SALIVARY TESTING

Policy Number: DCG037.04 **Effective Date**: January 1, 2020

Instructions for Use

Table of Contents **Page**

Related Dental Policy

- Miscellaneous Diagnostic Procedures

COVERAGE RATIONALE

Collection, Preparation and Analysis of Saliva Sample for Laboratory Diagnostic Testing

Collection, preparation and analysis of saliva sample for laboratory diagnostic testing may be indicated as part of oral disease Risk Assessment and subsequent management.

Assessment of Salivary Flow by Measurement

Assessment of salivary flow by measurement may be indicated for individuals with systemic disease, polypharmacy and radiation therapy to the head and neck. It may also be indicated to monitor the effectiveness of Sialagogues.

DEFINITIONS

Risk Assessment: Analysis of risks involved prior to action being taken

Sialagogue: a drug that promotes the secretion of saliva

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Clinical Policies and Coverage Guidelines may apply.

CDT Code	Description
D0417	Collection and preparation of saliva sample for laboratory diagnostic testing
D0418	Analysis of saliva sample
D0419	assessment of salivary flow by measurement

CDT® is a registered trademark of the American Dental Association

DESCRIPTION OF SERVICES

Saliva is made of water, mucus, proteins, minerals, and an enzyme called amylase. It lubricates the mouth, provides protection to the teeth from bacterial acids, helps rebuild damaged enamel, and begins the first stage of the digestive process. Salivary biomarkers for oral cancers have been explored for their role in earlier detection of oral cancer, particularly oral squamous cell carcinoma (OSCC). This is an active and promising area of research.

While xerostomia is a subjective feeling of a dry mouth, hyposalivation is the objective measure of decreased salivary gland function. Hyposalivation and poor quality saliva increases risk for dental diseases. The information gathered

from saliva testing (bacteria, biomarkers, quality and quantity of saliva) can be an additional diagnostic tool to lower incidence and/or severity of oral disease.

CLINICAL EVIDENCE

Caries

Piekoszewska-Ziętek et al. (2019) conducted a systematic review of the literature to assess the relationship of chosen salivary proteins and peptides levels with the occurrence of caries in children. Twenty-two studies were included in the review, from which the issue of glycoproteins (including immunoglobulins), AMPs and salivary enzymes was discussed. The research involved primary dentition (13 papers), as well as mixed (7) and permanent dentition (5). Caries assessment included visual inspection, dmft/s and DMFT/S indexed; quantity of Streptococcus mutans and Lactobacillus spp. bacteria; and caries risk assessment. The authors concluded that the results are promising; however, further investigations should be undertaken. The majority of studies included are case-control and cross-sectional; however, it is necessary to conduct more cohort studies with adequate follow-up prior to considering this as markers for caries risk assessment.

Chokshi et al (2016) conducted a study to estimate the salivary levels of Streptococcus mutans, Lactobacilli and Actinomyces and to correlate it with dental caries experience in mixed and permanent dentition. The sample size comprised 110 subjects. The decayed, missing and filled teeth (DMFT) index of all the individuals participating in the study was calculated. Saliva samples were collected from patients and samples were inoculated on specific culture media and incubated for a period of 48 hours, and colony characteristics, S. mutans, Lactobacilli and Actinomyces were identified. A positive correlation exists between DMFT and S. mutans, Lactobacilli and Actinomyces in mixed dentition and permanent dentition group samples ($P < 0.001$). The conclusion from the results obtained was that S. Mutans, lactobacilli and Actinomyces which are the components of the normal microbial flora of the oral cavity play an important role in the pathogenesis of dental caries and increased number of microorganisms is associated with an increased caries frequency.

Edelstein et al (20016). The purpose of this retrospective cohort study was to examine mutans streptococci (MS) from children's saliva, and its ability in predicting caries progression and determine sensitivity, specificity, and likelihood ratios of a very high "too numerous to count" (TNTC) MS test result. There were 200 preschoolers (50 percent no recoverable MS, 50 percent TNTC MS at first dental visit) followed for five or more years, and caries experience of both groups was compared to identify predictors of caries presence and its progression. Controlling for demographic, oral health, and dental visit factors, TNTC preschoolers had both greater presence and extent of caries at the first dental visit and caries progression at five or more years. Fewer TNTC preschoolers remained caries free over five years or longer (13 percent versus 77 percent for no MS). Overall, sensitivities and specificities exceeded 75 percent. This study showed that despite engagement in preventive dental care, children with TNTC MS were six times more likely to experience cavity increments than preschoolers with no recoverable MS at first visit.

Ghasempour et al (2014). One of the causative factors in development of dental caries is microorganisms. Two species of mutans streptococci including Streptococcus mutans and Streptococcus sobrinus are associated with dental caries in human beings. The aim of this analytical case-control study was to investigate the frequency of S. mutans and S. sobrinus in saliva of children with different caries activity and ability to form biofilm and acid susceptibility of these microorganisms. 83 preschool children, 4-6 years old were selected and divided into two groups: 41 caries-active and 42 caries-free children. Non-stimulated saliva samples were collected and culture and polymerase chain reaction techniques were used. Statistical analysis was performed using t-test, Chi-square, ANOVA, and Kappa tests. S. mutans and S. sobrinus were found in 65% and 21.6% of the samples respectively. S. mutans was isolated from 75.6% of caries-active and 54.8% of caries-free children. Figures for S. sobrinus were 29.2% and 14.3% respectively. Acid susceptibility of microorganisms isolated from saliva was 87.43 in caries-active children and 94.30 for caries-free children. Biofilm formation of microorganisms in caries-active and caries-free children was 0.77 and 0.73, respectively. This study showed the frequency of S. mutans in caries-active children to be significantly higher than caries-free children, but the difference in frequency of S. sobrinus was not significant. Acid susceptibility of microorganisms in caries-active children was significantly lower, but the ability to form biofilm was not significantly different in two groups.

Yang et al (2015) The purpose of this study was to determine the relationships among early childhood caries (ECC), root caries (RC), the quantity of Streptococcus mutans in saliva, and the concentrations of total and specific secretory IgA (sIgA). Saliva samples were collected from 70 children, 3-4 years of age, with and without ECC, and from 43 adults, ≥60 years of age, with and without RC. The decayed, missing, and filled teeth (DMFT) and decayed, missing, and filled surfaces (DMFS) scores of each child, and the root decayed and filled teeth (RDFT) and root decayed and filled surfaces (RDFS) scores of each elderly subject, were determined. The S. mutans levels, total sIgA, and specific sIgA against two virulence antigens of S. mutans in saliva were analyzed using quantitative real-time PCR (qPCR) and ELISAs. The quantity of S. mutans was significantly higher in caries-positive subjects within the two populations than in the caries-free subjects; and a positive correlation was found between the quantity of S. mutans and the DMFT,

DMFS, RDFT, and RDFS scores. In addition, the salivary total sIgA was significantly higher in children with severe early childhood caries (SECC) and in the elderly subjects with RC. Moreover, although the S. mutans level was significantly higher, the concentrations of specific sIgA against S. mutans antigens were significantly lower in samples from elderly subjects than in samples from children. The authors concluded that these results support the concept that S. mutans is positively associated with ECC and RC.

Periodontal Disease

Liebsch et al. (2019) Periodontitis is one of the most prevalent oral diseases worldwide and is caused by multifactorial interactions between host and oral bacteria. Altered cellular metabolism of host and microbes releases a number of intermediary end products known as metabolites. There is an increasing interest in identifying metabolites from oral fluids such as saliva to widen the understanding of the complex pathogenesis of periodontitis. It is believed that some metabolites might serve as indicators toward early detection and screening of periodontitis and perhaps even for monitoring its prognosis in the future. Because contemporary periodontal screening methods are deficient, there is an urgent need for novel approaches in periodontal screening procedures. To this end, we associated oral parameters (clinical attachment level, periodontal probing depth, supragingival plaque, supragingival calculus, number of missing teeth, and removable denture) with a large set of salivary metabolites (n = 284) obtained by mass spectrometry among a subsample (n = 909) of nondiabetic participants from the Study of Health in Pomerania (SHIP-Trend-0). Linear regression analyses were performed in age-stratified groups and adjusted for potential confounders. A multifaceted image of associated metabolites (n = 107) was revealed with considerable differences according to age groups. In the young (20 to 39 y) and middle-aged (40 to 59 y) groups, metabolites were predominantly associated with periodontal variables, whereas among the older subjects (≥60 y), tooth loss was strongly associated with metabolite levels. Metabolites associated with periodontal variables were clearly linked to tissue destruction, host defense mechanisms, and bacterial metabolism. Across all age groups, the bacterial metabolite phenylacetate was significantly associated with periodontal variables. Our results revealed alterations of the salivary metabolome in association with age and oral health status. Among our comprehensive panel of metabolites, periodontitis was significantly associated with the bacterial metabolite phenylacetate, a promising substance for further biomarker research.

Nisha et al. (2018) conducted a cross sectional study designed to estimate the levels of macrophage inflammatory protein-1 alpha (MIP-1α) and monocyte chemo attractant protein-1 (MCP-1) in whole unstimulated saliva from 75 patients and to evaluate their role as reliable salivary biomarkers in discriminating gingivitis and periodontitis from health. Participants were divided into healthy (Group 1, n = 25), gingivitis (Group 2, n = 25) and chronic generalized periodontitis (Group 3, n = 25). MIP-1α and MCP-1 levels were estimated by using ELISA and were correlated with clinical parameters. ROC curve analysis was done to determine the sensitivity and specificity of these biomarkers in distinguishing periodontal disease from health. The results showed both biomarkers were detected in all the saliva samples. There was a statistically significant difference in the concentration of both the analytes in Group 3 and Group 2 compared with Group 1 ($p < 0.001$). ROC curve analysis showed 100% sensitivity and specificity for MIP-1α and MCP-1 in discriminating periodontitis from health. For discriminating gingivitis from health, MIP-1α had a higher sensitivity and specificity (100% & 88% respectively) compared to MCP-1(84.1% & 80% respectively). The authors concluded there is a substantial increase in the concentration of both MIP-1α and MCP-1 with increasing severity of periodontal disease. Both the analytes showed promising results as biomarkers for discriminating periodontal disease from health.

de Lima et al (2016) conducted a systematic review and meta-analysis to evaluate the accuracy of host-derived salivary biomarkers in the diagnosis of periodontal disease by assessing the published literature. 4 studies were included for full analysis. One biomarker, macrophage inflammatory protein-1 alpha (MIP-1a), had excellent diagnostic accuracy (sensitivity 95% and specificity 93%) and interleukin-1 beta (IL-1b) and IL-6 showed acceptable diagnostic values: IL-1b sensitivity varied from 54% to 88% and specificity varied from 55% to 100% and IL-6 sensitivity varied from 59% to 88% and specificity varied from 60% to 97%. The meta-analysis forest plot showed that MIP-1a was the best marker evaluated. The authors concluded that MIP-1a had high diagnostic capability and excellent accuracy and that biomarkers IL-1b and IL-6 had acceptable accuracy. However, they also indicated that the evidence reviewed was too restricted to endorse the use of salivary biomarkers as a diagnostic tool based on the available data and suggested more and larger multi centered studies.

Kuboniwa et al (2016). In this pilot study, the authors explored the use of salivary metabolites to reflect periodontal inflammation severity with a recently proposed parameter-periodontal inflamed surface area (PISA)-used to quantify the periodontal inflammatory burden of individual patients with high accuracy. Following PISA determination, whole saliva samples were collected from 19 subjects before and after removal of supragingival plaque and calculus (debridement) with an ultrasonic scaler to assess the influence of the procedure on salivary metabolic profiles. Metabolic profiling of saliva was performed with gas chromatography coupled to time-of-flight mass spectrometry, followed by multivariate regression analysis with orthogonal projections to latent structures (OPLS) to investigate the relationship between PISA and salivary metabolic profiles. Sixty-three metabolites were identified. OPLS analysis showed that postdebridement saliva provided a more refined model for prediction of PISA than did predebridement

samples, which indicated that debridement may improve detection of metabolites eluted from subgingival areas in saliva, thus more accurately reflecting the pathophysiology of periodontitis. Based on the variable importance in the projection values obtained via OPLS, 8 metabolites were identified as potential indicators of periodontal inflammation, of which the combination of cadaverine, 5-oxoproline, and histidine yielded satisfactory accuracy (area under the curve = 0.881) for diagnosis of periodontitis. The authors' findings identified potential biomarkers that may be useful for reflecting the severity of periodontal inflammation as part of monitoring disease activity in periodontitis patients.

Morozumi et al (2016). A diagnosis of periodontitis progression is presently limited to clinical parameters such as attachment loss and radiographic imaging. The aim of this multicenter study was to monitor disease progression in patients with chronic periodontitis during a 24-month follow-up program and to evaluate the amount of bacteria in saliva and corresponding IgG titers in serum for determining the diagnostic usefulness of each in indicating disease progression and stability. A total of 163 patients with chronic periodontitis who received trimonthly follow-up care were observed for 24 months. The clinical parameters and salivary content of Porphyromonas gingivalis, Prevotella intermedia and Aggregatibacter actinomycetemcomitans were assessed using the modified Invader PLUS assay, and the corresponding serum IgG titers were measured using ELISA. The changes through 24 month period were analyzed using cut-off values calculated for each factor. One-way ANOVA or Fisher's exact test was used to perform between-group comparison for the data collected. Diagnostic values were calculated using Fisher's exact test. Of the 124 individuals who completed the 24-month monitoring phase, 62 exhibited periodontitis progression, whereas 62 demonstrated stable disease. Seven patients withdrew because of acute periodontal abscess. The ratio of P. gingivalis to total bacteria and the combination of P. gingivalis counts and IgG titers against P. gingivalis were significantly related to the progression of periodontitis. The combination of P. gingivalis ratio and P. gingivalis IgG titers was significantly associated with the progression of periodontitis. The authors suggest this study shows that the combination of P. gingivalis ratio in saliva and serum IgG titers against P. gingivalis may be associated with the progression of periodontitis.

Zhang et al (2016). In periodontitis, activated macrophages not only initiate immune responses to periodontal-pathogen infections, but also damage the periodontal tissues by releasing a series of inflammatory cytokines. Macrophage-activating factor (MAF) and macrophage-chemotactic factor (MCF) are two important mediators involved in macrophage accumulation, activation and function. This study analyzed the levels of salivary MAF and MCF in healthy individuals and those with different periodontal diseases, and assessed the usefulness of salivary MAF and MCF as diagnostic biomarkers in periodontal tissue health status. Ninety-five saliva specimens were collected from healthy individuals and patients with gingivitis, mild periodontitis, moderate periodontitis, and severe periodontitis. Pocket probing depth (PPD) and alveolar bone loss (ABL) were recorded via periodontal probing and dental radiography, respectively. Salivary MAF and MCF concentrations were assayed using enzyme-linked immunosorbent assays. MAF level tended to increase in saliva as periodontal diseases progressed. The concentration of salivary MAF in periodontitis correlated positively with ABL and PPD. In contrast, salivary MCF levels increased significantly only in periodontitis. The authors concluded that salivary MAF levels correlate positively with tissue destruction in periodontal diseases. It is a potential valuable biomarker that could be used to assess periodontal health status.

Oral Cancer

In a 2019 comparative study, Chu et al. sought to identify oral squamous cell carcinoma (OSCC) biomarkers by salivary proteomes, of OSCC patients. Individuals with oral potentially malignant disorders (OPMDs), and healthy volunteers were comparatively profiled with isobaric tags for relative and absolute quantitation (iTRAQ)-based mass spectrometry (MS). The salivary levels of 67 and 18 proteins in the OSCC group are elevated and decreased compared to that in the noncancerous group (OPMD and healthy groups), respectively. The candidate biomarkers were further selected using the multiple reaction monitoring (MRM)-MS and validated with the immunoassays. More importantly, the higher salivary level of three proteins, complement factor H (CFH), fibrinogen alpha chain (FGA), and alpha-1-antitrypsin (SERPINA1) was correlated with advanced stages of OSCC. The authors concluded that analysis of salivary proteome is a feasible strategy for biomarker discovery, and the three proteins are potential salivary markers for OSCC diagnosis.

Guerra et al (2015). The purpose of this systematic review and meta-analysis was to evaluate the diagnostic value of salivary biological markers in the diagnosis of head and neck carcinoma. Studies were gathered by searching Cochrane, EMBASE, LILACS, MEDLINE, and PubMed. The references were also crosschecked and a partial grey literature search was undertaken using Google Scholar. The methodology of selected studies was evaluated using the 14-item Quality Assessment Tool for Diagnostic Accuracy Studies. 15 articles were identified and subjected to qualitative and quantitative analyses. The studies were homogeneous, and all had high methodological quality. Combined biomarkers demonstrated better accuracy with higher sensitivity and specificity than those tested individually. Furthermore, the salivary biomarkers reviewed predicted the early stages of head and neck carcinoma better than the advanced stages. A restricted set of five single biomarkers (interleukin-8, choline, pipecolinic acid, l-phenylalanine, and S-carboxymethyl-l-cysteine) as well as combined biomarkers demonstrated excellent diagnostic test accuracy. The results of this systematic review confirm the potential value of a selected set of salivary biomarkers as diagnostic tools for head and neck carcinoma.

Ishikawa et al (2016). The objective of this study was to explore salivary metabolite biomarkers by profiling both saliva and tumor tissue samples for oral cancer screening. Patients with oral cancer and healthy controls were recruited at the Department of Dentistry, Oral and Maxillofacial Plastic and Reconstructive Surgery of Yamagata University Hospital from 2012 to 2014. None had received any prior treatment such as chemotherapy or radiotherapy. All oral cancer patients provided both tumor tissues and saliva samples. No controls had a history of prior malignancy or autoimmune disorders. Paired tumor and control tissues were obtained from oral cancer patients and whole unstimulated saliva samples were collected from patients and healthy controls. The comprehensive metabolomic analysis for profiling hydrophilic metabolites was conducted using capillary electrophoresis time-of-flight mass spectrometry. In total, 85 and 45 metabolites showed significant differences between tumor and matched control samples, and between salivary samples from oral cancer and controls, respectively ($P < 0.05$ correlated by false discovery rate); 17 metabolites showed consistent differences in both saliva and tissue-based comparisons. Of these, a combination of only two biomarkers yielded a high area under receiver operating characteristic curves (0.827; 95% confidence interval, 0.726-0.928, $P < 0.0001$) for discriminating oral cancers from controls. Various validation tests confirmed its high generalization ability. The demonstrated approach, integrating both saliva and tumor tissue metabolomics, helps eliminate pseudo-molecules that are coincidentally different between oral cancers and controls. These combined salivary metabolites could be the basis of a clinically feasible method of non-invasive oral cancer screening.

Polz-Dacewicz et al (2016). Each year approximately 6,000 new cases of head and neck cancer are registered in Poland. Human papillomavirus (HPV) and Epstein-Barr virus (EBV) have been associated with tumour formation. Cytokines have been shown to play an important role both in inflammation and carcinogenesis and they can be detected in saliva and serum with ELISA assays. Salivary biomarkers may be used as markers of early cancer detection. The aim of this study was the analysis of the serum and salivary levels of IL-10, TNF-α, TGF-β and VEGF in patients with oropharyngeal cancer and in healthy individuals. The level of these biomarkers was also analyzed in HPV- and EBV-related cases. The study involved 78 patients with histopathologically confirmed oropharyngeal squamous cell carcinoma and 40 healthy controls. Serum and salivary levels of IL-10, TNF-α, TGF-β and VEGF were analyzed both in patients and in healthy individuals by ELISA method using Diaclone SAS commercially available kits (France). EBV DNA was detected by the nested PCR for amplification of EBNA-2. HPV detection and genotyping was performed using the INNO-LiPA HPV Genotyping Extraassay (Innogenetics N. V, Gent, Belgium). The obtained results were subjected to statistical analysis using Mann-Whitney and Kruskal Wallis tests. The level of tested cytokines was higher in patients than in controls both in serum as well as in saliva. EBV DNA was detected in 51.3 % of patients and 20 % of controls, HPV DNA was present in 30.8 % of patients and 2, 5 % of controls. The level of IL-10 was statistically higher in patients infected with EBV, HPV and co-infected with EBV/HPV. The level of TNF-α was significantly higher in patients infected with EBV, while TGF-β in patients with HPV infection and EBV/HPV co-infection. The authors concluded that the detection of salivary cytokines may be very helpful in early diagnosis, treatment and prognosis of OSCC.

Salivary Flow by Measurement

Löfgren et al. (2012) conducted a systematic review to evaluate the quality of the evidence for the efficacy of diagnostic methods used to identify oral dryness. The most advocated clinical method for diagnosing salivary dysfunction is to quantitate unstimulated and stimulated whole saliva (sialometry). Since there is an expected and wide variation in salivary flow rates among individuals, the assessment of dysfunction can be difficult. A literature search, with specific indexing terms and a hand search, was conducted for publications that described a method to diagnose oral dryness. The electronic databases of PubMed, Cochrane Library, and Web of Science were used as data sources. Four reviewers selected publications on the basis of predetermined inclusion and exclusion criteria. Data were extracted from the selected publications using a protocol. Original studies were interpreted with the aid of Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. A total of 18 original studies were judged relevant and interpreted for this review. In all studies, the results of the test method were compared to those of a reference method. Based on the interpretation (with the aid of the QUADAS tool) it can be reported that the patient selection criteria were not clearly described and the test or reference methods were not described in sufficient detail for it to be reproduced. None of the included studies reported information on uninterpretable/intermediate results nor data on observer or instrument variation. Seven of the studies presented their results as a percentage of correct diagnoses. The authors concluded that the evidence for the efficacy of clinical methods to assess oral dryness is sparse and improved standards for the reporting of diagnostic accuracy are needed in order to assure the methodological quality of studies. There is need for effective diagnostic criteria and functional tests in order to detect those individuals with oral dryness who may require oral treatment, such as alleviation of discomfort and/or prevention of diseases.

Villa et al. (2015) conducted a systematic review to assess the literature on the prevalence, diagnosis, treatment, and prevention of medication-induced salivary gland dysfunction (MISGD). Electronic databases were searched for articles related to MISGD through June 2013. Four independent reviewers extracted information regarding study design, study population, interventions, outcomes, and conclusions for each article. Only papers with acceptable degree of relevance, quality of methodology, and strength of evidence were retained for further analysis. There were limited data on the

epidemiology of MISGD. Furthermore, various methods were used to assess salivary flow rate or xerostomia. Preventive and therapeutic strategies included substitution of medications, oral, or systemic therapy with sialagogues, use of saliva substitutes or of electro-stimulating devices. Although there are promising approaches to improve salivary gland function, most studies are characterized by small numbers and heterogeneous methods. Physicians and dentists should identify the medications associated with xerostomia and salivary gland dysfunction through a thorough medical history. Preferably, health care providers should measure the unstimulated and stimulated whole salivary flow rates of all their patients so that these values can be used as a baseline to rate the complaints of patients who subsequently claim to experience xerostomia or salivary gland dysfunction as well as the possibilities of effectively treating this condition.

Professional Societies

American Academy of Pediatric Dentistry (AAPD)

In the Guideline on Caries-Risk Assessment and Management for Infants, Children, and Adolescents, revised in 2014, the AAPD recommends the following:

- Due to a child's Mutans Streptococci (MS) levels and the age at which a child becomes colonized with cariogenic flora as being valuable in assessing risk, especially in preschool children, baseline testing on all children regardless of other risk factors/ risk level through the age of 5 is recommended.

American Dental Association (ADA) Council on Scientific Affairs

In a report by the ADA Council on Scientific Affairs, the following recommendation was made:

- Initial evaluation of patients with dry mouth should include a detailed health history to facilitate early detection and identify underlying causes. Comprehensive evaluation, diagnostic testing and periodic assessment of salivary flow, followed by corrective actions, may help prevent significant oral disease. A systematic approach to xerostomia management can facilitate interdisciplinary patient care, including collaboration with physicians regarding systemic conditions and medication usage. Comprehensive management of xerostomia and hyposalivation should emphasize patient education and lifestyle modifications. It also should focus on various palliative and preventive measures (Plemons et al 2014)

American Dental Association (ADA) Statement on Salivary Diagnostics

Large-scale, multicenter clinical trials and independent validation studies are required to establish evidence of clinical utility of salivary and oral fluid diagnostics in the early diagnosis and/or monitoring of oral cancer and other diseases or conditions. Current challenges include identification of disease-specific markers, establishing sensitivity and specificity of developed tests, and standardization of collection/storage of salivary samples. Refinement of oral fluid screening and diagnostic tests may further elucidate our understanding of the relationship between oral health and overall health. Presently, as of August 2018, there are no FDA approved salivary diagnostic tests for evaluating risk of periodontal disease, dental caries, or head and neck cancer.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Examples of salivary diagnostic devices include, but are not limited to the following:

- MyPerioPath® (Oral DNA Labs, Inc.)
- DentocultSM® Strip Mutans (Orion Diagnostica)
- CRT® Bacteria (Ivoclar)
- Saliva-Check Mutans (GC America)
- Saliva-Check BUFFER (GC America)

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as "panels". Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device:

- Class I General Controls
  - With Exemptions
  - Without Exemptions
- Class II General Controls and Special Controls
  - With Exemptions
  - Without Exemptions
- Class III General Controls and Premarket Approval

Select testing devices are a Class I device. The FDA has exempted almost all class I devices (with the exception of reserved devices) from the premarket notification requirement, including those devices that were exempted by final regulation published in the Federal Registers of December 7, 1994, and January 16, 1996. If a manufacturer's device falls into a generic category of exempted class I devices as defined in 21 CFR Parts 862-892, a premarket notification application and FDA clearance is not required before marketing the device in the U.S. however, these manufacturers are required to register their establishment. Please see the following website for additional information:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=31793. Accessed July 29, 2019.

Specific information regarding classification of dental devices may be found here: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?start_search=1&submission_type_id=&devicename=&productcode=&deviceclass=&thirdparty=&panel=de&regulationnumber=&pagenum=500&sortcolumn=devicename. Accessed July 8, 2019.

Laboratories that perform salivary diagnostic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.cms.gov/clia/. Accessed July 8, 2019.

REFERENCES

American Academy of Pediatric Dentistry Guideline on Caries-risk Assessment and Management for Infants, Children, and Adolescents Council on Clinical Affairs Committee. Adopted 2002. Revised 2014.

American Dental Association Center for Scientific Information, ADA Science Institute. Scientific Information Subcommittee, ADA Council on Scientific Affairs. Salivary Diagnostics. 2018.

Chokshi A, Mahesh P, Sharada P, et al. A correlative study of the levels of salivary Streptococcus mutans, lactobacilli and Actinomyces with dental caries experience in subjects with mixed and permanent dentition. J Oral Maxillofac Pathol. 2016 Jan-Apr;20(1):25-8.

Chu HW, Chang KP, Hsu CW, et al. Identification of salivary biomarkers for oral cancer detection with untargeted and targeted quantitative proteomics approaches. Mol Cell Proteomics. 2019 Jun 28.

de Lima CL, Acevedo AC, Grisl DC, et al. Host-derived salivary biomarkers in diagnosing periodontal disease: systematic review and meta-analysis. J Clin Periodontol 2016; 43(6): 492-502.

Edelstein BL, Ureles SD, Smaldone A. Very High Salivary Streptococcus Mutans Predicts Caries Progression in Young Children. Pediatr Dent. 2016; 38(4):325-30.

Ghasempour M, Rajabnia R, Irannejad A, et al. Frequency, biofilm formation and acid susceptibility of streptococcus mutans and streptococcus sobrinus in saliva of preschool children with different levels of caries activity. Dent Res J (Isfahan). 2013 Jul; 10(4):440-5.

Guerra EN, Acevedo AC, Leite AF, et al. Diagnostic capability of salivary biomarkers in the assessment of head and neck cancer: A systematic review and meta-analysis. Oral Oncol. 2015 Sep; 51(9):805-18.

Ishikawa S, Sugimoto M, Kitabatake K, et al. Identification of salivary metabolomic biomarkers for oral cancer screening. Sci Rep. 2016 Aug 19; 6:31520.

Liebsch C, Pitchika V, Pink C, et al. The Saliva Metabolome in Association to Oral Health Status. J Dent Res. 2019 Jun;98(6):642-651.

Kuboniwa M, Sakanaka A, Hashino E, et al. Prediction of Periodontal Inflammation via Metabolic Profiling of Saliva. J Dent Res. 2016 Jul 28.

Löfgren CD, Wickström C, Sonesson M, et al. A systematic review of methods to diagnose oral dryness and salivary gland function. BMC Oral Health. 2012 Aug 8; 12:29.

Medical Dictionary for the Health Professions and Nursing. (2012).

Morozumi T, Nakagawa T, Nomura Y, et al. Salivary pathogen and serum antibody to assess the progression of chronic periodontitis: a 24-mo prospective multicenter cohort study. J Periodontal Res. 2016 Jan 20.

Nisha KJ, Suresh A, Anilkumar A, Padmanabhan S. MIP-1α and MCP-1 as salivary biomarkers in periodontal disease. Saudi Dent J. 2018 Oct;30(4):292-298.

Piekoszewska-Ziętek P, Turska-Szybka A, Olczak-Kowalczyk D. Salivary proteins and peptides in the aetiology of caries in children: Systematic literature review. Oral Dis. 2019 May;25(4):1048-1056.

Plemons JM, Al-Hashimi I, Marek C et al; American Dental Association Council on Scientific Affairs. Managing xerostomia and salivary gland hypofunction: executive summary of a report from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc. 2014 Aug; 145(8):867-73.

Polz-Dacewicz M, Strycharz-Dudziak M, Dworzański J, et al. Salivary and serum IL-10, TNF-α, TGF-β, VEGF levels in oropharyngeal squamous cell carcinoma and correlation with HPV and EBV infections. Infect Agent Cancer. 2016 Aug 20; 11:45.

Villa A, Wolff A, Aframian D. et al. World Workshop on Oral Medicine VI: a systematic review of medication-induced salivary gland dysfunction: prevalence, diagnosis, and treatment. Clin Oral Investig. 2015 Sep; 19(7):1563-80.

Yang Y, Li Y, Lin Y, et al. Comparison of immunological and microbiological characteristics in children and the elderly with or without dental caries. Eur J Oral Sci. 2015 Apr; 123(2):80-7.

Zhang P, Fan Y, Li Q, et al. Macrophage activating factor: A potential biomarker of periodontal health status. Arch Oral Biol. 2016 Jun 9; 70:94-99.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2020	**Coverage Rationale** • Simplified content ***Assessment of Salivary Flow by Measurement*** • Added language to state: ○ Assessment of salivary flow by measurement may be indicated for individuals with systemic disease, polypharmacy and radiation therapy to the head and neck; it may also be indicated to monitor the effectiveness of Sialagogues **Definitions** • Added definition of "Sialagogue" **Applicable Codes** • Updated list of applicable CDT codes to reflect annual code edits; added D0419 **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version DCG037.03

INSTRUCTIONS FOR USE

This Dental Clinical Policy provides assistance in interpreting UnitedHealthcare standard dental benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard dental plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Dental Clinical Policy is provided for informational purposes. It does not constitute medical advice.