
There is insufficient evidence in the published, peer-reviewed literature to support the clinical utility of oral cancer screening systems. The available evidence is primarily in the form of case reports or case series with conflicting outcomes. The specificities, sensitivities, positive predictive values and negative predictive values vary significantly (e.g., 0%–100%) and are not consistent across studies.

**ViziLite:** Awan et al. (2011) conducted a case series (n=126) to evaluate the utility of ViziLite for the examination of potentially oral malignant disorders. Patients underwent ViziLite examination followed by surgical biopsy. Of 126 lesions, 70 were clinically diagnosed as oral leukoplakia/erythroplakia, 32 lichen planus, nine hyperplastic candidiasis, 13 frictional keratosis, and two submucous fibrosis. A total of 95 (75.4%) showed aceto-whitening. Following biopsy, 44 had oral epithelial dysplasia (29 mild, 8 moderate, 7 severe). Although aceto-whitening was seen in the majority of dysplastic lesions, the device failed to distinguish between dysplastic and non-dysplastic lesions. The sensitivity and specificity of chemiluminescence for detecting a dysplastic lesion were 77.3% and 27.8%, respectively. The authors concluded that although ViziLite has the ability to detect oral potentially malignant disorders, it does not accurately delineate dysplastic lesions.

Epstein et al. (2008) evaluated the adjunctive value of ViziLite and application of toluidine blue to further assess lesions identified during a conventional oral soft tissue examination (97 lesions/84 patients). The ViziLite exam improved the brightness and/or sharpness of margins in 61.8% of identified lesions. No lesions that had not previously been identified by oral exam, however, were identified by the adjunctive use of ViziLite. Toluidine blue staining reduced the number of false positive biopsies by 55.26%. Approximately two-thirds of lesions with no dysplasia and 41.18% of lesions with mild or moderate dysplasia were identified as true negatives when TBlue staining was used. The authors stated that further research was needed in other populations using different

study designs before practitioners can be confident that specificity is improved significantly over conventional visual examination while the negative predictive value remains near 100%.

Farah and McCullough (2007) evaluated the efficacy of ViziLite in enhancing visualization of oral mucosal white lesions and in highlighting malignant and potentially malignant lesions (n=55). Patients referred to an oral medicine specialist service over a three month period for evaluation of an oral mucosal white lesion were examined by two oral medicine specialists under routine incandescent light. The examination was repeated with ViziLite chemiluminescent illumination. Although chemiluminescence subjectively enhanced visualization of 26 white lesions, there was no significant difference in lesions size, ease of visibility or border distinctness for oral lesions examined with or without ViziLite. In addition, ViziLite could not distinguish between epithelial hyperplasia, dysplasia, carcinoma or inflammatory mucosal conditions; all appeared aceto-white under chemiluminescent light and were considered ViziLite-positive. The examination with ViziLite did not change the provisional diagnosis or alter the biopsy site. The authors noted that the updated product, ViziLite Plus, includes a staining solution similar to toluidine blue that is used to further delineate ViziLite positive lesions. The authors stated that this is unlikely to make a significant change to the usefulness of the product, given the documented inherent problem with toluidine blue staining as a diagnostic adjunct in the detection of epithelial dysplasia, and its high false-negative rate for carcinoma in site and mild to moderate dysplasia.

Oh et al. (2007) investigated the efficacy of the individual components of the ViziLite system in providing improved visualization of early oral mucosal lesions in 100 patients who presented to a dental school for screening. The oral cavity was examined under incandescent light for soft tissue abnormalities. Re-examination was performed following a one-minute rinse with 1% acetic acid. The mouth was examined a third time using ViziLite chemiluminescent light. Any lesions detected by these three examinations that were clinically undiagnosable were brush biopsied (OralCDx) for determination. In the original examination of 100 patients, 57 clinically diagnosable (i.e., recognizable) benign lesions, such as linea alba, leukoedema, were found, and 29 clinically undiagnosable lesions were found. Six additional diagnosable lesions and three undiagnosable lesions were found following the rinse. No additional lesions were found using chemiluminescent light. Of the 32 undiagnosable lesions that were brush biopsied, two were characterized as atypical and were scalpel biopsied. Neither lesion was found to be premalignant or malignant. The authors stated that most of the lesions were found during the initial examination under incandescent light. The acetic acid rinse allowed detection of three new undiagnosable lesions which were found to be benign. No additional lesions were found with ViziLite illumination, and this illumination was reported to make visualization more difficult due to distracting highlights on the oral mucosa.

Earlier non-comparative studies also reported no statistically significant difference in lesion detection with the use of ViziLite (Epstein, et al., 2006; Kerr, et al., 2006).

**VELscope:** Studies evaluating the effectiveness of VELscope for the detection of oral cancer lesions have primarily been in the form of case series and retrospective reviews with small patient populations and conflicting outcomes regarding sensitivity, specificity, positive predictive value and negative predictive values. Some studies reported high false positive results and have concluded that VELscope offers no additional clinical value in this patient population (Canjau, et al., 2018; Ganga, et al., 2017; McNamara, et al., 2012; Farah, et al., 2011; Mehrotra, et al., 2010).

In an observational study (Ganga, et al., 2017), 200 subjects with oral mucosal lesions underwent conventional oral exam followed by VELscope. Biopsies were divided into two groups based on autofluorescence characteristics. Group 1 included lesions that exhibited a loss of autofluorescence and appeared dark compared to the surrounding unaltered tissue indicating a malignant or

dysplastic change. Group 2 included lesions that exhibited retention of autofluorescence and showed no change in autofluorescence when compared to the surrounding unaltered tissue. VELscope exam showed 78 lesions in Group 1 and 122 lesions in Group 2. Histopathological exam showed 175 lesions were benign and 25 were malignant. Comparison of VELscope results to histopathological exam showed the number of true-positives were 19, false-positives were 59, true-negatives were 116 and false-negatives were six. The VELscope examination showed sensitivity of 76% and specificity of 66.29%. The positive predictive value was 24.36% and the negative predictive values were 95.08%. The data showed that VELscope examination cannot provide a definitive diagnosis for oral cancers and the high number of false positives limits its effectiveness as an adjunctive therapy for oral examination.

Awan and Patil (2015) conducted a systematic review of the literature to evaluate the efficacy of autofluorescence (VELscope) imaging systems for the detection of oral premalignant and malignant lesions. Eleven studies met inclusion criteria with nine studies confirming all suspicious lesions histologically. The sensitivity of VELscope ranged from 30%–90%, specificity was 15%–92.3%, positive predictive values (PPV) ranged from 6.4%–58.1% and negative predictive values 57.1%–100%. In the studies that reported improvement with VELscope in detecting oral epithelial dysplasia, the lesions did not undergo histopathological assessment to check the validity of the VELscope results. Based on this review, the evidence in the published literature does not support direct tissue fluorescence visualization with VELscope as a screening tool for oral cancer. VELscope' s ability to distinguish precancerous or cancerous lesions from benign lesions has not been proven.

Sawan and Mashiah (2015) reported on 748 patients who were evaluated for premalignant and malignant oral soft lesions using VELscope. Patients underwent clinical and fluorescent light analysis of the entire oral cavity. All lesions initially underwent excision biopsy and histology, and the results were compared to VELscope analysis. A total of 9.4% of lesions detected were abnormal and 83.09% had loss of fluorescent light effect. Compared to biopsy, VELscope had a sensitivity of 74.1% and specificity of 96.3%. A total of 26 cases were considered high-risk lesions. Out of 71 lesions there were 15 false positives, 13 true positives, 43 true negatives and no false negatives with VELscope analysis.

McNamara et al. (2012) evaluated the benefit of direct visual fluorescent examination (DVFE) using VELscope in screening for potentially malignant mucosal lesions in 130 consecutive patients presenting to a dental clinic for initial oral evaluation and routine dental care. A comprehensive oral examination (COE) was performed under regular dental incandescent (white) light, followed by a DVFE examination. Clinically suspicious areas based on COE or with positive DVFE exam (i.e., visual fluorescence loss) were surgically biopsied. The association between COE and DVFE was assessed and compared to histopathology. A total of 42 patients had one or more areas of visual fluorescence loss, yet histologic evidence of premalignancy or malignance was only identified in one patient. In addition, one lesion negative for DVFE exhibited epithelial dysplasia. DVFE was statistically different from a scalpel biopsy ($p=0.0001$) No difference was found between COE and scalpel biopsy ($p=1.0$). The authors noted that, as has been seen in other studies, common inflammatory conditions, such as traumatic ulceration, benign migratory glossitis, inflammatory papillary hyperplasia and chronic mucositis consistently demonstrated visual fluorescence loss, as did areas rich in lymphoid tissue or melanin pigmentation. As a result of these and other factors that result in reduced fluorescence, the significance of a given VFL area would appear to ultimately rest on conventional oral exam and the knowledge or experience of the clinician. If DVFE does not yield useful independent or additive information beyond COE alone, the benefit of VELscope in the routine practice of dentistry is unclear. The authors stated that the results suggested that a comprehensive oral examination is more valid than DVFE in discrimination benign mucosal alterations form premalignancy and do not support use of this technology as an adjunct to oral cancer screening.

In a randomized controlled trial, Rana et al. (2012) evaluated the use of VELscope for oral cancer detection in patients with premalignant lesions (n=289). All patients were evaluated using a conventional oral examination with light, but because of time restrictions in the daily diagnostic process, only 123 of 289 patients were examined with VELscope in addition to the white light examination. Biopsies were performed on all suspicious areas identified in both groups (n=52). The use of VELscope led to higher sensitivity compared to white light alone (100% vs. 17%) but lower specificity (74% vs. 97%). A loss of fluorescence was detected in all dysplastic lesions, but 37.84% of cases of leukoplakia/erythroplakia and 81.08% of cases of lichen planus also showed loss of tissue fluorescence. Of all examined lesions, 64.23% showed loss of fluorescence, while only 4.88% of the lesions could be identified as dysplasia.

A case series conducted by Farah et al. (2011) assessed the efficacy of direct tissue autofluorescence imaging using VELscope in detection of oral mucosal lesions. Patients referred to an oral medicine specialist unit (n=112) with a potentially malignant oral mucosal lesion were examined under routine incandescent light, followed by examination with VELscope. Incisional biopsies were performed for definitive histopathological diagnosis. VELscope enhanced the visibility of 41 lesions and helped detect 5 clinically undetected lesions. VELscope examination alone demonstrated a sensitivity of 30% and a specificity of 63%. The accuracy of dysplasia identification 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 without relevant clinical interpretation.

Mehrotra et al. (2010) conducted a cross-sectional study to evaluate the use of ViziLite Plus with TBlue (n=102) and VELscope (n=156) as adjunct aids in diagnosing lesions deemed clinically innocuous according to conventional light examination. Patients were screened with an overhead examination light and with VELscope or ViziLite. Patients with clinically innocuous lesions underwent a biopsy, and the results of tissue pathological analysis were compared with findings from the screening aid tests. Three dysplasias and one cancer were found Of 102 patients in the ViziLite group who underwent biopsy. None of these were detected with the adjunctive screening device, ViziLite. The sensitivity of ViziLite was 0%. ViziLite findings were negative in 74 patients with benign lesions and positive in 24 patients with benign lesions, with a specificity of 75.5%. The positive predictive value was 0 %, and the negative predictive value was 94.8%. Eleven dysplasias and one cancer were found in 156 patients in the VELscope group who underwent a biopsy. Five dysplasias and one cancer were also detected with VELscope. The sensitivity of VELscope was 50%. VELscope findings were negative in 56 patients with benign lesions and positive in 88 patients with benign lesions. The specificity was 38.9%; the positive predictive value was 6.4%, and the negative predictive value was 90.3 percent. Neither adjunctive technique identified any lesions that were not already apparent during the conventional overhead light exam.

VELscope has also been suggested as a method to identify subclinical high-risk fields with precancerous or cancerous changes in the operating room setting (Poh, et al., 2006-1). This proposed application is not addressed in this Coverage Policy. Additional published information on the use of VELscope consists of case reports (Poh, et al., 2006-2; Kois and Truelove, 2006).

**Microlux/DL :** Ibrahim et al. (2014) evaluated the effectiveness of Microlux/DL with and without toluidine blue (TB) in screening patients (n=599) with potentially malignant and malignant oral lesions. The subjects were tobacco users randomly assigned to one of two teams. They were evaluated by clinical examination and any visually identified lesion was then evaluated using Microlux/DL with and without TB. Biopsies of the visualized lesions were performed. A total of 53 suspicious lesions were detected by examination compared to 52 and 51 by Microlux/DL and Microlux/DL plus TB, respectively. Compared to oral examination the sensitivity of Microlux was

94.3%, the specificity was 99.6% and the positive predictive value was 96.2%. Compared to biopsy the sensitivity of Microlux was 100%, the specificity was 32.4% and the positive predictive value was 17.9%. Microlux/DL plus TB yielded significantly better ease of visualization and border distinctness compared to examination ($p<0.05$). Although Microlux/DL uncovered new lesions not seen on examination, it did not alter the provisional clinical diagnosis or alter the biopsy site. Toluidine blue dye did not improve the effectiveness of the outcomes of Microlux/DL. The authors concluded that conventional oral examination and histopathological examination remain the gold standard for this population. Limitations of the study include the exclusion of borderline cases and use of a high-risk group.

McIntosh et al. (2009) conducted a case series to assess the efficacy of acetic acid mouthwash and diffused light illumination (Microlux/DL) as a diagnostic aid in visualizing oral mucosal lesions, and to assess its ability to highlight malignant and potentially malignant lesions. Patients referred to an oral medicine specialist unit for assessment of an oral white lesion (n=50) were initially examined using routine incandescent light. The location, size, ease of visibility, border distinctness, and presence of satellite lesions were documented. Examination was then repeated using Microlux/DL diffused light illumination kit. An excisional biopsy was performed to obtain definitive histopathological diagnosis. Microlux/DL enhanced visibility of 34 lesions, but it did not help detect any clinically undetected lesions, change the provisional diagnosis, or alter the biopsy site. Microlux/DL demonstrated a sensitivity of 77.8% and a specificity of 70.7%, and a positive predictive value of 36.8%. The authors stated that although Microlux/DL appears useful at enhancing visibility of lesions, it is a poor discriminator of inflammatory, traumatic, and malignant lesions.

**Systematic Reviews of Multiple Systems:** Moffa et al. (2021) conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of autofluorescence-based (AF) and chemiluminescence-based (CL) systems in the diagnosis of oral dysplastic and malignant lesions compared to conventional oral examination (COE). Seventeen studies utilized autofluorescence (VELscope [n = 1844, 88.8%], Horus UOC 100 [one study, n=120, 5.8%], Identifi [one study, n=80, 3.8%], GOCCLES [one study, n=32, 1.5%]) and nine studies used chemiluminescence (ViziLite [n=505, 91%], MicroLux/DL [one study, n=50, 9%]). Patient populations (total n=2,517) ranged from 33-517 with a median age of 58.5 years in AF group and 56.6 years in CL group and majority male (AF=54.4%, CL=63%). Pooled sensitivity rates for AF-based and CL-based systems were 81.3% and 84.9% respectively with pooled specificity rates of 52.1% and 51.8%, respectively. The false negative rate was 18.7% for AF and 15.1% for CL. The false positive rate was 47.9% for AF and 48.2% for CL. Adverse events were not reported. Author noted limitations include heterogeneity of data, inability to perform subgroup analysis on specific device used and lack of follow up. Although the sensitivity rate of both systems is high, the false positive rate is poor. The role of AF-based and CL-based systems in the context of oral cancer screening programs is not clear.

In a 2021 Cochrane Review, Walsh et al. conducted a systematic review to evaluate the diagnostic accuracy of index tests for the detection of oral cavity squamous cell carcinoma and oral potentially malignant disorders (OPMD) in patients with clinically evident suspicious and harmless lesions. Sixty three studies evaluated the diagnostic accuracy of conventional oral examination with: vital staining (22 datasets), oral cytology (24 datasets), light-based detection or oral spectroscopy (24 datasets) and two combined index tests (nine datasets). Outcome results: vital staining: sensitivity 0.86, specificity 0.68; oral cytology: sensitivity 0.90, specificity 0.94; light-based: sensitivity 0.87, specificity 0.50; combined tests: sensitivity 0.78, specificity 0.71. The authors concluded that none of the adjunctive tests can be recommended in place of the current standard of a surgical biopsy and histological assessment.

Nagi et al. (2016) conducted a systematic review to evaluate the effectiveness of chemiluminescence and tissue autofluorescence devices as adjuncts in the detection of oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD). A total of 20 observational studies met inclusion criteria with ten studies utilizing chemiluminescence (ViziLite, ViziLite plus, MicroluxTM and/or MicroluxDL) and ten studies using tissue autofluorescence (VELscope). The sensitivity of ViziLite for detecting OSCC and OPMD ranged from 77.1% to 100% and specificity ranged from 0% to 27.8%. ViziLite preferentially detected leukoplakia and may have failed to spot red patches. The sensitivity of VELscope in detecting malignancy and OPMD ranged from 22% to 100% and specificity ranged from 16% to 100%. Some studies suggested that VELscope could help the experienced clinician to find oral precursor malignant lesions but could not differentiate between dysplasia and benign inflammatory conditions. In conclusion, the authors noted that both techniques have limited ability to discriminate high-risk lesion and have limitations that limit their use. Conventional visual inspection under normal incandescent light, followed by biopsy of suspicious lesions, will remain the gold standard for the immediate future.

Rashid and Warnakulasuriya (2015) conducted a systematic review to evaluate the effectiveness of chemiluminescence and tissue autofluorescence as adjuncts used in the detection of oral cancer. Thirteen studies utilized chemiluminescence (ViziLite, ViziLite Plus, MicroLux/DL [one study]) and 12 studies used autofluorescence (VELscope). Although chemiluminescence showed good sensitivity for detecting oral potentially malignant disorders (OPMD), it preferentially detected leukoplakia which may lead to failure of identifying spot red patches. Tissue autofluorescence was sensitive at detecting white, red and white, and red patches, and the area of fluorescence visualization loss (FVL) often extended beyond the clinically visible lesion. However, VELscope also detected erythematous lesions of benign inflammation resulting in false-positive results. In some studies the sensitivities and specificities could not be determined due to lack of biopsy comparator. Limitations of the studies included: some diagnoses were made by clinical exam and others by pathology; definition used for leukoplakia varied across studies; lack of a comparator; and several studies did not report sensitivity or specificity and of those who did the rates varied. The authors noted that the studies were conducted in specialist clinics by experienced clinicians and the results may not be applied to a general population with lower prevalence rates of OSCC and high incidences of benign conditions. There is inadequate evidence to draw valid conclusions on the effectiveness of chemiluminescence and autofluorescent imaging devices as screening adjuncts.

In a 2013 Cochrane report, Brocklehurst et al. reviewed randomized controlled trials (RCT) to evaluate screening tools for oral cancer or potentially malignant disorders using visual examination, toluidine blue, fluorescence imaging or brush biopsy. Only one RCT (n=13) on visual examination was found. 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.

Patton et al. (2008) conducted a systematic review to evaluate the effectiveness of adjunctive techniques for oral cancer examination and lesion diagnosis. The review evaluated various techniques that are promoted to improve earlier detection and diagnosis of oral malignancies, including toluidine blue, ViziLite Plus with toluidine blue, ViziLite, VELscope, MicroLux/DL, Orascoptic DK, and OralCDx brush biopsy. A total of 23 studies met the inclusion criteria. The largest evidence base was for toluidine blue. No studies were found for MicroLux DL or Orascoptic DK. The authors concluded that there is insufficient evidence to support or refute the use of visually-based examination adjuncts. The review concluded that, given the lack of effectiveness data in general dental practice settings, clinicians must rely on a thorough oral mucosal examination supported by specialty referral and/or tissue biopsy for oral premalignant and malignant lesions.

**Professional Societies/Organizations**

**American Academy of Oral Medicine (AAOM):** Based on a systematic review of the literature, the 2016 AAOM clinical practice guideline on oral cancer screening stated that there is a paucity of evidence to support or refute the practice of oral cancer screening.

**American Dental Association (ADA):** In 2017, the American Dental Association (ADA) updated the 2010 recommendations on the early diagnosis of potentially malignant disorders (PMD) in the oral cavity (Lingren, et al., 2017). The guideline evaluated the following adjunctive screening aids as triage tools: tissue reflectance, autofluorescence, vital staining, salivary adjuncts and other adjuncts of interest (i.e.., Identafi [StarDental]). The Association concluded that no available adjuncts demonstrated sufficient diagnostic test accuracy to support their routine use as triage tools during the evaluation of lesions in the oral cavity. The ADA did not recommend autofluorescence (i.e., VELscope, OralID, tissue reflectance (i.e., ViziLite Plus, MicroLux/DL), or vital staining adjuncts (i.e., OraBlu Lesion Marking System) for the evaluation of PMDs among adult patients with clinically evident, seemingly innocuous, or suspicious lesions.

**National Cancer Institute (NCI):** NCI (2022) states that no population-based screening programs for oral cancers have been implemented in developed countries. There is no definitive evidence to show that screening can reduce oral cancer mortality and there are no randomized controlled trials in any Western or other low-risk populations to support screening. Unnecessary treatment of lesions that would not have progressed (over diagnosis) and psychological consequences of false-positive tests are associated harms of screening. Techniques such as toluidine blue staining, brush biopsy/cytology or fluorescence imaging as the primary screening tool or as an adjunct for screening have not been shown to have superior sensitivity and specificity for visual examination alone or to yield better health outcomes.

**U.S. Preventive Services Task Force (USPSTF):** In an updated recommendation issued November 2013, the USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults. The task force reported that they found no evidence on screening a general or a selected high-risk population for oral cancer in the United States. Screening subjects in a high-prevalence population outside the United States lowered the stage of oral cancer at diagnosis and improved 5-year survival. However, survival differences could represent length or lead-time bias. Screening subjects in the subgroup who used tobacco or alcohol reduced the mortality rate from oral cancer. Subgroup analyses, however, were post-hoc and should be viewed as exploratory. The performance characteristics of the screening examination varied widely, with applicable results only from dentists addressing higher-risk patients in the United Kingdom. No evidence was found that any adjunctive device affects the performance of the screening examination.

## Medicare Coverage Determinations

| | Contractor | Determination Name/Number | Revision Effective Date |
|---|---|---|---|
| NCD | National | No National Coverage Determination found | NA |
| LCD | Local | No Local Coverage Determination found | NA |

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

## Coding Information

**Notes:**

1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Experimental/Investigational/Unproven when used to report oral cancer screening systems:**

| CPT®* Codes | Description |
|---|---|
| 41599 | Unlisted procedure, tongue, floor of mouth |
| 82397 | Chemiluminescent assay |
| 88104 | Cytopathology, fluids, washings or brushings, except cervical or vaginal; smears with interpretation |
| 88305 | Level IV - Surgical pathology, gross and microscopic examination |
| 88312 | Special stain including interpretation and report; Group I for microorganisms (eg, acid fast, methenamine silver) |
| 88361 | Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology |

| CDT®** Codes | Description |
|---|---|
| D0431 | Adjunctive pre-diagnostic test that aids in detection of mucosal abnormalities including premalignant and malignant lesions, not to include cytology or biopsy procedures |
| D0418 | Analysis of a saliva sample |



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## Revision Details

| Type of Revision | Summary of Changes | Date |
|---|---|---|
| Annual Review | • Removed statements on Saliva Testing and oral CDX Brush Biopsy | 12/03/2023 |
| Focused Review | • No clinical policy statement changes. | 11/01/2024 |