Clinical Policy Bulletin: Oral Brush Biopsy

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Policy

Aetna considers oral brush biopsy (OralCDx Brush Test) experimental and investigational for screening or diagnosis of cancerous or pre-cancerous oral lesions because of insufficient evidence.

Aetna considers DNA-image cytometry of brush biopsies for early detection of oral malignancy experimental and investigational because of insufficient evidence.

See also CPB 0760 - Oral Screening and Lesion Identification Systems.

Background

The most definitive, accurate, and reliable method for diagnosing oral mucosal lesions is the scalpel biopsy. The oral brush biopsy coupled with computer-assisted analysis (OralCDx, OralScan Laboratories, Inc., Suffern, NY) has been developed as a technique for evaluating unexplained clinically detectable alterations of the surface epithelium of the oral mucosa whether cancer or pre-cancer is suspected (Sciubba et al, 2003). The goal of the oral brush biopsy is to provide a highly sensitive and specific technique that is less painful and simpler to perform than a scalpel or punch biopsy.

The oral brush biopsy, using a specially designed circular bristled brush, has been designed to access and sample all epithelial layers, including the basal cell layer and the most superficial aspects of the lamina propria (Sciubba et al, 2003). Thus, the cellular material obtained should include all epithelial layers in a disaggregated form spread over the surface of a glass slide.

The argument for oral brush biopsy raises 2 questions: (i) whether indications for oral mucosal biopsy should be expanded to include certain “benign-appearing” lesions, either in high-risk patients (e.g., current or former smokers, heavy drinkers), or in all persons regardless of risk, and (ii) what is the most effective and efficient method of biopsy of oral mucosal lesions.
Only 1 large-scale study has been published about the use of this technique in the oral cavity (Sciubba et al, 1999). The study reported that in 945 patients with oral mucosal lesions, the OralCDx had 100 % sensitivity and a zero false negative rate. The analysis, however, must be considered incomplete, as 618 of 945 brush samples, including 517 of the 699 negative brush samples (73.9 %), were not followed with definitive incisional biopsy for diagnostic confirmation. In addition, the investigators reported that 7 % of oral brush biopsy specimens were non-diagnostic (Sciubba et al, 1999), which is a much higher incidence than commonly seen with scalpel biopsy (Potter et al, 2002).

A smaller study by Svirsky et al (2002) compared oral brush biopsy results with scalpel biopsy and histology to determine the positive-predictive value (PPV) of an abnormal brush biopsy finding. Of 243 patients with abnormal brush biopsies, 93 proved positive for dysplasia (n = 79) or carcinoma (n = 14) and 150 were negative for either dysplasia or carcinoma. Therefore, the PPV of an abnormal brush biopsy was 38 % (93/243). This smaller study suffers from the same major weakness as the OralCDx Multicenter Study cited above (Sciubba et al, 1999), in that it does not adequately define the negative-predictive value (NPV) of the oral brush biopsy, because only a small proportion of normal brush biopsy results were followed by scalpel biopsy.

Christian (2002) reported on the results of oral brush biopsy in 930 dentists and oral hygienists who were screened for oral cancer while attending the American Dental Association annual session. Eighty-nine subjects (9.7 %) with 93 oral epithelial lesions were identified and evaluated by brush biopsy. Seven of the 93 oral lesions -- all benign appearing -- were determined to be “atypical” or “positive” on oral brush biopsy. Of these, three were diagnosed as precancerous by scalpel biopsy and histological evaluation. The study by Christian (2002) is of much weaker methodology than the OralCDx Multicenter study cited above. The study reported by Christian (2002) suffers from the same methodological weaknesses as the OralCDx Multicenter Study, as only some of the positive oral brush biopsy results and none of the negative results were followed by scalpel biopsy. In addition, the study by Christian (2002) was not a multi-center study, and the subjects (dentists and dental hygienists who volunteered for testing) is not representative of the patient group to which this test is directed (patients seen by their dentist for periodic check-ups and routine cleaning); this raises questions about the generalizability of the findings of this study.

There are some reports of significant rates of false negatives from brush biopsy. Potter et al (2003) examined all diagnoses of oral squamous cell carcinoma from a university oral pathology service over a 2-year period to determine if any had previously undergone brush biopsy reported to be "negative for epithelial abnormality". Those cases identified were further investigated to determine the time lapse between brush biopsy and definitive tissue diagnosis. Potter et al (2003) found 4 of 115 squamous cell carcinomas that were reported to be negative on brush biopsy, a false negative rate of 3.5 %. The authors noted that, because not all 115 squamous cell carcinomas were preceded by a brush biopsy, that the false negative rate for the oral brush biopsy technique may actually be greater.
Although the study by Potter et al (2003) is limited by its retrospective design, it is informative in that it helps define the false negative rate of oral brush biopsy and the clinical consequences of falsely negative results.

Potter et al (2003) stated that the false-negative rate for the oral brush biopsy may be unacceptably high for a diagnostic test. These researchers explained: "It has been argued that a 3.5% false-negative rate may be acceptable, particularly if one compares this result with a screening modality like mammography, which has a false-negative rate that varies from approximately 6% to 25%. This analogy, however, is flawed. Mammography is a screening test directed toward at-risk populations without known disease. The brush biopsy technique, on the other hand, is directed toward clinically obvious pathologic change, and thus a comparison of false-negative rates with mammography or other screening tests is inappropriate."

Potter et al (2003) went on to explain why the falsely negative results are unlikely to have resulted from an inaccuracy of the data reported by the authors. They concluded that "It seems that the most likely probability may be that the technique may not be of adequate sensitivity to detect all clinically dysplastic or malignant lesions." Furthermore, this study highlights the need to adequately evaluate the rate of false negatives with oral brush biopsy and its consequences.

Although it has been argued that the oral brush biopsy may provide earlier diagnosis of oral cancers and pre-malignant lesions, there are no clinical studies demonstrating this. The oral brush biopsy has been criticized for adding time and cost to the diagnosis of oral lesions without additional benefit to the patient. Because the brush biopsy detects only cellular atypia, positive oral brush biopsy results must be confirmed with a scalpel biopsy for definitive diagnosis. This results in the need for two procedures, rather than one, to establish a diagnosis. The need to perform two procedures may significantly delay diagnosis. In the study described above, Potter et al (2003) reported an "undeniably unacceptable" average delay in diagnosis of squamous cell carcinoma between brush and scalpel biopsies. In the 4 false negative oral brush biopsies identified, the average delay in diagnosis between negative oral brush biopsy and positive scalpel biopsy was 117.2 days (range of 5 to 292 days). The investigators stated that this delay "can be potentially disastrous."

The oral brush biopsy technique may also delay diagnosis if the results are negative. If oral brush biopsy results are negative, no diagnosis is rendered, making it difficult to determine appropriate treatment or anticipate whether an additional procedure is necessary (Potter et al, 2003).

There is insufficient evidence to support the use of oral brush biopsy as a general screening technique for oral cancer or pre-malignant lesions. A Cochrane evidence review found that there is no evidence from prospective clinical trials that screening with brush biopsy reduces mortality (Kujan et al, 2005; Kujan et al, 2006). The investigators concluded that "no robust evidence exists" to suggest that brush biopsy for screening of oral cancer or potentially pre-malignant lesions is either beneficial or harmful.
Although the oral brush biopsy technique has been promoted as “painless” (OralScan Laboratories, 2001), there are no studies examining the pain elicited by oral brush biopsy or comparing this pain with that elicited by scalpel biopsy preceded by administration of local anesthetic (Potter et al, 2002). Given that an adequate oral brush biopsy sample should include all epithelial layers, the contention has been questioned that oral brush biopsy is completely “painless” or that it is substantially less painful than scalpel biopsy with local anesthetic.

The oral brush biopsy technique has also been promoted as easier to perform than scalpel biopsy, such that dentists who are unskilled at performing scalpel biopsy may be able to perform oral brush biopsy (Sciubba et al, 2003). However, Potter et al (2002) stated that “[f]ear of performing a scalpel biopsy, or inadequate training in its performance, should not be construed as an indication to perform other tests that will further delay completion of the definitive diagnostic test.”

The National Cancer Institute (2004) and the U.S. Preventive Services Task Force (2004) have not recommended routine screening for oral cancer. Although the American Dental Association has issued a contrary recommendation regarding oral cancer screening, the ADA recommendation does not endorse any specific biopsy method (ADA, 2003; Engber, 2002; Potter et al, 2002; Oral cancer campaign: Editors note, 2002). The OralCDx Oral Brush biopsy has gained a seal of acceptance by the American Dental Association’s Council on Dental Therapeutics (ADA, 2001); however, the opinions and evaluations of medical professional organizations are considered according to the scientific quality of the evidence and supporting rationale.

Poate and colleagues (2004) reported that the sensitivity of detection of oral epithelial dysplasia or squamous cell carcinoma of the oral brush biopsy system was 71.4%; while the specificity was 32%. The PPV of an abnormal brush biopsy result (positive or atypical) was 44.1%; while the NPV was 60% (n = 112). These investigators concluded that not all potentially malignant disease is detected with this non-invasive investigative procedure. Scheifele et al (2004) concluded that further trials on OralCDx (computerized analysis of brush biopsies) as a screening tool of oral lesions are still necessary. van der Waal (2005) stated that the value of cytological examination, whether obtained by exfoliation of cells or by a brush technique, is somewhat questionable.

Furthermore, in a systematic review on the effectiveness of oral cancer screening, Kujan et al (2006) stated that no robust evidence exists that indicates whether other screening methods including toluidine blue, fluorescence imaging, or brush biopsy are either beneficial or harmful. These authors noted that further high-quality studies are needed to evaluate the effectiveness of these methods in screening oral cancer.

Driemel and colleagues (2008) assessed the performance of oral brush biopsies using standard morphological analysis and hematoxylin and eosin (HE) staining for detecting oral squamous cell carcinomas and their respective precursor lesions. Brush biopsies were obtained in 169 consecutive patients who underwent routine biopsies and histological examination for clinically suspicious oral lesions. Air-dried smears were processed by acetone fixation and HE staining. Cytological assessment used well-established criteria of atypia to classify the specimen as
either tumor-negative (no signs of atypia, no malignant cells) or tumor-positive (malignant cells, any sign of atypia or doubtful cells). Despite a sufficient number of cells, a definite cytological diagnosis could not be established in 6 cases. According to the criteria specified above, these specimens were classified as tumor-positive. The cytological analysis identified 49 out of 62 oral malignancies (sensitivity 79 %). Seven out of 107 benign lesions were classified as false-positive (specificity 93 %). The positive and negative predictive values were each 88 %. The authors concluded that oral brush biopsies will identify only about 80 % of oral malignancies when the smears are processed by routine HE stains and are analyzed via standard morphological criteria. Thus, this technique should not be used for diagnostic proof or to exclude malignant cells in a lesion suspicious for cancer.

In a systematic review on adjunctive techniques for oral cancer examination and lesion diagnosis, 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. These investigators 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 histological 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 oral pre-malignant and malignant lesions. 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. Given the lack of evidence 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 oral pre-malignant and malignant lesions diagnosis.

In a cross-sectional study, Bhooepathi (2009) assessed the effectiveness of the oral brush biopsy technique as a diagnostic tool in detecting dysplastic oral lesions. Pathologic reports (n = 152) from the scalpel biopsies (tissue samples) in patients who previously tested either "positive" (n = 3) or "atypical" (n = 149) for dysplasia by brush biopsy (OralCDx) were evaluated. Information on the age and sex of the patient, the site of the lesion, the brush biopsy results, and the histopathological diagnosis of the scalpel biopsy was collected. The positive predictive values (PPVs) for "abnormal," "atypical," and "positive" brush biopsies were determined. Overall, the PPV of an abnormal brush biopsy was only 7.9 % (95 % confidence interval [CI]: 4.2 % to 13.4 %), and the PPV of an "atypical" brush biopsy was 7.4 % (95 % CI: 3.7 % to 12.8 %). Of the 3 positive brush biopsies, only 1 was identified as dysplastic. The proportion of false-positive biopsy results was as high as 92.1 % (95 % CI: 86.6 % to 95.9 %). The author concluded that the OralCDx technique over-estimated dysplastic lesions and produced a high number of false-
positive results. An evidence review by Juber and Huber (2012) noted limitations of this study, including: the “suspiciousness” of the lesions evaluated was not mentioned; the time frame between OralCDx brush test and scalpel biopsy was not defined; and the investigators were only able to calculate the PPV, because surgical biopsy was only used to evaluate lesions that had previously tested positive with the OralCDx test..

In a prospective, randomized, controlled study, Hohlweg-Majert and associates (2009) evaluated the advantage of computer-assisted analysis of the oral brush biopsy compared with synchronous scalpel biopsy in the early detection of oral lesions. Brush and scalpel biopsies were performed on 75 patients; 6 patients had to be excluded due to inadequate results, and 43 were shown to have dysplastic epithelium, 15 carcinoma, and 11 suspicious lesions. Thus, the sensitivity for the detection of abnormal cells by means of OralCDx was 52 %, specificity 29 %, and the PPV 63 %. According to these findings, the use of oral brush biopsy as a standardized, minimally invasive method of screening oral lesions should be reconsidered.

Fedele (2009) stated that the World Health Organization has clearly indentified prevention and early detection as major objectives in the control of the oral cancer burden worldwide. At the present time, screening of oral cancer and its pre-invasive intra-epithelial stages, as well as its early detection, is still largely based on visual examination of the mouth. There is strong available evidence to suggest that visual inspection of the oral mucosa is effective in reducing mortality from oral cancer in individuals exposed to risk factors. Simple visual examination, however, is well known to be limited by subjective interpretation and by the potential, albeit rare, occurrence of dysplasia and early oral squamous cell carcinoma (OSCC) within areas of normal-looking oral mucosa. As a consequence, adjunctive techniques have been used to increase the ability to differentiate between benign abnormalities and dysplastic/malignant changes as well as to identify areas of dysplasia/early OSCC that are invisible to the naked eye. These include TB, brush biopsy, chemi-luminescence and tissue auto-fluorescence.

The author reviewed the evidence supporting the efficacy of the afore-mentioned techniques in improving the identification of dysplastic/malignant changes of the oral mucosa; and concluded that available studies have shown promising results, but strong evidence to support the use of oral cancer diagnostic aids is still lacking. The author stated that further research with clear objectives, well-defined population cohorts, and sound methodology is strongly needed.

Trullenque-Eriksson and colleagues (2009) analyzed publications 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. Moreover, they noted 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.

Toyoshima et al (2009) determined the detection of cytokeratin (CK) mRNA in OSCC cells and evaluated the CK relevance for OSCC diagnosis in a brush biopsy test. A total of 52 pairs of OSCC cells and normal oral mucosal cells were obtained by brush biopsy from OSCC patients. Messenger RNA was extracted from cell pellets for real-time quantitative reverse transcriptase polymerase chain reaction (RT-qPCR). The over-expression levels of CK 17, CK 19 and CK 20 mRNA in OSCC cells were examined by SYBR green real-time RT-qPCR. Compared to normal mucosal cells, the over-expression of CK 17 mRNA was detectable in 40 OSCC cells (76.9 %), that of CK 19 mRNA in 19 (36.5 %), while that of CK 20 mRNA was not detectable. Compared with CK 19, the mean value of CK 17 mRNA expression level was significantly higher in all 52 patients ($p < 0.02$). Moreover, the value of CK 17 was significantly higher in T1 and T2 OSCC patients ($p < 0.03$, respectively), in patients without metastases of neck lymph nodes ($p < 0.04$), in stage I and stage II patients ($p < 0.03$ and $p < 0.05$, respectively) and in well-differentiated OSCC patients ($p < 0.05$). The authors concluded that brush biopsy properly serves for detection of CK mRNA using real-time RT-qPCR. This preliminary study demonstrated the CK 17 possibility for application; however, pivotal studies are needed to confirm CK 17 as a diagnostic marker of OSCC in a brush biopsy test.

Seoane Lestón and Diz Dios (2010) noted that conventional oral exploration (visual and palpation examination) constitutes the current gold standard for oral cancer screening, while biopsy and histopathological examination represents the indispensable study for the detection of cases in patients with an identified lesion. Imaging techniques (DPT, CT, and MRI) are frequently used to supplement the clinical evaluation and staging of the primary tumor and regional lymph nodes. There are also a number of techniques that may contribute to the diagnosis of oral cancer: toluidine blue test has been used as a diagnostic aid for the detection of oral cancer over decades. Recently developed light-based detection systems have progressively improved in sensitivity and specificity, but multi-center controlled studies conducted by general dental practitioners must be designed in order to justify their application. The oral brush biopsy appears to over-estimate dysplastic lesions and produces a high number of false-positive results.

Remmerbach and colleagues (2011) stated that OSCCs often present as advanced tumors requiring aggressive local and regional therapy and result in significant functional impairment. The objective is to develop pre-symptomatic screening detection of OSCC by a brush biopsy method that is less invasive than the conventional biopsy for histology. Given the molecular heterogeneity of oral cancer, it is unlikely that even a panel of tumor markers would provide accurate diagnosis. Thus, approaches such as the matrix-assisted-laser-desorption/ionisation-time-of-flight-mass-spectrometry (MALDI-TOF-MS) allow several biomarkers or peptide profile patterns to be simultaneously assessed. Brush biopsies from 27 patients with histology-proven OSCCs plus 40 biopsies from 10 healthy controls were collected. MALDI-TOF-MS profiling was performed and additional statistical analysis of the data was used to classify the disease status according to the biological behaviour of the lesion. For classification a
support vector machine algorithm was trained using spectra of brush biopsy samples to distinguish healthy control patients from patients with histology-proven OSCC. MALDI-TOF-MS was able to distinguish between healthy patients and OSCC patients with a sensitivity of 100 % and specificity of 93 %. The authors concluded that MALDI-TOF-MS in combination with sophisticated bioinformatic methods can distinguish OSCC patients from non-cancer controls with excellent sensitivity and specificity. Moreover, they stated that further improvement and validation of this approach is needed to determine its feasibility in aiding pre-symptomatic detection of head and neck cancer screening in routine daily practice.

In a cross-sectional study, Bhoopathi and Mascarenhas (2011) evaluated oral surgeons' effectiveness in diagnosing oral dysplastic lesions and compared it to OralCDx brush biopsy. In this study, the oral surgeon's ability to diagnose dysplasia among 152 consecutive cases (tissue samples) that had previously tested either "positive" (n = 3) or "atypical" (n = 149) for dysplasia by OralCDx brush biopsy was determined by calculating sensitivity, specificity, PPV, and negative predictive value using the scalpel biopsy as the gold standard. The PPV for oral surgeons and atypical brush biopsy was compared stratified by age, gender, and lesion site. The PPV, negative predictive value, sensitivity, and specificity for oral surgeons were 10.3 %, 100 %, 100 %, and 23.5 %, respectively. After controlling for age, gender, and lesion site, oral surgeons were 19 % to 58 % more likely to diagnose a dysplastic lesion compared to OralCDx brush biopsy. The authors concluded that oral surgeons' effectiveness in diagnosing oral dysplastic lesions was slightly better than the OralCDx brush biopsy; hence, it is recommended that patients be referred to an oral surgeon for evaluation.

Mehrotra, et al. (2011) performed oral brush biopsies and scalpel biopsies in 85 consecutive patients presenting with an oral lesion deemed to be "minimally suspicious" by clinical examination. Of 79 patients with adequate brush biopsy samples with matching scalpel biopsies, 27 revealed histopathologic evidence of dysplasia or carcinoma, 26 of which were independently identified with the oral brush biopsy, with a sensitivity of 96.3% (95% confidence interval, 87%-100%). Fifty-two oral lesions did not reveal any histopathologic evidence of dysplasia or carcinoma and of these, brush biopsy reported 47 as "negative" and 5 as "atypical." The authors reported that the specificity of a "positive" brush biopsy result was 100% (95% CI, 93%-100%); the specificity for "atypical" brush biopsy result was 90.4% (95% CI, 82%-97%). The authors found that the positive predictive value of an abnormal oral brush biopsy was 84% and the negative predictive value was 98%. An evidence review (Juber & Huber, 2012) noted limitations of the study by Mehrotra, including the fact that the study population has a higher tobacco use and higher prevalence of oral cancer compared to the United States; the definition "minimally suspicious" is open to interpretation; and the location of just under half the lesions was the buccal mucosa, which is considered a low risk area.

Balevi (2011) evaluated the performance of the OralCDx, the VELscope, and toluidine blue staining as clinical adjunctive diagnostic procedures in routine screening for oral cancer in dental practice. The author obtained the sensitivity and specificity for each device from a review of the literature. The author calculated the PPV and false positive rate, based on three clinical screening scenario, using
Bayes’ Theorem. The author found that, under three clinical scenarios (screening the general population, screening only adults (40 years or older) and screening adults that present with intraoral visible lesions), The author found that the VELscope produced the highest PPV's of 1.27%, 2.53% and 8.11%, respectively, indicating a false positive rate of between 91.89% and 98.73%. The author concluded that the VELscope, OralCDx and toluidine blue staining have high false positive rates when they are used to screen routinely for oral cancer.

Seijas-Naya and colleagues (2012) evaluated the effectiveness of the brush biopsy technique using OralCDx (OralScan Laboratories Inc., Suffern, NY) as a new method for early diagnosis and control of a "potentially malignant disorder" such as oral leukoplakia. These investigators performed a study in which samples were taken using OralCDx on 24 patients who visited the Master of Oral Medicine, Oral Surgery and Implantology of the University of Santiago de Compostela between February 2009 and May 2010. These patients presented clinical and histological lesions that were consistent with oral leukoplakia. These researchers evaluated the relationship between the keratinization degree of the lesions and cell representation; the diagnosis obtained through OralCDx and biopsies; and sensitivity, specificity, PPV and NPV. The average age of patients was 62.38 years and 50 % of them were men. The kappa coefficient relating keratinization of lesions and cell representation was 0.33, the OralCDx - biopsy diagnostic rate reached a kappa value of 0.66, recording 72.7 %, sensitivity and 92.3 % specificity, PPV was 88.8 %, while NPV reached 80 %. The authors concluded that cytology sampling with OralCDx showed high sensitivity and specificity values, which make it a good tool for monitoring oral leukoplakia, but nowadays the most reliable method that allows confirmation of the exact diagnosis of the lesions and their anatomical and pathological characteristics is still conventional biopsy using a surgical scalpel.

Huber (2012) stated that during the past 10 years, 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 premalignant 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 conventional oral examination (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 needed to ascertain the true value of these products as marketed to the general practitioner. The attainment of a complete history and the accomplishment of a thorough and disciplined COE remains the foundation upon which the practitioner evaluates the patient for OPMLs. Findings deemed suspicious or equivocal should be referred to an expert for further assessment or undergo immediate biopsy, while findings deemed innocuous should be re-evaluated within 2 weeks and referred to an expert for further assessment or undergo biopsy if still present.

An evidence review by Juber and Huber (2012) concluded: “The OralCDx brush test may have the ability to detect dysplasia in innocuous looking oral lesions, but recently published reports continue to have contrasting results pertaining to its
overall clinical applicability. Surgical biopsy is still considered the gold standard and should be used to achieve the correct detection and diagnosis”.

In a Cochrane review, Brocklehurst et al (2010) evaluated the effectiveness of current screening methods in decreasing oral cancer mortality. The following electronic databases were searched: the Cochrane Oral Health Group Trials Register (to May 20, 2010), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 2), MEDLINE via OVID (1950 to May 20, 2010), EMBASE via OVID (1980 to May 20, 2010) and CANCERLIT via PubMed (1950 to May 20, 2010). There were no restrictions regarding language or date of publication. 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 review. The original review identified 1,389 citations and this update identified an additional 330 studies, highlighting 1,719 studies for consideration. Only 1 study met the inclusion criteria and validity assessment, data extraction and statistics evaluation were undertaken by 6 independent review authors. One 9-year RCT has been included (n = 13 clusters: 191,873 participants). There was no statistically significant difference in the age-standardized oral cancer mortality rates for the screened group (16.4/100,000 person-years) and the control group (20.7/100,000 person-years). A 43 % reduction in mortality was reported between the intervention cohort (29.9/100,000 person-years) and the control arm (45.4/100,000) for high-risk individuals who used tobacco or alcohol or both, which was statistically significant. However, this study had a number of methodological weaknesses and the associated risk of bias was high. The authors concluded that although there is evidence that a visual examination as part of a population based screening program reduced the mortality rate of oral cancer in high-risk individuals, while producing a stage shift and improvement in survival rates across the population as a whole, the evidence is limited to 1 study and was associated with a high risk of bias. This was compounded by the fact that the effect of cluster randomization was not accounted for in the analysis. Furthermore, no robust evidence was identified to support the use of other adjunctive technologies like toluidine blue, brush biopsy or fluorescence imaging within a primary care environment. The authors concluded that further RCTs are recommended to assess the efficacy, effectiveness and cost-effectiveness of a visual examination as part of a population based screening program.

The HealthPartners Dental Group and Clinics’ (Minneapolis, MN) oral cancer guideline (2012) stated that “The brush "biopsy", an exfoliative cytologic technique was developed as a means of harvesting a transepithelial sample of cells from an oral surface lesion without having to anesthetize and remove an actual tissue sample (i.e., biopsy specimen) with the scalpel. This, too, is simply a screening tool similar to one that has been used in gynecology for a number of years and is known as a Papanicolaou ("Pap") smear. Many dysplastic lesions are first identified by histopathologically evident changes in the morphology of cells in the epithelial basal cell layer. Therefore, in order to be of use, the brush must obtain cells from this layer. This test can be used as a preliminary tool in helping to confirm a clinician's suspicion regarding an oral lesion. It must be emphasized that a brush "biopsy" sample analysis does not and cannot provide a definitive diagnosis for oral cancer. A tissue biopsy must be obtained to confirm the diagnosis”.
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 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; further RCTs are recommended to evaluate the efficacy and cost-effectiveness of a visual examination as part of a population-based screening program in low-, middle- and high-income countries.

Siebers and colleagues (2013) stated that despite advances in surgical and other treatment modalities, the prognosis of patients with OSCC remains poor. It is well-known that the early detection of OSCC and recurrent lesions is of utmost importance in obtaining disease control. Besides difficulty in visually differentiating between benign and (pre) cancerous lesions, the detection is hampered by the fact that scalpel biopsy is an invasive activity with potential morbidity. It is therefore not recommended to biopsy lesions on a regular basis. An easily performed, non-invasive screening method suitable to monitor lesions over time is urgently needed. In addition, the current histopathological examination suffers
from inter- and intra-observer variability. In a previous study these researchers showed the prognostic value of DNA image cytometry (DNA-ICM). The objective of the present study is assessment of the possibility to determine ploidy status using an oral brush. This prospective study included 85 (23 pre-malignancies, 27 stage T1 and 31 stage T2 OSCC) patients with a suspected (pre) malignant lesion of the oral cavity. Newly discovered lesions as well as suspected recurrent OSCC were included. Both a brush and biopsy specimen were obtained for each patient. All specimens were analyzed using ICM according to a well-established procedure. A significant difference was observed between brushes from diploid biopsies and brushes from non-diploid biopsies (p < 0.01). The brush was able to significantly differentiate between diploid and non-diploid lesions. This technique was able to correctly identify 50 % of the non-diploid lesions with a corresponding specificity of 80 %. The authors concluded that the oral brush biopsy is not suitable to replace the conventional surgical biopsy, however it may be of additional value in monitoring (pre) malignant lesions over time.

Kammerer et al (2013) stated that adjunctive techniques like DNA-ICM, a non-invasive method, have been attributed to enhance the diagnostic performance of oral brush biopsies. The aim of the study was an evaluation of brush biopsies, analyzed according to morphological criteria and by DNA-ICM versus histological findings in a blinded prospective trial. A total of 88 brush biopsies of 70 patients were sampled. Only clinical suspicious but not evident malignant oral lesions were included. Clinical diagnosis was leukoplakia (n = 36), lichen planus (n = 18), verruciform erythroplakia (n = 12), erythroleukoplakia (n = 9), erosion (n = 7) and induration (n = 6). Evaluation was conducted via histology, cytology and DNA-ICM. Histological diagnosis revealed 8 cases of squamous intraepithelial dysplasia (SIN 1 n = 6, SIN 2 n = 2), 4 cases of carcinoma-in situ and 25 cases of oral T1-cancer. Remaining cases were leukoplakia (n = 28), lichen planus (n = 15) and local inflammation (n = 8). Brush biopsy detected malignant lesions including SIN 1 with a sensitivity of 55 % and a specificity of 100 %. DNA-ICM had a sensitivity of 70 % and a specificity of 100 %. The combination of both methods showed a sensitivity of 76 % and a specificity of 100 %. The predominant reason for false negative results was sampling errors with insufficient cells (86 % in brush biopsy and 100 % in DNA-ICM). The authors concluded that DNA-ICM has the potential to substantially improve the sensitivity of a pure morphological interpretation of oral brush biopsies. Method inherent sampling errors may be accountable for a lower sensitivity compared to conventional histological diagnosis. Therefore, DNA-ICM should not be used to rule out malignancy, when lesions are already clinically suspicious for oral cancer.

Ma and colleagues (2014) estimated the diagnostic accuracy of brush biopsy with DNA-ICM for potentially malignant oral disorders compared with tissue biopsy pathology in China. Exfoliative cells were obtained using a cytobrush cell collector from oral mucosa of 52 subjects, followed by scalpel biopsy from the same region. Nuclear DNA contents (ploidy) were measured after Feulgen re-staining, using an automated DNA image cytometer. Exfoliative cytology with DNA-ICM and histopathological diagnosis were performed separately at different institutions. Histological investigation was considered the gold standard. These researchers reported that the sensitivity of DNA aneuploidy for the detection of cancer cells in potentially malignant oral disorders was 86.36 %; its specificity was 90.00 %, its PPV was 86.36 %, and its NPV was 90.00 %. The authors concluded that brush
biopsy with DNA-ICM is a useful method for monitoring potentially malignant oral disorders. The findings of this small, uncontrolled study need to be validated by well-designed studies.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes not covered for indications listed in the CPB:

88104

99000

Other CPT codes related to the CPB:

40808

41108

42800

42804

42806

88160

HCPCS codes not covered for indications listed in the CPB:

D0486  Laboratory accession of transepithelial cytologic sample, microscopic examination, preparation and transmission of written report

D7288  Brush biopsy - transepithelial sample collection

Other HCPCS codes related to the CPB:

D7287  Exfoliative cytological sample collection

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

210.0 - 210.9  Benign neoplasm of lip, oral cavity, and pharynx

230.0  Carcinoma in situ of lip, oral cavity, and pharynx

235.1  Neoplasm of uncertain behavior of lip, oral cavity, and pharynx

528.0 - 528.9  Diseases of the oral soft tissues, excluding lesions specific for gingiva and tongue

529.0 -529.9  Diseases and other conditions of the tongue

V76.42  Special screening for malignant neoplasm of oral cavity
The above policy is based on the following references:


42. Cook D, Huber MA. In the primary care setting, the value of adjunctive aids for oral cancer examinations remains unanswered. Critically Appraised Topics (CATS). ID# 265. San Antonio, TX: Oral Health Evidence-based Practice Program, Dental School, University of Texas Health Science Center at San Antonio; revised December 14, 2011.

43. Juber S, Huber M. OralCDx Brush Test should not replace surgical biopsy in oral cancer examinations. Critically Appraised Topics (CATS). ID# 2194. San Antonio, TX: Oral Health Evidence-based Practice Program, Dental School, University of Texas Health Science Center at San Antonio; April 5, 2012.


