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Corporate Medical Policy

Oral Screening Lesion Identification Systems and Genetic Screening AHS – G2113

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Description of Procedure or Service

Oral cancer is defined as cancer occurring in the oral cavity between the vermilion border of the lips and the junction of the hard and soft palates or the posterior one third of the tongue. Squamous cell carcinoma is the most common type of oral cancer. (Gross, Lee, Okuno, & Rao, 2019).

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

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

Human papillomavirus (HPV) is a common sexually transmitted infection that may lead to the development of warts or cancer in various parts of the body including the back of the throat, tonsils and base of the tongue. This type of cancer is known as oropharyngeal cancer. HPV is also a major contributor to the development of head and neck squamous cell carcinoma (HNSCC), which can develop in the mouth, nose and throat (Borsetto et al., 2018). According to the CDC (2019), there is no test to determine an individual's HPV status, and "there is no approved HPV test to find HPV in the mouth or throat."

Oral Screening Lesion Identification Systems and Genetic Screening

Diagnosing and treating dermatologic lesions of the mouth and gums is challenging for most clinicians because of the wide variety of disease processes that can present with similar appearing lesions and the fact that most clinicians receive inadequate training in mouth diseases (Lodi, 2019). A number of index tests have been proposed as adjuncts to a conventional oral examination (COE) to improve diagnostic test accuracy (Fedele, 2009; Lingen, Kalmar, Karrison, & Speight, 2008; Patton, Epstein, & Kerr, 2008; Rethman et al., 2010; Seoane Leston & Diz Dios, 2010). These tests include vital staining, brush cytology, light-based detection, and blood or saliva analysis. The COE is the standard visual and tactile exam of the mucosa under normal light. Although it is quick and minimally invasive, abnormalities may not be malignant or even visible (Macey et al., 2015). These screening tests are not only used for diagnostic purposes but can also be utilized as a tool to measure any changes that may be signs of future disease development (Speight et al., 2017).

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

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

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

Finally, blood or saliva can be tested for biomarkers for cancer. The tests are non-invasive but have low standardization and are not widely used in clinical practice (Macey et al., 2015). Nonetheless, saliva has been identified as an ideal diagnostic medium for the early detection of HNSCC activity because it is close to the tumor site and is an easy sample to obtain (Lim et al., 2016). Macey et al. (2015) concluded that none of the adjunctive biomarker tests can be recommended as a replacement for the currently used standard of COE followed by a scalpel biopsy and histological assessment. However, the NCCN has stated that that "Expression of p16 as detected by IHC [immunohistochemistry] is a widely available surrogate biomarker that has a very good agreement with HPV status as determined by the gold standard of HPV E6/E7 mRNA expression (NCCN, 2020)." The protein known as p16 slows cell division, therefore acting as a tumor suppressor. Researchers have identified p16INK4a, RASSF1A, TIMP3, and PCQAP/MED15 as tumor suppressor genes that exhibited "excellent diagnostic accuracy in the early detection of OC [oral cancer] at 91.7% sensitivity and 92.3% specificity and of OPC [oropharyngeal cancer] at 99.8% sensitivity and 92.1% specificity from healthy controls (Liyanage et al., 2019)." A review by Kaur, Jacobs, Huang, Salvo, and Politis (2018) that researched salivary biomarkers for oral cancer and pre-cancer screening have identified a plethora of salivary biomarkers which showed an improvement in oral cancer diagnoses including mRNAs, salivary transcriptomes (IL-8, IL-IB, DUSP1, HA3, OAZ1, S100P, and SAT were highly

specific (91%) and sensitive (91%) for oral cancer detection), and salivary biomarkers (M2BP, profilin, CD59, MRP14, and catalase had a sensitivity of 83% and a specificity of 90% for oral cancer detection) (Kaur et al., 2018)."

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

Clinical Validity and Utility

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

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

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

Another systematic review was completed that focused on the use of oral brush cytology for the early detection of oral cancer and OPMDs (Alsarraf, Kujan, & Farah, 2018). Thirty-six of the 343 abstracts

and articles identified met the inclusion criteria, with publication dates ranging from 1994 to 2017. These articles led to the inclusion of 4302 total samples from OPMDs, oral squamous cell carcinoma, and healthy controls. The results were somewhat troubling. "Findings from this study indicate that meaningful evidence-based recommendations for the implementation of a minimally invasive technique to be utilized as an adjunctive tool for screening and early detection of oral cancer and OPMDs are complicated from the reported studies in the literature (Alsarraf et al., 2018)."

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

Lim et al. (2016) competed a study to determine the diagnostic ability of four HNSCC biomarkers (RASSF1α, p16INK4a, TIMP3, PCQAP/MED15) isolated from saliva. The DNA methylation status of these biomarkers was measured via methylation-specific PCR (MSP). Data from a total of 88 HNSCC patients and 122 healthy controls was analyzed. The authors found that a "Salivary DNA tumour-suppressor methylation gene panel has the potential to detect early-stage tumours in HPV-negative HNSCC patients. HPV infection was found to deregulate the methylation levels in HPV-positive HNSCC patients"; biomarker analysis of HPV-negative HNSCC patients compared to healthy controls generated a sensitivity of 71% and specificity of 80%, while biomarker analysis of HPV-positive HNSCC patients compared to healthy controls generated a sensitivity of 80% and a specificity of 74% (Lim et al., 2016).

Applicable Federal Regulations

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

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for oral screening lesion identification systems and genetic screening when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Oral Screening Lesion Identification Systems and Genetic Screening is covered

For individuals with oropharyngeal squamous cell carcinoma, reimbursement is allowed for high-risk HPV testing by one of the following methods:

a. HPV E6/E7 mRNA expression testing **OR**;

b. Expression of p16 as detected by immunohistochemistry

When Oral Screening Lesion Identification Systems and Genetic Screening is not covered

Reimbursement is not allowed for oral screening, lesion identification systems and genetic testing for all uses. This includes, but is not limited, to the following:

- OraRisk® HPV Complete Genotyping Test and OraRisk® HPV 16/18/HR Test (OralDNA labs, Brentwood, TN)
- MOP™ testing
- SaliMark OSCC® (PeriRx)

Reimbursement is not allowed for the use of salivary biomarkers to screen, detect, or diagnose oral cancer. This includes, but is not limited, to the following:

a. Salivary peptides and proteins, such as protein 14, Mac-2 binding protein, profilin 1, CD59, defensin-1, IL-1β, IL-8, lactate dehydrogenase, and catalase

b. Salivary nucleic acids, such as methylated DNA testing, mRNAs, modified nucleotides (such as 8-OHdG), microRNA (miRNAs)

c. Salivary metabolites, such as valine, lactic acid, and phenylalanine

Policy Guidelines

Guidelines and Recommendations

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

- "The panel does not recommend autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of PMDs among adult patients with clinically evident, seemingly innocuous, or suspicious lesions."

- "The panel does not recommend commercially available salivary adjuncts for the evaluation of PMDs among adult patients with or without clinically evident, seemingly

innocuous, or suspicious lesions, and their use should be considered only in the context of research."

- "The panel does not recommend cytologic adjuncts for the evaluation of PMDs among adult patients with clinically evident, seemingly innocuous, or suspicious lesions. Should a patient decline the clinician's recommendation for performing a biopsy of the lesion or referral to a specialist, the clinician can use a cytologic adjunct to provide additional lesion assessment."

- "The panel suggests that for adult patients with a clinically evident oral mucosal lesion considered to be suspicious of a PMD or malignant disorder, or other symptoms, clinicians should perform a biopsy of the lesion or provide immediate referral to a specialist (Lingen et al., 2017)."

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

In 2013, the USPSTF published final recommendations for screening of oral cancer. The recommendation stated that "the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults." The USPSTF also noted that "additional tests proposed as adjuncts to the oral cancer screening examination include toluidine blue dye staining, chemiluminescent and autofluorescent lighting devices, and brush cytopathology. These screening and adjunct tests have not been adequately tested in primary care nondental settings. Although there is interest in screening for oral HPV infection, medical and dental organizations do not recommend it (Moyer, 2014)."

National Comprehensive Cancer Network (NCCN) (NCCN, 2019, 2020)

NCCN clinical practice guidelines on head and neck cancers does not mention the use of adjunctive screening aids based on autofluorescence or tissue reflectance as a management tool (NCCN, 2019, 2020). Regarding biomarker testing, the NCCN states that "A few HPV testing options are available for use in the clinical setting. Expression of p16 as detected by IHC [immunohistochemistry] is a widely available surrogate biomarker that has a very good agreement with HPV status as determined by the gold standard of HPV E6/E7 mRNA expression." They also state, "P16 expression is highly correlated with HPV status and prognosis and is widely available (NCCN, 2020)." HPV testing by p16 IHC is a required portion of the workup of the cancer of the oropharynx algorithm.

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

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

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

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

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

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81599, 82397, 87623, 87624, 87625, 88341, 88342

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 2/2020

Policy Implementation/Update Information

1/1/19 New policy developed. Oral screening lesion identification systems and genetic screening is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)

8/13/19 Reviewed by Avalon 2nd Quarter CAB. Added SaliMark OSCC® (PeriRx) test to the Non Covered list. In the When Not Covered section, the investigational statement is revised to read "Oral screening, lesion identification systems and genetic testing are *not covered* for any use…" Code 81599 to Billing/Coding section. Medical Director review 8/2019. Policy noticed 8/13/2019 for effective date 10/15/2019. (an)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)

03/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statement. (eel)

07/28/20 Description, Policy Guidelines and Reference sections updated. High-risk HPV testing reimbursement added to When covered section. When not covered section updated with salivary biomarkers. Coding section updated with 81599, 88341 and 88342. Policy statement updated from "not covered" to reimbursement language. Reviewed by Avalon 2nd Quarter CAB. Medical Director review 7/2020. (eel)

APPENDIX

Table from (Macey et al., 2015)

COE = conventional oral examination; PMD = potentially malignant disorders

Test	Characteristics	Classification of response	Other information
Conventional oral examination (COE)	A standard visual and tactile examination of the oral mucosa under normal (incandescent) light.	The presence of an oral mucosal abnormality with a suspicion of malignancy or potential malignancy is classified as a positive test result; the presence of oral mucosal abnormality without a suspicion of malignancy or potential malignancy is classified as a negative test result.	Traditionally used as a oral cancer screen rather than diagnosis, but its utility is debated (Lingen 2008). **Advantages:** quick and easy once trained, minimally invasive. Disadvantages: oral mucosal abnormalities are not necessarily clinically or biologically malignant; only a small percentage of leukoplakias are progressive or become malignant, COE cannot distinguish between those that are or are not; some precancerous lesions may exist within oral mucosa that appears clinically normal by COE alone (Lingen 2008).
Vital staining (e.g. toluidine blue, tolonium chloride)	Vital staining refers to the use of dyes such as toluidine blue or tolonium chloride to stain oral mucosa tissues for PMD or malignancy (Leston 2010; Lingen 2008; Patton 2008). The procedure is as follows: Pre-rinse with acetic acid Rinse with water Apply toluidine blue Post rinse with acetic acid Rinse with water Observe mucosa to check for staining	The result of the test is classified as positive if tissue is stained and negative if no tissue is stained, or equivocal if no definitive result can be obtained.	**Advantages:** ability to define areas that could be malignant or abnormal but cannot be seen; assess the extent of the PMD for excision. **Disadvantages:** benign inflammatory lesions are subject to stain; possibility
Brush cytology (e.g. OralCDx brush biopsy)	Brush cytology refers to the microscopic assessment and interpretation of cell samples from PMD that are flaked off from the oral mucosa by the brushing, smearing, scraping or lavage to collect cell samples, which are then sealed on glass slides. They are then analysed using an imaging system that assesses the sampled cells (Leston 2010; Lingen 2008; Patton 2008).	Following analysis, cytopathologists classify test results as positive, atypical or negative.	Advantages: include the ability to collect information from, and detect large or multiple lesions and to access "the basement membrane collecting cells from all three epithelial layers of the oral mucosa. The liquid-based cytology reduces the problems relating to sampling and fixation and presents a better cytological morphology" (Divani 2009). Disadvantages: smaller or less obvious lesions may be overlooked; difficulties in detecting lesions when there is necrosis or coagulated blood; inadequate training of operators (Divani 2009); cells are potentially seen out of context.
Light-based detection (chemiluminescence e.g. ViziLite plus, tissue fluorescence imaging e.g. ViziLite, Microlux DL; VELscope, Identafi 3000; tissue fluorescence spectroscopy)	Light-based systems to identify malignant and potentially malignant lesions and to highlight their presence through tissue reflectance (Leston 2010; Lingen 2008; Patton 2008) e.g. using Microlux DL, the procedure is as follows (Lingen 2008). Pre-rinse with acetic acid Use blue-light source to visually assess the oral cavity. ViziLite Plus also provides a tolonium chloride solution (toluidine blue) to aid in the marking of the lesion for biopsy once the light source is removed.	The result of the test is classed as negative if the appearance of the epithelium is lightly bluish white and positive if the appearance of the epithelium is distinctly white (acetowhite).	**Advantages:** simple to use; non-invasive; do not require consumable reagents; provide real-time results; can be performed by a wide range of operators after a short training period. **Disadvantages:** the necessity of a dark environment; high initial set up (for VELscope) or recurrent costs (for ViziLite in low-income countries); lack of permanent record unless photographed; inability to objectively measure visualisation results.
Blood and saliva analysis	These novel technologies are at an early stage of development and evaluation. Analysis of blood or saliva samples which tests for the presence of biomarkers of PMD and oral cancer (Brinkmann 2011; Lee 2009; Li 2006).	Cut-off probabilities vary widely and are dependent on the individual biomarker or combination of biomarkers examined.	**Advantages:** non-invasive (saliva tests) or minimally invasive (blood tests). **Disadvantages:** there is a tendency for the estimated diagnostic accuracy of new health technologies to decline over time as evidence from independent evaluations accumulate (Wyatt 1995). This bias, which can be substantial, has been demonstrated in other domains, e.g. acute abdominal pain (Liu 2006) and clinical decision support systems (Garg 2005). Promising biomarker tests in several clinical areas were eventually been shown to be disappointing (Buchen 2011). It remains to be seen whether this is the case with oral cancer and PMDs.