

GENETIC TESTING FOR ORAL DISEASE

Policy Number: DCP036.02

Effective Date: January 1, 2018

Table of Contents	Page
INSTRUCTIONS FOR USE	1
BENEFIT CONSIDERATIONS	1
COVERAGE RATIONALE	1
DEFINITIONS	2
APPLICABLE CODES	2
DESCRIPTION OF SERVICES	2
CLINICAL EVIDENCE	2
U.S. FOOD AND DRUG ADMINISTRATION	5
REFERENCES	5
POLICY HISTORY/REVISION INFORMATION	6

Related Policies
None

INSTRUCTIONS FOR USE

This Dental Coverage Policy provides assistance in interpreting UnitedHealthcare dental benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Dental Coverage Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Dental Coverage Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Dental Coverage Policy. Other Clinical Policies and Coverage Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Dental Coverage Policy is provided for informational purposes. It does not constitute medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group health plans (inside and outside of Exchanges) to provide coverage for Pediatric Dental Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for Pediatric Dental EHBs. However, if such plans choose to provide coverage for benefits which are deemed Pediatric Dental EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute Pediatric Dental EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

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

Genetic Test for Susceptibility to Diseases – Specimen Analysis

The collection, preparation and testing of genetic samples are indicated for patients who have known human papilloma virus (HPV) infection, or have other related risk factors, to identify if the strain of HPV known to be related to oral and oropharyngeal cancers is present.

The clinical utility of genetic testing for susceptibility to periodontal diseases has not been established. Additionally, there is a lack of objective, high quality clinical evidence to support these tests.

DEFINITIONS

Clinical Utility: Refers to the likelihood that a given intervention (in this case, genetic information) will lead to an improved health outcome, or to whether a test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer (ACMG)

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
D0422	collection and preparation of genetic sample material for laboratory analysis and report
D0423	genetic test for susceptibility to diseases – specimen analysis

CDT® is a registered trademark of the American Dental Association

DESCRIPTION OF SERVICES

Genetic testing is available for a wide array of medical conditions. In dentistry, there is specific genetic testing available for susceptibility to periodontal disease, and the most common HPV infections known to more frequently progress to cancer- HPV16/18. Genetic tests are not appropriate for all patients and for all conditions.

CLINICAL EVIDENCE

HPV Related Oral Cancer

Castellsagué et al (2016) conducted a large international study to estimate fractions of head and neck cancers (HNCs) attributable to human papillomavirus (HPV-AFs) using six HPV-related biomarkers of viral detection, transcription, and cellular transformation. Formalin-fixed, paraffin-embedded cancer tissues of the oral cavity (OC), pharynx, and larynx were collected from pathology archives in 29 countries. All samples were subject to histopathological evaluation, DNA quality control, and HPV-DNA detection. Samples containing HPV-DNA were further subject to HPV E6*I mRNA detection and to p16 (INK4a), pRb, p53, and Cyclin D1 immunohistochemistry. Final estimates of HPV-AFs were based on HPV-DNA, HPV E6*I mRNA, and/or p16 (INK4a) results. A total of 3680 samples yielded valid results: 1374 pharyngeal, 1264 OC, and 1042 laryngeal cancers. HPV-AF estimates based on positivity for HPV-DNA, and for either HPV E6*I mRNA or p16 (INK4a), were 22.4%, 4.4%, and 3.5% for cancers of the oropharynx, OC, and larynx, respectively, and 18.5%, 3.0%, and 1.5% when requiring simultaneous positivity for all three markers. HPV16 was largely the most common type. Estimates of HPV-AF in the oropharynx were highest in South America, Central and Eastern Europe, and Northern Europe, and lowest in Southern Europe. Women showed higher HPV-AFs than men for cancers of the oropharynx in Europe and for the larynx in Central-South America. HPV contribution to HNCs is substantial but highly heterogeneous by cancer site, region, and sex. This study, the largest exploring HPV attribution in HNCs, confirms the important role of HPVs in oropharyngeal cancer and drastically downplays the previously reported involvement of HPVs in the other HNCs.

Chai et al (2016) Human papilloma virus-16 (HPV-16) infection is a major risk factor for a subset of head and neck squamous cell carcinoma (HNSCC), in particular oropharyngeal squamous cell carcinoma (OPSCC). Current techniques for assessing the HPV-16 status in HNSCC include the detection of HPV-16 DNA and p16 (INK4a) expression in tumor tissues. When tumors originate from hidden anatomical sites, this method can be challenging. A non-invasive and cost-effective alternative to biopsy is therefore desirable for HPV-16 detection especially within a community setting to screen at-risk individuals. The present study compared detection of HPV-16 DNA and RNA in salivary oral rinses with tumor p16 (INK4a) status, in 82 HNSCC patients using end-point and quantitative polymerase chain reaction (PCR). Of 42 patients with p16 (INK4a)-positive tumours, 39 (sensitivity = 92.9 %, PPV = 100 % and NPV = 93 %) had oral rinse samples with detectable HPV-16 DNA, using end-point and quantitative PCR. No HPV-16 DNA was detected in oral rinse samples from 40 patients with p16 (INK4a) negative tumours, yielding a test specificity of 100 %. For patients with p16 (INK4a) positive tumours, HPV-16 mRNA was detected using end-point reverse transcription PCR (RT-PCR) in 24/40 (sensitivity = 60 %, PPV = 100 % and NPV = 71 %), and using quantitative RT-PCR in 22/40 (sensitivity = 55 %, PPV = 100 % and NPV = 69 %). No HPV-16 mRNA was detected in oral rinse samples from the p16 (INK4a)-negative patients, yielding a specificity of 100 %. The authors demonstrated through this study, that the detection of HPV-16 DNA in salivary oral rinse is indicative of HPV status in HNSCC patients and can potentially be used as a diagnostic tool in addition to the current methods.

Rettig et al (2015) conducted a prospective cohort study to determine whether HPV DNA detection in oral rinses after treatment for HPV-OPC is associated with recurrence and survival. Although HPV-OPC has favorable prognosis, 10% to 25% of HPV-OPCs recur. Detection of human papillomavirus (HPV) DNA in oral rinses is associated with HPV-OPC, but its potential as a prognostic biomarker is unclear. Patients with incident HPV-OPC diagnosed from 2009 to 2013 at 4 academic tertiary referral cancer centers in the United States. Oral rinse samples were collected at diagnosis and after treatment (9, 12, 18, and 24 months after diagnosis), and evaluated for HPV DNA. Among an initial cohort of 157 participants with incident HPV-OPC treated with curative intent, 124 had 1 or more posttreatment oral rinses available and were included in this study. Disease-free survival (DFS) and overall survival (OS) were estimated by the Kaplan-Meier method, and the association of HPV DNA detection in oral rinses with survival was evaluated using Cox regression analysis. Oral HPV type 16 (HPV16) DNA was common at diagnosis (67 of 124 participants [54%]). In contrast, oral HPV16 DNA was detected in only 6 participants after treatment (5%), including 5 with HPV16 DNA also detected at diagnosis (persistent oral HPV16 DNA). Two-year DFS and OS were 92% (95% CI, 94%-100%) and 98% (95% CI, 93%-99%). Persistent oral HPV16 DNA was associated with worse DFS (hazard ratio, 29.7 [95% CI, 9.0-98.2]) and OS (hazard ratio, 23.5 [95% CI, 4.7-116.9]). All 5 participants with persistent oral HPV16 DNA developed recurrent disease, 3 with local disease involvement. In contrast, just 9 of 119 participants (8%) without persistent oral HPV16 DNA developed recurrent disease, only 1 (11%) with local disease involvement. Median (range) time from earliest posttreatment oral HPV16 DNA detection to recurrence was 7.0 (3.7-10.9) months. Human papillomavirus type 16 DNA in oral rinses is common at diagnosis but rare after treatment for HPV-OPC. The authors concluded that although infrequent, persistent HPV16 DNA in posttreatment oral rinses is associated with poor prognosis and is a potential tool for long-term tumor surveillance, perhaps more so for local recurrence.

Periodontal Disease

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 metaanalysis forest plot showed that MIP-1a was the best marker evaluated. Conclusions 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.

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.

Giannobile et al (2013) Prevention reduces tooth loss, but little evidence supports biannual preventive care for all adults. The authors used risk-based approaches to test tooth loss association with 1 vs. 2 annual preventive visits in high-risk (HiR) and low-risk (LoR) patients. Insurance claims for 16 years for 5,117 adults were evaluated retrospectively for tooth extraction events. Patients were classified as HiR for progressive periodontitis if they had ≥ 1 of the risk factors (RFs) smoking, diabetes, interleukin-1 genotype; or as LoR if no RFs. LoR event rates were 13.8%

and 16.4% for 2 or 1 annual preventive visits (absolute risk reduction, 2.6%; 95%CI, 0.5% to 5.8%; $p = .092$). HiR event rates were 16.9% and 22.1% for 2 and 1 preventive visits (absolute risk reduction, 5.2%; 95%CI, 1.8% to 8.4%; $p = .002$). Increasing RFs increased events ($p < .001$). Oral health care costs were not increased by any single RF, regardless of prevention frequency ($p > .41$), but multiple RFs increased costs vs. no ($p < .001$) or 1 RF ($p = .001$). For LoR individuals, the association between preventive dental visits and tooth loss was not significantly different whether the frequency was once or twice annually. A personalized medicine approach combining gene biomarkers with conventional risk factors to stratify populations may be useful in resource allocation for preventive dentistry (ClinicalTrials.gov, NCT01584479). (Participants in this involved several employees of Interleukin Genetics).

Karimbux et al (2012) conducted a systematic review and meta-analysis in an attempt to clarify whether IL-1 gene variants were associated with well-defined clinical phenotypes of chronic periodontitis (CP) in white patients. Study inclusion criteria focused on the analytic framework originally proposed for the IL-1 genetic effect in which overexpression of inflammatory mediators is hypothesized to result in more severe periodontitis in response to a bacterial challenge. Interleukin-1 (IL-1) gene polymorphisms have been associated with increased levels of inflammatory mediators and several inflammatory diseases. Periodontitis is a bacterially induced chronic inflammatory disease that destroys the connective tissues and bone that support the teeth, affects substantial numbers of adults, and has been implicated as a contributing factor in systemic diseases. IL-1 gene polymorphisms, most prominently IL1A (-889), IL1A (+4845), and IL1B (+3954), have been associated with CP in whites. Since the first report, ≥ 125 studies have examined IL-1 gene variation in relation to periodontal disease. These studies have produced mixed findings in diverse periodontal phenotypes and in different ethnic groups. One previous meta-analysis has been published on this topic and supported an association between IL-1 genes and periodontitis, but considerable doubt remains about the patient populations in which the association may be of clinical relevance. Twenty-seven studies were included in the qualitative analysis. Nineteen studies yielded significant associations between carriage of the minor IL-1 alleles and periodontitis. The meta-analysis, based on 13 qualifying studies, found significant effects for the two individual gene variations (IL1A odds ratio [OR] = 1.48; IL1B OR = 1.54) and for a composite genotype that combines minor alleles at each locus (OR = 1.51). Statistically significant heterogeneity was found that could not be explained, but there was no indication of publication bias. The authors concluded that this this review and meta-analysis shows that IL1A and IL1B genetic variations are significant contributors to CP in whites. (Participants in this systematic review and meta-analysis involved several employees of Interleukin Genetics. Additionally, Interleukin Genetics provided an unrestricted grant to fund this review).

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.

Professional Societies

American Dental Association (ADA) Council on Scientific Affairs

HPV Related Oral Cancer

Summary: The rising incidence of oropharyngeal cancer, specifically oropharyngeal squamous cell carcinoma (OSCC) associated with human papillomavirus (HPV), is a significant concern for the health care community. Over the past quarter-century, HPV infection has become firmly established as an etiologic risk factor for cancers of the oropharynx, specifically those of the tonsils and the base of the tongue. Based on data from U.S. cancer registries, an estimated 63 percent of oropharyngeal cancers each year — or over 11,000 cases — are associated with HPV infection. The ADA Council on Scientific Affairs encourages dentists to educate themselves and their patients about the relationship between HPV and oropharyngeal cancer, especially the growing prevalence of these cancers in younger non-smokers and non-drinkers. Further research is required to improve understanding of the natural history of oral HPV infection, transmission risks, screening/testing, and the predictive value of a positive HPV test for the subsequent development of oropharyngeal cancer (ADA 2012).

Genetics and Oral Health

A predictive test for dental caries or for periodontal disease does not currently exist. Since these are both complex diseases with multiple gene and environmental risk factors, quantifying risk will require multifaceted assessment. Similar to the situation with 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 (ADA 2017).

National Cancer Institute (NCI)

Based on case-controlled and cohort studies, (including one conducted using data collected prospectively (nested case-control study) the NCI has concluded the following:

- Factors with adequate evidence of an increased risk of oropharyngeal cancer human papillomavirus (HPV) infection:
 - Based on solid evidence, HPV 16 infection causes oropharyngeal cancer. HPV 16 is a sufficient but not necessary cause. Other high-risk HPV subtypes, including HPV 18, have been found in a small percentage of oropharyngeal cancers.
 - Tobacco and alcohol use does not appear to be associated with increased risk among people with evidence of HPV 16 L1 seropositivity or oral HPV 16 infection.
 - Oral infection with HPV 16 confers about a 15-fold increase in risk relative to individuals without oral HPV 16 infection.

United States Preventive Services Task Force (USPSTF)

Summary: Oral and oropharyngeal cancer have different causes. Oral cavity cancer is predominantly caused by tobacco and alcohol use. Oropharyngeal cancer, another subset of neck and head cancer, includes human papillomavirus (HPV) as an important risk factor. The incidence and mortality rate of oral cancer has been decreasing in the United States presumably because of reduced tobacco and alcohol use. However, HPV-related oropharyngeal cancer is increasing in incidence. If HPV continues to become a more clinically significant risk factor for oropharyngeal cancer, the benefits of screening for HPV and selection of populations for oral cancer screening based on HPV status will need to be assessed. As the epidemiology evolves, the most effective screening examination will need to be determined. The epidemiology of HPV-related oropharyngeal cancer is evolving and could have important implications for identifying high-risk populations that might benefit from screening.

The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of screening for oral cancer in asymptomatic adults by primary care providers. Although there is interest in screening for oral HPV infection, medical and dental organizations do not recommend it. Currently, no screening test for oral HPV infection has been approved by the U.S. Food and Drug Administration (FDA). Evaluating the accuracy of tests that detect oral HPV infection is a potentially promising area of research.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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

- MyPerioID[®] (OralDNA Labs),
- OraRisk[®] HPV,
- Complete genotyping (Oral DNA 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 November 14, 2017)

Information regarding regulation of Laboratory Developed Tests may be found here:

<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm> (Accessed November 14, 2017)

REFERENCES

American College of Medical Genetics and Genomics, Clinical utility of genetic and genomic services: a position statement. February 2015.

American Dental Association Council on Scientific Affairs, Statement on Human Papillomavirus and Squamous Cell Cancers of the Oropharynx. November 2012.

American Dental Association Genetic Testing Work Group, Council on Scientific Affairs. Oral Health Topics. September 2017

Castellsagué X, Alemany L, Quer M, et al. HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients. J Natl Cancer Inst. 2016 Jan 28; 108

Chai RC, Lim Y, Frazer IH, et al. A pilot study to compare the detection of HPV-16 biomarkers in salivary oral rinses with tumour p16 (INK4a) expression in head and neck squamous cell carcinoma patients. BMC Cancer. 2016 Mar 3; 16:178

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

Diehl SR, Kuo F et al. Interleukin 1 genetic tests provide no support for reduction of preventive dental care. J Am Dent Assoc. 2015 Mar; 146(3):164-173

Giannobile WV, Braun TM, Caplis AK, et al. Patient stratification for preventive care in dentistry. J Dent Res. 2013 Aug; 92(8):694-701.

Karimbux NY, Saraiya VM, Elangovan S, et al. Interleukin-1 gene polymorphisms and chronic periodontitis in adult whites: a systematic review and meta-analysis. J Periodontol. 2012 Nov; 83(11):1407-19

National Cancer Institute: Oral Cavity and Oropharyngeal Cancer Prevention. Updated 2/4/2016.

Rettig EM, Wentz A, Posner MR, et al. Prognostic Implication of Persistent Human Papillomavirus Type 16 DNA Detection in Oral Rinses for Human Papillomavirus-Related Oropharyngeal Carcinoma. JAMA Oncol. 2015 Oct; 1(7):907-15.

United States Preventive Services Task Force. Final Recommendation Statement Oral Cancer: Screening. November 2013. Available at:

Yücel OO, Berker E, Mescil L, et al. Association of interleukin-1 beta (+3954) gene polymorphism and gingival crevicular fluid levels in patients with aggressive and chronic periodontitis. Genet Couns. 2013; 24(1):21-35

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2018	<ul style="list-style-type: none">Updated supporting information to reflect the most current clinical evidence, FDA information and references; no change to coverage rationale or list of applicable codesArchive previous policy version DCP036.01