Genetic Testing for Oral Disease (For Ohio Only)

Policy Number: CSDEN315OH.A
Effective Date: December 1, 2023

Instructions for Use

Table of Contents Page

Related Dental Policies
None

Application

This Dental Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

Coverage Rationale

Collection and Preparation of Genetic Sample Material for Laboratory Analysis and Report

The collection, preparation and testing of genetic sample material including oral Human Papillomavirus (HPV) is not indicated due to insufficient evidence of efficacy.

Genetic Test for Susceptibility to Diseases – Specimen Analysis

Genetic testing for susceptibility to oral disease, including oral HPV related cancer, is not indicated due to insufficient evidence of efficacy.

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 Policies and Guidelines may apply.

CDT Code	Description
D0422	Collection and preparation of genetic sample material for laboratory analysis and report
D0423	Genetic test for susceptibility to diseases – specimen analysis

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Description of Services

Genetic testing is available for assessing the risk for developing diseases for a wide array of medical conditions. Periodontal disease and caries are both complex diseases, and individual patient behaviors , lifestyles, and overall health affect the risk of developing these oral diseases, regardless of the genetic profile (ADA 2021). Chronic infection with high-risk HPV can cause cancer in parts of the body where HPV infects cells, including the oropharynx. Oropharyngeal cancer is now the most common cancer caused by HPV in the United States. Specific genotypes of HPV are considered independent risk factors for developing oral cancers, namely HPV16 and HPV18. Genetic tests specific for identifying these genotypes may help to establish risks for developing oral cancer (NCI). It is unclear if having HPV alone is enough to cause oropharyngeal cancers, or if other factors (such as smoking or chewing tobacco) interact with HPV to cause these cancers. HPV is not known to cause other head and neck cancers, including those in the mouth, larynx, lip, nose, or salivary glands (CDC).

Clinical Evidence

Periodontal Disease

Al-Rawi et al. (2020) conducted a pilot study to validate 4 MicroRNAs (miRNAs) in saliva as potential predictive biomarkers of periodontal disease in patients with and without periodontal disease. The Human microRNA Disease Database (HMDD) and FANTOM5 (Functional ANnoTation of the Mammalian genome) databases were searched and miRNA and disease associations and further filtered to include those specific to immune and epithelial cells specific to periodontal diseases and diabetes mellitus only. The resultant miRNA targeted genes were searched for the cell/tissue/ organ specificity using Enricher gene list enrichment analysis tool, which identified four miRNAs (146a and b, 155, and 203) as promising biomarkers for periodontal diseases and diabetes. These are also enriched in immune related pathways and related to immune response. The authors concluded that evidence of these levels of salivary miRNAs could be considered biomarkers for periodontal disease progression in non diabetics, and diabetic related periodontitis. This study is limited by a small number of participants and a lack of randomization

Fujimori et al. (2019) conducted a cross-sectional pilot study was to find salivary microRNAs (miRNAs) reflecting periodontal condition in chronic periodontitis. One hundred and twenty patients with chronic periodontitis participated and unstimulated whole saliva was collected. A multiphase study was conducted to explore salivary miRNAs as biomarkers of periodontitis. First, a polymerase chain reaction (PCR) array was performed to compare salivary miRNAs profiles in no and mild (no/mild) and severe periodontitis patients. Then, the relative expression of salivary miRNAs on individual samples was assessed by real-time reverse transcription-PCR. The numbers of patients were 26 (21.6%, no/mild), 58 (48.3%, moderate) and 36 (30.0%, severe), respectively. Among 84 miRNAs, only the relative expression of hsa-miR-381-3p in the severe periodontitis group was significantly higher than that of the no/mild periodontitis group ($p < 0.05$). Among the 120 patients, there was also a significant correlation between the relative expression of hsa-miR-381-3p and the mean probing pocket depth (PPD) ($r = 0.181$, $p < 0.05$). The authors concluded that the salivary hsa-miR-381-3p correlated with periodontitis in chronic periodontitis patients.

In a 2019 literature review, Toy et al. sought to clarify the possible role of genetic polymorphisms in periodontal diseases. The authors searched PubMed for studies published from 1997 to June 2018 and obtained data from original studies, meta analyses, and systematic reviews. They included only case–control studies with large study populations. Several genes with a possible relationship to periodontal disease were analyzed, and the authors concluded that gene polymorphisms may cause phenotypic differences in inflammatory response, which is important in the individual's sensitivity to disease, in the progression of disease, or in the response to treatment. The incidence of genetic polymorphisms may differ according to ethnicity, so a potential association between a genetic polymorphism and disease for a population may not be valid for others.

de Coo et al. (2018) conducted a systematic review to evaluate the various genotyping tools and study strategies employed to define genetic susceptibility to periodontitis. Following data base searches, 25 studies satisfied the established inclusion criteria and were processed for data extraction. The review revealed marked heterogeneity between studies, caused in part by the lack of a universally accepted definition for periodontitis phenotypes and by the variety of genotyping tools available. The most commonly used technique was genotyping candidate genes. The authors concluded that the few rigorous studies that have been published on genetic susceptibility to periodontitis are subject to severe methodological bias due to their design and the genotyping tools employed. Despite their limitations, candidate gene studies continue to be the predominant methodological approach, rather than genome-wide association studies. Further studies must be designed using a universally

accepted, validated diagnostic criterion for periodontitis, analyzing multiple genes and polymorphisms in combination with rare variants. There is need for much more comprehensive studies including thousands of individuals to identify the effects of polymorphisms accurately with regard to statistical power. The findings demonstrate a possible association between the FccRIIIb, IL1B, VDR, IL1RN, and TLR4 polymorphisms and aggressive periodontitis; and between the TLR4, IL6, IL1B, MMP1, IL10, VDR, CD14, and IL1RN polymorphisms and chronic periodontitis susceptibility in specific populations.

Diehl et al (2015) conducted a reanalysis of a large scale study that proposed to show that the PST and PerioPredict genetic tests that are based on polymorphisms in interleukin 1 (IL-1) genes identify a subset of patients who experience fewer tooth extractions if provided with 2 annual preventive visits (see reference directly below, Giannobile et al). Economic analyses indicate rationing preventive care to only "high-risk" genotypes, smokers, patients with diabetes, or combinations of these risk factors would reduce the cost of dental care by $4.8 billion annually in the United States. The data presented in the original study that claimed clinical utility for the PST and PerioPredict tests were obtained for reanalysis using logistic regression to assess whether the PST genetic test, smoking, diabetes, or number of preventive visits were risk factors for tooth extraction during a span of 16 years. Data in the original article on risk factors for tooth extraction and patient stratification were insufficient to perform an independent reanalysis. Specifically, patients who have diabetes and/or were smokers—2 well established risk factors for tooth loss—were pooled together within “high-risk groups” that also included patients who were classified as “high risk” based solely on their PST genotype test. Consequently, it was not possible to evaluate whether the PST genetic test itself had any effect on the clinical outcomes independent of smoking and/or diabetes. Consistency of risk classification by the PST (version 1) and PerioPredict (version 2) genetic tests was evaluated in different ethnic groups from the 1000 Genomes database. Multivariate analyses revealed association of tooth extraction with diabetes ($p < .0001$), smoking ($p < .0001$), and number of preventive visits ($p = .004$), but no support for the PST genetic test ($p = .96$) nor indication that the benefit of 2 preventive visits was affected by this genetic test ($p = .58$). Classification of risk was highly inconsistent between the PST (version 1) and PerioPredict (version 2) genetic tests. The authors concluded that this reanalysis indicates two annual preventive visits were supported as beneficial for all patients, and there was no evidence that the IL-1 PST genetic test has any effect on tooth extraction risk or influences the benefits of 2 annual preventive visits. Neither IL-1 PST nor PerioPredict genetic tests are useful for rationing preventive dental care. Further research is needed to identify genetic biomarkers with robust clinical validity and clinical utility to effectively personalize the practice of dentistry.

Yücel et al (2013). The immune mechanisms and genetic variations that regulate genetic expression, production and biological activity of IL-1beta, are thought to play an important role in the pathogenesis of periodontal disease. The aims of his controlled study were to analyze interleukin (IL)-1beta (+3954) genotype and allele frequency in both chronic and aggressive periodontitis patients, and also to investigate whether this polymorphism is associated with gingival crevicular fluid (GCF) IL-1beta levels, periodontal disease severity and clinical parameters in subjects of Turkish origin. A total of 147 individuals were enrolled in the study including 56 aggressive periodontitis (AP), 44 chronic periodontitis (CP) patients and 47 healthy controls (C). Single nucleotide polymorphism at IL-1beta (+3954) is analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). GCF samples were analyzed for IL-1beta, using enzyme linked immunosorbent assay (ELISA). The distributions of genotypes and allele frequencies for IL-1beta (+3954) were similar among the groups, in spite of a trend toward a higher frequency of allele 2 in the patient groups. The genotype distribution and allele frequencies were also not different after stratification of subjects according to the clinical attachment level (CAL < 4 mm and CAL > 4mm). No differences were found between the GCF IL-1beta levels of the different genotypes. Allele 2 was associated with increased bleeding on probing (BOP) sites in chronic periodontitis patients. The results of this study do not support that genetic polymorphism in the IL-1beta (+3954) could be identified as susceptibility or severity factor in aggressive periodontitis, in the present population. The association of allele 2 frequency and higher percentage of BOP sites in chronic periodontitis suggest that IL-1beta (+3954) potentially play a significant but not major role in the clinical outcome.

Human Papillomavirus (HPV)

The relationship between oropharyngeal cancer and HPV is well established, however there is a paucity of published evidence demonstrating that genetic testing for the risk of developing these cancers impacts potential disease management or clinical outcomes. Furthermore, there are no guidelines, clinical trials in progress or FDA approved genetic tests of oral HPV infection for oropharyngeal cancer risk.

D’Souza et al. (2017) conducted an analysis of the data from 13,089 people ages 20–69 years old who participated in National Health and Nutrition Examination Survey (NHANES) between 2009 and 2014 and had oral HPV DNA testing of exfoliated cells collected from an oral rinse and gargle sample using PCR amplification using PGMY 09/11 consensus primers and line blot for the detection of 37 specific HPV types. Also analyzed were data related to smoking history and number of oral

sex partners. The purpose was to gain understanding of how common HPV16, oncogenic HPV and HPVoropharyngeal cancer (OPC) are in groups of people with different risk factor profiles. The results showed that the prevalence of oncogenic HPV was higher in men than women across all age groups (6% vs 1.1% respectively), and while oncogenic oral HPV is detected in 3.5% of all adults age 20–69, the lifetime risk of OPC is low (37 per 10,000). The authors concluded that with the increase in orophyaryngeal cancer incidence, there is a need to identify those that might be at risk. Women across all categories of risk factors have low prevalence of infection and low risk of OPC and therefore benefits of screening are unlikely to outweigh harms in this group. Even among men, the majority do not have prevalent oncogenic oral HPV, and screening based upon oncogenic oral HPV infection will not be useful.

Professional Societies

College of American Pathologists (CAP)

In the 2017 evidence based clinical practice guidelines, the CAP make the following recommendations regarding HPV testing in head and neck carcinomas:

- Pathologists should perform high-risk human papillomavirus (HR-HPV) testing on all patients with newly diagnosed oropharyngeal squamous cell carcinoma (OPSCC), including all histologic subtypes (Strong Recommendation)
- For oropharyngeal tissue specimens (ie, noncytology), pathologists should perform HR-HPV testing by surrogate marker p16 immunohistochemistry (IHC). Additional HPV-specific testing may be done at the discretion of the pathologist and/or treating clinician, or in the context of a clinical trial (Recommendation)
- Pathologists should not routinely perform HR-HPV testing on patients with nonsquamous carcinomas of the oropharynx (Expert Consensus)
- Pathologists should not routinely perform HR-HPV testing on patients with nonoropharyngeal primary tumors of the head and neck (Recommendation)
- Pathologists should routinely perform HR-HPV testing on patients with metastatic squamous cell carcinoma (SCC) of unknown primary in a cervical upper or mid jugular chain lymph node (Recommendation)
- Pathologists should not routinely perform low-risk HPV testing on patients with head and neck carcinomas.

National Cancer Care Network (NCCN)

Tumor human papillomavirus (HPV) testing by p16 immunohistochemisty (IHC) is required for the work up of cancers of the oropharynx (base of tongue, tonsil, posterior pharyngeal wall, and soft palate). A small proportion of tumors at non-oropharyngeal sites are HPV related, however routine testing for these sites is not recommended.

American Dental Association (ADA) Council on Scientific Affairs

Genetics and Oral Health

Predictive tests for dental caries or for periodontal disease do not currently exist. These are both complex diseases with multiple gene and environmental risk factors, and quantifying risk requires a multifaceted assessment. Similar to cardiovascular disease, environmental factors affect one's risk, regardless of genetic profile, and no gene to date has been identified that has as large an impact on periodontal disease as do environmental influences, such as smoking or diabetes. While genetic testing holds potential for clinical application in the future, clinical measurements remain the best approach for the assessment of caries and periodontal disease risk (ADA 2017; Updated July 2021).

ADA Science and Research Institute

Early Detection and Prevention of Oral and Oropharyngeal Cancer

In a 2022 policy update the ADA recognizes that early diagnosis can potentially impact treatment decisions and outcomes, and supports routine visual and tactile examinations for all patients.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Products for genetic testing for oral disease include, but are not limited to the following:

- MyPerioID® (OralDNA Labs)
- OraRisk® HPV

- Complete genotyping (OralDNA Labs)

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.cms.gov/clia/. (Accessed April 20, 2023)

Information regarding regulation of Laboratory Developed Tests may be found here: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm. (Accessed April 20, 2023)

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Policy History/Revision Information

Date	Summary of Changes
12/01/2023	New dental policy

Instructions for Use

This Dental Policy provides assistance in interpreting the UnitedHealthcare Community Plan of Ohio dental benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plans may differ. 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 Policy is provided for informational purposes. It does not constitute the practice of medicine or medical advice.

Archived Policy Versions

Effective Date	Policy Number	Policy Title
N/A	N/A	