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Salivary Testing

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Related Policies (if applicable)
OB402.023 Services for Infertility and Recurrent Fetal Loss

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

EXCEPTION: For Illinois only: Illinois Public Act 103-0445 (HB 3202 Saliva Cancer Screening) requires coverage for medically necessary home saliva cancer screening every 24 months if the patient is asymptomatic and at high risk for the disease being tested for, or if the patient demonstrates symptoms of the disease being tested for at a physical exam. This mandate applies to the following lines of business: Individual PPO/HMO/POS; Fully Insured and Non-ERISA Small Group, Mid-Market, Large Group, Municipalities/Counties/Schools, State Employee PPO/HMO/POS amended, delivered, issued, or renewed on or after January 1, 2025.

Late night salivary cortisol testing **is considered medically necessary** for diagnosing Cushing's Syndrome.

Salivary tests **are considered experimental, investigational and/or unproven**, for all other indications, including but not limited to:

- Serial monitoring of estradiol and progesterone levels to detect/predict ovulation during the menstrual cycle;
- Serial monitoring of salivary estriol levels as a technique of risk assessment of preterm labor or delivery;
- Diagnosing or monitoring for the evaluation and management of menopause and aging;
- Chronic kidney disease;
- Laryngopharyngeal reflux disease (LPRD) or gastro-esophageal reflux disease (GERD);
- Cancer, including but not limited to, oral cancer, head and neck cancer, breast cancer;
- Diagnosis and screening for the risk of developing periodontal disease.

Home saliva cancer screening and saliva-based DNA kits, included but not limited to the following, **are considered experimental, investigational and/or unproven** (except as mandated by legislation cited above)**:**

- Viome Cancer Detect-Oral & Throat Test for diagnosis of oral cancer;
- ZRT;
- 23andMe;
- Ancestry.

NOTE 1: Laboratory tests are not covered unless they are ordered by a physician or other qualified health care professional.

NOTE 2: Information and coverage for infertility services can be found in Medical Policy Services for Infertility and Recurrent Fetal Loss, OB402.023.

Policy Guidelines

The unlisted chemistry CPT code 84999 is most commonly used for salivary testing. CPT code 82677 describing the measurement of estriol levels may also be reported. In the past this code has been used to describe measurement of estriol in the blood, urine or amniotic fluid, but the CPT code does not limit the site of collection. There are 2 HCPCS "S" codes available that measure hormone levels, S3650 (menopause) and S3652 (preterm labor).

Description

For several decades, there has been interest in testing various hormone levels using saliva as the specimen rather than blood plasma or urine. Salivary testing has been viewed as potentially more advantageous due to its noninvasive nature and the relative ease and convenience of sample collection, which can be done in the home.

Background

Saliva and other oral fluids (e.g., gingival crevicular fluid, combined secretions of minor salivary glands) support the health of soft and hard tissues in the oral cavity. Produced primarily by the

parotid, sublingual and submandibular glands, salivary fluid may contain various amounts of hormones, cytokines, antibodies, and proteins/enzymes. Many of these hormones leave the blood, penetrating through or around the salivary membranes, and diffuse into the saliva and may be detectable by testing for the hormone itself.

Early diagnosis of a disease is vital to enable early medical intervention to efficiently manage a patient and ensure the best outcome. With limitations and pressure on the current healthcare systems, there is an urgent need for non-invasive testing. Saliva represents an ideal non-invasive biofluid for detecting biomarkers because it is readily available in large quantities and analyte levels reflect those in blood. Saliva-based point of care (POC) testing is one of the best options to increase accessibility, reduce expenses through early diagnosis of diseases and enable early treatment. The transition to salivary diagnostics is attractive because while upholding current testing standards, sample collection is non-invasive and risk free when compared to blood-based methods, leading to an increase in patient compliance for testing. (1) Saliva testing has been used for detection of oral cancer such as squamous cell carcinoma, identification of infectious diseases, hormone monitoring, and screening for chronic kidney disorders. Saliva testing has facilitated an increase in research on periodontal disorders and has been used for drug level monitoring. (2)

Although saliva testing has a wide range of clinical applications, its use in clinical facilities is still limited by some intrinsic features; saliva composition (mostly water and small amounts of protein, electrolytes, urea, ammonia, glucose, free fatty acids, triglycerides, amino acids, white blood cells, epithelial cells, cytokines, nucleic acids, etc.) precludes the feasibility of coagulation tests, as well as blood cell counts and blood gas level assessment. Additionally, the cutoff for evaluating analytes and compounds in saliva differs from that of serum. On the one hand, some analytes may naturally be more concentrated in saliva than in serum, leading to an overestimation of the substance concentration in the absence of an appropriate correction coefficient; on the other hand, some saliva tests may underestimate the true titer of the analyte under investigation and interference-causing compounds (such as tea, coffee, food, etc.) can impact the testing result. (2)

Cushing’s Syndrome

Cushing's syndrome is a disorder caused by the body’s exposure to an excess of the hormone cortisol. Cortisol affects all tissues and organs in the body. These effects together are known as Cushing's syndrome. An estimated 10-15 per million people are affected every year. Cushing’s syndrome most commonly affects adults ages 20-50 and is more prevalent in females. (3) Late night salivary cortisol is one of the most sensitive diagnostic tests for Cushing’s syndrome. Elevated cortisol between 11:00 p.m. and midnight appears to be the earliest detectable abnormality in many patients with this disorder. Cortisol secretion is usually very low at this time of the day, but in patients with Cushing’s syndrome, the value is usually elevated. It is the most widely studied single test for the diagnosis of Cushing’s syndrome with many studies from all over the world demonstrating a sensitivity of 93-100% for the diagnosis of Cushing’s syndrome; however, like all the tests for Cushing’s syndrome there are many things which may cause a false positive result and additional testing is always needed. Collection of saliva requires

special sampling tubes; however, this is a very easy test for patients to perform and can be done on multiple occasions. Salivary cortisol is very stable at room temperature and the samples can be mailed to a reference laboratory. This test is now widely available. Normal levels of late night salivary cortisol usually exclude the diagnosis of Cushing's syndrome due to an adrenocorticotropic hormone (ACTH) secreting tumor; however, some patients with Cushing's caused by an adrenal tumor will have normal late-night salivary cortisol levels. (4)

Ovulation, Pre-Term Birth, Menopause

Identification of ovulation is critical for some patients determining the most fertile time of the menstrual cycle. For some women, it has been observed that fern-shaped patterns in saliva will indicate what days of the cycle ovulation may be expected.

Preterm birth is defined as a birth prior to the 37th week of pregnancy and range from 5% to 18% in industrialized and developing countries. Identification of women at risk for preterm labor has been a research focus for many years, with the hope that early intervention can prevent the progression from preterm labor to preterm birth. Current techniques include a scoring system based on a patient's past medical history (the Creasy system), home uterine activity monitoring, and measurements of fetal fibronectin collected on a cervical swab. It has also been observed that levels of salivary estriol (an estrogen hormone) surge several weeks before the onset of spontaneous preterm labor. Therefore, measurement of salivary estriol has been explored as a risk predictor for preterm labor.

Tests that measure the amount of free hormones found in the saliva of women are designed to help aid in the management of menopause, as well as other conditions related to aging. Testosterone levels have been tested in saliva for men. Occasionally salivary hormone testing is used as a baseline measurement.

Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is a condition in which the kidneys are damaged and can't filter blood as well as they should. As a result, excess fluid and waste remain in the body and may cause health problems such as heart disease. CKD usually gets worse over time, though treatment has been shown to slow progression. Research is being conducted on creatinine levels in saliva as a substitute for serum or plasma in the diagnosis of chronic kidney disease. The studies are mainly focusing on end-stage renal disease, using saliva as an alternative to glomerular filtration rate (GFR) estimation to identify individuals with CKD. (5)

Laryngopharyngeal Reflux Disease (LPRD)/Gastro-esophageal Reflux Disease (GERD)

Gastroesophageal reflux disease is a digestive disorder characterized by nausea, regurgitation, and heartburn, and is the primary cause of laryngeal symptoms, especially chronic posterior laryngitis. GERD is a common disease affecting about 10% to 40% of the Western adult population and 17% of the Asian adult population. When the stomach contents backflow into supra-esophageal, it causes extraesophageal symptoms, such as laryngopharyngeal reflux disease (LPRD), which is defined as the backflow of gastric or gastroduodenal contents into the

laryngopharynx. Approximately 50% of patients with LPRD are affected in the voice center and account for consultation of about 10% of outpatients of the ear, nose, and throat department. LPRD not only causes annoying symptoms such as hoarseness, sore throat, odynophagia, globus sensation, and throat clearing, but also may be related to reflux laryngitis, reflux asthma, dental erosion, pharyngitis, sinusitis, idiopathic lung fibrosis, and even laryngeal malignancy. Pepsin, produced in the stomach, is a specific biomarker for gastric reflux and can be detected in saliva, sputum, secretory otitis media, and in tears. Salivary pepsin measured using a lateral flow device (Pep-test) has been suggested as an indirect marker of laryngopharyngeal reflux disease (LPRD). (6)

Cancer

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells that can result in death if not treated. Although the cause of most cancers is not well understood, numerous factors are known to increase risk, including many that are potentially modifiable (e.g., tobacco use and excess body weight) and others that are not (e.g., inherited genetic mutations). These risk factors may act simultaneously or in sequence to initiate and/or promote cancer growth. According to the American Cancer Society, a little over 2 million new cancer cases are expected to be diagnosed in the United States in 2024, with approximately 611,720 deaths expected. Oral cancers, which include the tongue, mouth, pharynx, and other oral cavity, accounts for an estimated 58,450 new cases, while breast cancer accounts for an estimated 313,510 new cases in 2024. (7) Salivary biomarkers are being looked as a non-invasive approach for the early detection of oral squamous cell carcinoma (OSCC), especially for individuals in known high-risk groups such as those with oral lichen planus (OLP) and those with a previous history of OSCC who remain at risk although they have been treated and currently show no visible sign of the disease. (8) The use of saliva for breast cancer diagnosis is being examined as a tool prior to the development of clinical, histological, and radiological signs of the disease, offering a promising approach for developing personalized medicine strategies. (9)

Periodontal Disease

Periodontal disease is a chronic inflammatory disorder affecting 10-15% of the world population and is considered the greatest cause of tooth loss, causing damage to all structures that support the teeth. As it progresses, neutrophils at the site increase and, associated with macrophages, produce cytosines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and prostaglandins. During this inflammatory process, fibroblasts are stimulated by interleukin-1 and extracellular matrix metalloproteinases (MMPs) are secreted, particularly collagenase produced by polymorphonuclear neutrophils. (27) The use of saliva for disease diagnostics and surveillance has considerable potential for future diagnostic tests for oral and systemic diseases, including biosensors that could potentially provide continuous monitoring of salivary analytes associated with oral or systemic health. Extensive research, however, is still required to identify and assess oral fluid biomarkers and to validate saliva-based testing modalities for future clinical application. Challenges to the use of oral fluids for diagnostic purposes include identification of disease-specific markers, sensitivity and specificity of tests, and standardization of collection/storage of salivary samples. According to the American Dental

Association (ADA), there are no FDA-approved salivary diagnostic tests for evaluating risk of periodontal disease, dental caries, or head and neck cancer. (10)

Direct-to-Consumer Tests (DTC)

Consumers now have the ability to order home saliva tests over the internet for some hormones such as estrogen, progesterone, testosterone, melatonin, and dehydroepiandrosterone (DHEA). A physician's prescription is not required for these saliva tests, which are primarily promoted for monitoring ovulation cycles in infertility treatment or the evaluation of menopause and aging. Once the patient completes an online questionnaire to determine if saliva testing is needed, an order can be placed for the desired test. Per the U.S. Food and Drug Administration (FDA), DTC tests have varying levels of evidence that support their claims. Some tests may have a lot of scientific and clinical data supporting the information they are providing, while others do not. (11)

Regulatory Status

The U.S. Food and Drug Administration (FDA) has cleared for 510(k) marketing certain tests that use a sample of saliva and enzyme immunoassay procedures to estimate a patient's circulating cortisol levels. There were no FDA clearances for salivary testing for other hormones or indications. The FDA only regulates commercially marketed tests. Some direct-to-consumer (DTC) tests are reviewed by the FDA. In general, DTC tests for non-medical, general wellness, or low risk purposes are not reviewed by the FDA before they are offered. Those DTC tests for moderate to high-risk medical purposes, which may have a higher impact on medical care, are generally reviewed by the FDA to determine the validity of test claims. (11)

The following DTC tests relevant to this medical policy have received marketing authorization by the FDA. They have undergone an evaluation by the FDA for accuracy, reliability, and consumer comprehension.

Table 1. Direct-to-Consumer Tests with Marketing Authorization

Test Trade Name (FDA Submission Number)	Sponsor	Intended Use/Indications for Use
23andMe PGS Genetic Health Risk Test (DEN160026)	23andMe, Inc.	Uses qualitative genotyping to detect the following clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD-500.001 for the purpose of reporting and interpreting Genetic Health Risks (GHR): • The 23andMe PGS GHR Report for Celiac Disease is indicated for reporting of a variant associated with the HLA-DQ2.5 haplotype. The report describes if a person has a haplotype associated with an increased risk of developing celiac disease, but it does not describe a person's overall risk for

		developing celiac disease. This report is most relevant for people of European descent. **NOTE**: There are other Genetic Health Risk Reports available under this test not addressed by this medical policy.
23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) (DEN170046)	23andMe, Inc.	Uses qualitative genotyping to detect select clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD500.001 for the purpose of reporting and interpreting genetic health risks, including the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants). The report describes if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer. The three variants included in this report are most common in people of Ashkenazi Jewish descent and do not represent the majority of the BRCA1/BRCA2 variants in the general population. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This test is not a substitute for visits to a health care provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

(Adapted from U.S. Food and Drug Administration [11])
FDA: U.S. Food and Drug Administration; PGS: Personal Genome Service.

Rationale

This policy was created in 2004 and updated regularly with searches of the PubMed database. The most recent literature search is through May 2024.

Use in Diagnosing Cushing's Syndrome
Cushing's syndrome (CS) is defined as chronic excess free cortisol in circulation. According to recent studies, midnight salivary cortisol is an accurate and non-stress method for screening and diagnosing Cushing's syndrome. Salivary hormone testing for cortisol may be utilized as part of a two-step process to screen for and diagnose Cushing's disease. If screening tests are positive, confirmatory tests are then performed. Carroll et al. (2009) published a meta-analysis

of late night salivary cortisol (LNSC) testing for the diagnosis of Cushing syndrome. (12) Medline and Embase computer databases were searched to identify relevant articles published between January 1950 and December 2007. Seven articles contained sufficient information to be included in the analysis. A total of 947 patients (339 with Cushing syndrome) were identified. Pooled data from the 7 studies revealed a sensitivity of 92% (95% confidence interval [CI], 88%-94%), specificity of 96% (95% CI, 94%-97%), and diagnostic odds ratio of 311 (95% CI, 92-1059). Likelihood ratio positive was 21 (95% CI, 10-43), with a likelihood ratio negative of 0.08 (95% CI, 0.02-0.32). Inconsistencies for each of these results measured by the I^2 statistic ranged from moderate to high. This analysis demonstrated that late night salivary cortisol had excellent diagnostic characteristics and as such, is a robust, convenient test for screening and diagnosis of Cushing syndrome.

In 2008, Doi et al. conducted a study to evaluate the usefulness of the measurement of late night salivary cortisol as a screening test for the diagnosis of CS in Japan. (13) They studied 27 patients with various causes of CS, consisting of adrenocorticotropic hormone (ACTH)-dependent Cushing's disease and ectopic ACTH syndrome and ACTH-independent adrenal CS and subclinical CS. Eleven patients with type 2 diabetes and obesity and 16 normal subjects served as control group. Saliva samples were collected at late-night (23:00) in a commercially available device and assayed for cortisol by radioimmunoassay. There were highly significant correlations (P<0.0001) between late-night serum and salivary cortisol levels in normal subjects (r = 0.861) and in patients with CS (r = 0.788). Late-night salivary cortisol levels in CS patients (0.975 +/- 1.56 microg/dl) were significantly higher than those in normal subjects (0.124 +/- 0.031 microg/dl) and in obese diabetic patients (0.146 +/- 0.043 microg/dl), respectively. Twenty-five out of 27 CS patients had late-night salivary cortisol concentrations greater than 0.21 microg/dl, whereas those in control group were less than 0.2 microg/dl. Receiver operating characteristic curve (ROC) analysis showed that the cut-off point of 0.21 microg/dl provides a sensitivity of 93% and a specificity of 100%. Therefore, it is concluded that the measurement of late night salivary cortisol is an easy and reliable noninvasive screening test for the initial diagnosis of CS, especially useful for large high-risk populations, such as diabetes and obesity.

In 2013, Doi et al. found LNSC measurements to be concordant with the 24-hour urine test, with 97% concordance at ≥4 nmol/L and 69% concordance at ≥10 nmol/L. The two tests become equivalent at the more sensitive cutoff (>4 nmol/L). (14) The authors conclude that, given its many benefits and the currently documented equivalence to the urinary free cortisol (UFC), the LNSC should replace the conventional 24-h UFC as the frontline test when screening for CS.

Section Summary

A meta-analysis in addition to the smaller sample size studies corroborate that late night salivary cortisol testing is a reliable and convenient test for diagnosing of Cushing syndrome.

Use in Ovulation Detection or Prediction

Prediction of ovulation has been used as a method to avoid pregnancy for many years. Within the last several decades, devices to detect and predict ovulation have become more readily available to consumers for home use to determine the most fertile time of the menstrual cycle to maximize outcome of conceiving. At that time, multiple studies compared urine or blood to saliva samples to detect estradiol and progesterone confirming ovulation, the luteal phase, and changes within the woman's body during the menstrual cycle. (15-17) Recent studies are small, completed in controlled environments or lifestyles (non-smoking, healthy, medication-free, and middle-income, etc.). However, the standard evaluation of basal body temperature, urinary luteinizing hormone, and urinary estrone-3-glucuronide are the more reliable detection and predictive methods.

Section Summary

The lack of recent evidence in scientific literature and ongoing clinical studies do not permit conclusions in the utility of salivary hormonal testing to detect or predict ovulation during the menstrual cycle. Therefore, the use of serial monitoring of estradiol and progesterone levels to detect/predict ovulation during the menstrual cycle is considered experimental, investigational and/or unproven.

Use in Preterm Labor

In 1999, Heine et al. reported on a study that the use of biweekly salivary estriol determinations evaluating the predictive value of salivary estriol for preterm labor when compared to the Creasy system. (18) Of the original 714 patients with evaluable data, 113 were excluded, including 35 patients treated with betamethasone and 55 patients with preterm labor, but delivered at term. In the remaining patients, only 23 experienced preterm labor, and thus 4 times as many patients with preterm labor were excluded as were included. The incidence of preterm labor in the evaluated patients was only 4%, less than half the incidence commonly reported in other series. This low incidence falsely elevates the negative predictive value of salivary estriol testing, because the predictive value of a test depends on the incidence of the disease in the population studied. A negative salivary estriol test resulted in a minimal change in the negative predictive value, from a baseline of 96% for the whole study population to 98% for the subset with negative tests. In addition, the test is not very sensitive, ranging from 42% to 64%, depending on the subgroup studied and the criteria for a positive test.

In addition, this study did not present the data separately for asymptomatic patients and those with possible symptoms of preterm labor. Thus, the sensitivity and specificity of salivary estriol testing is unknown in the context of the asymptomatic patient, the patient with some symptoms suggestive of preterm labor, or the patient who meets criteria for hospitalization and tocolysis. The data presented in Heine's study apply to the average patient (both asymptomatic and symptomatic), and the estimates of preterm labor risk would undoubtedly be revised upward or downward based on the patient's clinical status at the time of the test. Thus, the risk estimated by salivary estriol testing may be misleading or less accurate than a clinical assessment based on physical examination at the same time. Without this information, it is impossible to evaluate the use of testing in specific clinical situations where a positive or negative test might make an important difference in the management of the patient.

Beneficial outcomes for those correctly identified to have preterm labor might include a reduction in the incidence of preterm labor or birth, or both; decrease in the incidence of hospitalization in the neonatal intensive care unit (NICU); or degree of cervical dilation at the time of diagnosis of preterm labor.

The data reported in 1999 by Heine et al. (18), which was published in a supplemental issue of a journal, was published again in 2000 (19).

Section Summary

Since the publication of this one study, the lack of recent evidence in scientific literature and the absence of clinical studies do not permit conclusions in the safety and utility of salivary hormonal testing in preterm labor. Therefore, the use of serial monitoring of salivary estriol levels to monitor for preterm labor or delivery is considered experimental, investigational and/or unproven.

Use in Treatment of Menopause and Aging

In the results of a clinical trial reported by Flyckt et al. in 2009 (20), the study compared salivary versus serum measurement of total testosterone (total T [TT]), bioavailable testosterone (BT; consisting of free T [FT] and albumin-bound T), and FT from samples collected simultaneously in women who were either receiving transdermal testosterone patch supplementation (300 microg/d) or a placebo patch. There was no correlation of salivary testosterone levels with any of the serum testosterone subtype levels. The authors concluded "Although salivary testing of T-concentrations is an appealing alternative because it is inexpensive and noninvasive, our results do not support the routine use of salivary T levels in postmenopausal women."

Kobori et al. (2009) (21) tested serum and saliva samples for testosterone and cortisol in 103 men aged 32-72 years who were not taking hormone medication. Questionnaires were distributed regarding sexual dysfunction and depression. Serum levels of testosterone were inversely correlated with age. In patients not taking anti-depressants, there was an inverse association between serum bioavailable cortisol/saliva cortisol and ratings of sexual dysfunction. The authors concluded the active forms of cortisol (Bio-F and Sa-F) showed negative correlations with sexual function in men who did not take psychotropic drugs, although there was no such correlation for testosterone. Erectile dysfunction is thought to occur in patients with high levels of cortisol because of the relations between cortisol and stress. Cortisol may thus become a useful index for the evaluation of sexual function.

Section Summary

The lack of recent evidence in scientific literature and the ongoing clinical studies do not permit conclusions in the utility of salivary hormonal testing to manage menopause or imbalances of hormones in aging. Therefore, the use of diagnosing or monitoring for the evaluation and management of menopause and aging is considered experimental, investigational and/or unproven.

Chronic Kidney Disease

Temilola et al. (2019) (5) published the results of a study evaluating the use of salivary creatinine as a safe and non-invasive alternative for identifying patients with chronic kidney disease (CKD). A cross-sectional study was conducted on 230 patients across all stages of CKD. An estimated 40 participants in each stage were initially set; and the number of participants included in stages 1, 2 and 3 was increased to 50 each as these stages were the most prevalent. Stages 4 and 5 included 40 participants each. CKD staging was based on participants' estimated glomerular filtration rate (GFR [eGFR]). Those with evidence of kidney disease for more than 3 months with GFR greater or equal to 90 mL/min/1.73 m were classified into stage 1; GFR between 60 and 89 mL/min/1.73 m were classified into stage 2; GFR between 30 and 59 mL/min/1.73 m was classified into stage 3; GFR between 15 and 29 mL/min/1.73 m was classified into stage 4 and those with GFR less than 15 mL/min/1.73 m were classified into stage 5. Patients on dialysis were excluded from the study. Saliva samples were obtained from each participant, followed immediately by blood draws. The ranges of serum and salivary creatinine values were 46–1581 µmol/L and 3–400 µmol/L, respectively. There was a strong positive correlation (r = 0.82) between serum and salivary creatinine when considering all samples, and a moderate correlation for patients in CKD stages 2 to 5. It was determined 8.50 µmol/L was the best cut-off value to diagnose CKD based on a GFR value < 60 mL/min/1.73 m. This cut-off point yielded a sensitivity of 78.3% (false negative rate 21.7%), a specificity of 74.0% (false positive rate 26%) and a positive predictive value (PPV)of 79.6%. The authors concluded salivary creatinine concentrations above 8.50 µmol/L may identify patients with CKD and should prompt referral for further diagnostic evaluation. Noted limitations in the study include the use of estimated GFR for evaluating renal function, rather than measured GFR as determined by the clearance of iohexol or other exogenous makers. Only a single salivary sample was taken from each patient, and there was an absence of healthy controls. Additional studies are needed to test the utility of salivary creatinine in these settings where most of the subjects would be expected to have normal or near-normal concentrations of serum creatinine. Future studies should investigate whether salivary creatinine is correlated with other clinical and laboratory parameters.

Poposki et al. (2023) (22) examined the possibility of using saliva as a diagnostic and prognostic tool for screening and monitoring kidney function. This study included 32 patients with different stages of chronic kidney disease (CKD) and 20 healthy individuals for the control group. Saliva was collected using the spitting method, and on the same day blood was also drawn to determine serum concentrations of urea and creatinine. The salivary values of uric acid, urea, creatinine, and albumin were determined with a spectrophotometer, as well as the serum concentrations of urea and creatinine. Results showed a statistically significant positive correlation between salivary and serum levels of urea and creatinine in patients with CKD (Pearson's correlation coefficient for urea was r = 0.6527, p = 0.000, while for creatinine it was r = 0.5486, p = 0.001). They detected a statistically significant positive correlation between the salivary levels of urea and the clinical stage of CKD (r = 0.4667, p = 0.007). The authors did not register a significant correlation between the salivary levels of creatinine and the clinical stage of CKD (r = 0.1643, p = 0.369). They concluded salivary urea is a valid marker for determining kidney function and a potential salivary marker for screening and monitoring kidney function.

Salivary creatinine can be used as a qualitative marker, only indicating the existence of a disease. Additional clinical trials are needed to determine the diagnostic value of uric acid determination in patients with CKD.

Section Summary

The lack of recent evidence in scientific literature and the ongoing clinical studies do not permit conclusions in the utility of salivary testing for the diagnosis of chronic kidney disease (ckd). Therefore, the use of salivary testing in the diagnosis of CKD is considered experimental, investigational and/or unproven.

Laryngopharyngeal reflux or gastro-esophageal reflux disease (GERD)

In 2016, Dy et al. reported on a cross-sectional study of 50 children aged 1-19 years undergoing pH-multichannel intraluminal impedance (pH-MII) and esophagogastroduodenoscopy (EGD) for the evaluation of gastroesophageal reflux disease (GERD). (23) Patients were excluded if they had undergone fundoplication or had prior esophageal or gastric surgery. Recruited patients were asked to provide a random saliva sample for pepsin testing. Alternatively, for young patients who were unable to spontaneously produce a salivary sample, a saliva aspirate was obtained from the oropharynx. All samples were obtained after a minimum 2 hour period of fasting, prior to pH-MII testing. Patients or their guardians completed a baseline symptom questionnaire as well as 2 validated questionnaires, the Pediatric Quality of Life Questionnaire (PedsQL) and the Pediatric GERD Symptom and Quality of Life Questionnaire (PGSQ). Eleven patients (22%) had abnormal impedance studies and 19 patients (38%) had abnormal pH monitoring. Twenty-four patients (48%) remained on acid suppression therapy while undergoing pH-MII testing; there was no significant difference across reflux variable between patients who were on and off these medications ($p>0.05$). Twenty-one patients (42%) had pepsin detected in their saliva. There were no differences in the number of patients with abnormal pH testing (pepsin positive 38% versus pepsin negative 38%, P=0.99) or abnormal MII testing (pepsin positive 29% versus pepsin negative 17%, P=0.49). No differences in reflux profiles between pepsin positive and negative patients were found. Patients who were pepsin positive were less likely to have a history of recent cough compared with pepsin negative patients (57% versus 89%, P=0.01), but no other differences in extraesophageal symptoms and quality of life scores were found. The use of a positive PepTest® for predicting abnormal pH-MII testing (defined as either abnormal pH or MII measurements) resulted in 42% sensitivity, 58% specificity, and 50% accuracy. Pepsin concentrations were lower among patients with a recent history of daily chronic cough than those without cough [median (IQR): 0 (0,10) versus 18 (5, 49), P=0.007]. No other differences were found. There was no significant relationship between pepsin concentration and the number of acid ($r = 0.06$, P=0.67), nonacid ($r = 0.11$, P=0.46), pH only ($r = -0.10$, P=0.47) and total ($r = 0.14$, P=0.32) reflux events. There was also no significant correlation between pepsin concentration and the % of total proximal reflux ($r = 0.02$, P=0.88), % proximal acid reflux ($r = 0.09$, P=0.55) or proximal nonacid reflux ($r = 0.02$, P=0.88). Salivary pepsin detection using an immunoassay has been proposed as a rapid, convenient, noninvasive, and easily-interpretable means of diagnosing GERD – particularly as it relates to extraesophageal symptoms. However, based on this study, single-point-in-time salivary pepsin does not appear to correlate well with pathologic reflux by pH-MII testing in children.

Additional studies are still needed to determine if repeated salivary sampling increases the sensitivity of the test or if a different reference standard for extraesophageal reflux needs to be considered.

A multicenter, non-interventional pilot study by Bozzani et al. (2020) (24) was conducted on 86 suspected patients of laryngopharyngeal reflux (LPR) and 59 asymptomatic individuals as controls. A reflux symptom index questionnaire was used to differentiate patients with LPR (score >13) from controls (score <5). Two saliva samples were collected, and comparisons between the groups were performed using 2-sided statistical tests, according to variable distributions. Pep-test analysis was performed by trained staff. The prevalence of pepsin positivity in at least one expectorated post-prandial saliva sample was 76% in LPR (65/86) and 88% (52/59, 37/42 in GERD impact scale [GIS]=36 subgroup) in controls (P=0.059). Pepsin was present in both the collected samples in 56% (36/66) of LPR subjects and in 56% (25/45) or 61% (22/36 in GIS=36 subgroup) of controls (P=0.916). The data showed a high prevalence of positive Pep-test in healthy controls (higher than in LPR subjects). Therefore, the findings demonstrate that there was no difference in the prevalence of pepsin positivity between patients with suspected LPR symptoms and asymptomatic control subjects. Moreover, the concentration of pepsin did not change. Performing a salivary pepsin test alone is not recommended for LPR diagnosis in the primary care setting, and further invasive and accurate diagnostic tests are required to confirm the diagnosis of GERD.

A prospective observational study by Ma et al. (2023) aimed to assess diagnostic performance of salivary pepsin thresholds for GERD and determine optimal collection protocol of saliva in an external validation cohort. (25) Over 10 months, twenty adults with symptoms of GERD undergoing esophagogastroduodenoscopy with wireless pH-monitoring off proton pump inhibitors (PPI) were enrolled, with 18 participants completing the entire protocol. Saliva was self-collected by participants over 4 days across three different time points: fasting ante meridiem (AM), post-prandial, and bedtime (PM). Pepsin levels were calculated via PepTest. Pepsin variability and agreement were determined using linear mixed effects models and intraclass correlation. Validation of diagnostic threshold and performance characteristics were evaluated by receiver–operator curve analysis. Twenty participants enrolled in the study; 50% with physiologic acid exposure (acid exposure time < 4% no GERD) and 50% with elevated acid exposure (GERD). Mean pepsin concentrations were significantly lower in the AM (22.6 ± 25.2 ng/mL) compared to post-prandial (44.5 ± 36.7 ng/mL) and PM (55.4 ± 47.0 ng/mL). Agreement between pepsin concentrations across 3 days was substantial for AM samples (kappa 0.61), with lower agreement for post-prandial and PM samples. A single AM pepsin concentration of 25 ng/mL was 67% accurate for GERD with 56% sensitivity and 78% specificity. This validation study highlights fair accuracy and performance characteristics of a single fasting AM salivary pepsin concentration for the diagnosis of GERD. Although additional studies need to be done, salivary pepsin currently shows comparable performance characteristics to commonly used noninvasive diagnostic methods with the additional benefit of objective data and the avoidance of unnecessary medication trials.

Section Summary

Several small studies have looked at the use of salivary pepsin levels to diagnose laryngopharyngeal reflux (LPR) and/or gastroesophageal reflux disease (GERD). Data is conflicting as to the benefit of salivary pepsin testing as a means of diagnosing LPR or GERD. Therefore, the use of salivary pepsin to diagnose LPR and/or GERD is considered experimental, investigational and or unproven.

Cancer

Benito-Ramal et al. (2023) published the results of a systematic review and meta-analysis assessing whether the cytokines IL-6, IL-8, and TNF-α were potential salivary biomarkers that allow early diagnosis of cancer. (26) They looked at 23 articles for the systematic review and 15 for the meta-analysis and observed that the majority of oral squamous cell carcinoma (OSCC) patients express higher salivary concentrations of interleukin-6, interleukin-8 (IL-6, IL-8) and tumor necrosis factor alpha (TNF-α) compared to the control (CL) and premalignant lesion (OPML) groups. They also found that the different premalignant lesions do not have statistically significant differences in the salivary concentrations of cytokines, and differences were observed between the different tumor/node/metastasis (TNM) stages. The meta-analysis has shown that the difference in concentration of IL-6, IL-8 and TNF-α is statistically significant between the CL group and the OSCC, and between the CL group and OPML. Based on their review, the authors felt there is sufficient evidence to affirm IL-6, IL-8 and TNF-α are useful salivary cytokines in the early diagnosis and prognosis of OSCC, and that future studies were necessary to establish greater reliability of these markers and thus develop a valid diagnostic test. Being able to develop a diagnostic test, based on the salivary concentration of any of the three cytokines analyzed, that makes it possible to detect premalignant and malignant lesions in early stages, would be a favorable development for the prevention, prognosis, and survival of oral cancer, in addition to control and follow-up, in patients treated with OSCC.

A systematic review and diagnostic meta-analysis by Koopaie et al. (2022) looked at the diagnostic value of salivary biomarkers in differentiating between patients with breast cancer (BC) and controls. (9) Their systematic review and meta-analysis included 14 papers containing 121 study units with 8639 adult subjects (4149 breast cancer patients and 4490 controls without cancer). The pooled specificity and sensitivity were 0.727 (95% confidence interval [CI]: 0.713–0.740) and 0.717 (95% CI: 0.703–0.730), respectively. The pooled negative and positive likelihood ratios (NLR and PLR) were 0.396 (95% CI: 0.364–0.432) and 2.597 (95% CI: 2.389–2.824), respectively. The pooled diagnostic odds ratio (DOR) was 7.837 (95% CI: 6.624–9.277), with the area under the curve (AUC) equal to 0.801. The Fagan's nomogram showed post-test probabilities of 28% and 72% for negative and positive outcomes, respectively. They also conducted subgroup analyses to determine specificity, sensitivity, DOR, PLR, and NLR based on the mean age of patients (≤52 or >52 years old), saliva type (stimulated and unstimulated saliva), biomarker measurement method (mass spectrometry [MS] and non-MS measurement methods), sample size (≤55 or >55), biomarker type (proteomics, metabolomics, transcriptomics and proteomics, and reagent-free biophotonic), and nations. The authors stated although a number of systematic reviews have examined the utility of saliva in the diagnosis of oral, head and neck malignancies, limited review studies on the use of salivary biomarkers for diagnosis of distant cancers, especially breast cancer, are available. One of the

main limitations is dissemination bias because studies with positive diagnostic results are more accessible than those which reveal negative findings. Another drawback is the risk of bias in small, unmatched studies, which cannot be controlled. Another limitation of this meta-analysis that could affect the results was the inclusion of studies with small sample size which could lead to higher bias risk. In addition, their analysis was potentially subject to a variety of confounders because many of the articles reviewed did not provide adequate information. For example, the majority of studies did not specify the type of BC. Moreover, only a limited number of studies provided information about tumor, node, metastasis (TNM) stage, or tobacco and alcohol use history. Many studies did not report correlation analysis between TNM stages and salivary biomarkers either. Therefore, controlled studies with larger sample sizes with clinical and demographical details of BC and matching are needed to confirm and provide additional evidence for clinical application of salivary biomarkers in BC diagnosis. The current study also has a number of strengths. The authors used systematic review and meta-analysis to unravel the value of salivary biomarkers for the BC diagnosis, a malignancy distant from the oral cavity. The analysis showed that unstimulated saliva could have higher diagnostic accuracy for BC. The results of this study suggest that combinations of transcriptomic and proteomic data, as well as clinical information, help to improve future studies and potential applications for clinical diagnosis.

Summary of Evidence

Small systematic reviews and meta-analyses looking at the use of salivary biomarkers to diagnose and differentiate between individuals with either oral cancer or breast cancer (BC) and controls without cancer, both conclude these tests are promising, but larger studies are needed. Those studies should be randomized controlled trials comparing current methods of diagnosing cancers with the use of salivary biomarkers. Therefore, the use of saliva for the diagnosis of oral cancers, including oral squamous cell carcinoma, and breast cancer, is considered experimental, investigational and/or unproven.

Periodontal Disease

Paredes-Sánchez et al. (2018) provided the results of a meta-analysis of 9 studies looking at the use of 8-hydroxy-2'-deoxyguanosine (8-OHdG) as a salivary marker of periodontal disease. (27) The criteria employed to diagnose both the presence of periodontal disease and the absence of both gingivitis and periodontitis were as follows: periodontitis when a minimum of 2 teeth had pocket depths of 4 millimeters or more, absence of gingivitis and periodontitis when the participant presented no history of periodontal disease, no gingival inflammation, and good oral hygiene. Both stimulated and unstimulated saliva samples were included in the analysis. To estimate the 8-OHdG concentration in healthy subjects, 9 studies were included in the meta-analysis. When combined, they showed high heterogeneity (Q test = 1924, $p \leq 0.001$, I^2= 99.6%). The levels of 8-OHdG in saliva of the healthy individuals were estimated as 2.42 ng/ml with a 95% confidence interval of 2.07–2.78 ng/ml. The estimated difference in mean salivary concentration of 8-OHdG between healthy subjects and patients with periodontal disease was 2.11 ng/ml, with a 95% confidence interval of 1.23–2.98, showing that the concentration was significantly higher in the periodontal disease patients (Z test = 4.70, $p \leq 0.001$). The meta-analysis presented high heterogeneity (Q test = 4188.3, $p \leq 0.001$, I^2 =99.81%). 8-Hydroxy-2'-

deoxyguanosine (8-OHdG) is formed through oxidation of guanine from damaged DNA, causing severe damage to periodontal tissues. Higher salivary 8-OHdG reflect increased oxygen radical activity during periodontal inflammation. The present review has shown that although 8-OHdG is present both in subjects with no periodontal disease and in those with this illness, its levels are significantly higher in the saliva of the periodontal disease patients. The concentration of 8-OHdG in saliva of the subjects with periodontal disease was 2.11 ng/ml higher than that of healthy subjects, almost double the concentration in the latter, with a 95% confidence interval of 1.12–2.98. The authors concluded there is clear evidence that 8-OHdG is a powerful marker of periodontal disease.

A systematic review and meta-analysis by de Brouwer et al. in 2022 looked at the possibility of tissue inhibitors of metalloproteinases (TIMPs), specifically TIMP-1, as a biomarker to monitor periodontal disease progression. (28) Of the 322 studies initially reviewed, 10 met all inclusion criteria. Two studies investigated TIMP-1 concentrations in gingival crevicular fluid (GCF), three studies in unstimulated saliva, and five studies investigated TIMP-1 concentrations in stimulated saliva. Three studies revealed that TIMP-1 levels in oral fluids were significantly decreased in periodontal disease. Meta-analysis revealed that there is no statistically significant difference between TIMP-1 concentration in oral fluids of periodontitis/gingivitis patients in comparison to healthy individuals. All selected studies were published between 2006 and 2019 and accounted for 1336 participants with a mean of 128 participants per study and an age range between 15 and 64 years. Of 597 patients suffering from periodontal disease salivary TIMP-1 levels were measured. The range of TIMP-1 concentrations varied considerably between the included studies, from 0.32 ± 0.15 ng/mL to 719 ± 24 ng/mL in periodontitis/gingivitis patients, and from 0.37 ± 0.20 ng/mL to 721 ± 24 ng/mL in healthy individuals (mean ± standard deviation [SD]). This variance was not directly related to type of oral fluid investigated, sample handling, or study population. Among the 10 included studies, a wide variety of conclusions was presented. In seven studies, TIMP-1 concentrations were lower in patients with periodontal disease than in healthy individuals, of which two found a significant difference. In three studies, theTIMP-1 values were higher in patients with periodontal disease compared to the healthy individuals, of which one study found a significant difference. Three studies found that the matrix metalloproteinase 8 (MMP-8)/TIMP-1 ratio was significant higher in periodontitis patients. The increase in MMP-8/TIMP-1 ratio in these studies was predominantly related to increased salivary MMP-8 levels in periodontitis patients and not necessarily to decreased TIMP-1 concentrations in saliva. Only one article observed a significant decrease in TIMP-1 level, whereas all three articles found a significant increase in MMP-8 concentration. Important criteria for a good biomarker are validity, reliability, and consistency. Whereas TIMP-1 plays a role in a broad set of biological processes, its concentration shows a wide variation among healthy individuals which affects the consistency and reliability of TIMP-1 as a biomarker. This is confirmed by the results presented in this systematic review with meta-analysis in which no significant changes in TIMP-1 concentrations in oral fluids were found between periodontal disease and healthy individuals. In conclusion, TIMP-1 is not a reliable biomarker for screening and diagnostic purposes of periodontal disease.

Section Summary

Two small meta-analyses have looked at either 8-hydroxy-2'-deoxyguanosine (8-OHdG) or tissue inhibitors of metalloproteinases (TIMPs), specifically TIMP-1, as potential biomarkers for periodontal disease monitoring or screening and diagnostic purposes. The authors of the review of 8-OHdG concluded there is evidence that 8-OHdG is a powerful marker of periodontal disease, while TIMP-1 shows not to be reliable as a marker for screening and diagnostic purposes. There needs to be large, preferably randomized controlled trials with consistent criteria to determine if biomarkers found in saliva are beneficial for monitoring, screening, and diagnostic purposes for periodontal disease. The use of saliva as a biomarker tool for periodontal disease is considered experimental, investigational and/or unproven.

Summary of Evidence

Late night salivary cortisol testing for use in diagnosing Cushing's syndrome, the evidence includes guideline recommendations from the Endocrine Society for the use of late-night salivary cortisol measurements for diagnosis of Cushing's syndrome. Available studies are small sample size studies, in addition to a meta-analysis that demonstrate that late night salivary cortisol testing is a reliable and convenient test for diagnosing of Cushing syndrome.

The promotion of saliva testing has been criticized. Critics cite a lack of scientific evidence supporting the use of salivary hormone levels for the determination and monitoring of hormone therapy or reduction of the risk of preterm labor and delivery. They have concluded that the claim of hormone concentrations in saliva are highly variable and may not correlate with the biological or clinical response to treatment, particularly in menopause and aging. The saliva hormone levels are inadequate to show the correlated free hormone levels found in serum samples. These variabilities render salivary hormone testing unreliable. Therefore, the medical literature fails to demonstrate that salivary testing is appropriate to screen, diagnose, or monitor patients for any condition other than diagnosing Cushing's syndrome, including assessment of ovulation, the risk of preterm labor and delivery, menopause, aging, chronic kidney disease (CKD), laryngopharyngeal reflux (LPR) or gastro-esophageal reflux disease (GERD); cancer, including but not limited to, oral cancer, head and neck cancer, breast cancer(BC); or for the diagnosis and screening for the risk of developing periodontal disease.

Professional Guidelines and Position Statements

Endocrine Society (ES)

The ES recommends a test of at least two late night salivary cortisol measurements for diagnosis of Cushing's Syndrome. (29) In UpToDate (2024), Nieman stated they are in agreement with the diagnostic approach outlined by these evidence-based 2008 ES clinical guidelines. (30)

American Association of Clinical Endocrinology (AACE)

The 2007 AACE guideline, updated July 15, 2017 (31, 32) on management of menopause recommends against the use of salivary tests for sex hormone concentrations and noted large intra-subject variability. Individualized bioidentical hormone (BH) therapy, not endorsed by the ACCE, is additionally addressed in the 2007 guideline: "Salivary hormone level testing is recommended by many BH proponents as a way of providing patients with "individualized"

therapy. Such tests are available to consumers over the Internet. Some of the websites include elaborate questionnaires supposedly designed to establish the type of saliva testing needed. The results of these tests are subsequently used to determine the type and dosage of compounded formulations. Only a few types of salivary hormone testing methods are FDA/CLIA [Clinical Laboratory Improvement Amendments] approved. In fact, the vast majority of the salivary hormone tests results contain the disclaimer that those tests are not FDA/CLIA approved and should be used only for research purposes. Yet such tests are still utilized to support clinical decisions by some supporters of BH."

American College of Obstetrics and Gynecologists (ACOG)

The 2023 ACOG Clinical Consensus on Compounded Bioidentical Menopausal Hormone Therapy states: "Data on the interpretation of adjunct hormone tests for prescribing and dosing compounded bioidentical menopausal hormone therapy are limited; thus, these tests are not recommended for these indications….As steroid hormones, estrogen and progesterone do not meet these criteria and do not require individualized testing. …Although proponents claim that salivary testing can help tailor hormone therapy, salivary testing does not offer accurate or precise assessment of hormone levels. Currently, there are no FDA-approved salivary or urinary tests for steroid hormone measurement." (33)

North American Menopause Society (NAMS)

The 2022 NAMS hormone therapy position statement (34) stated that salivary hormone testing for hormone therapy "is considered unreliable because of differences in hormone pharmacokinetics and absorption, diurnal variation, and interindividual and intraindividual variability."

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	82530, 82533, 84999, 0296U, 0429U
HCPCS Codes	S3650, S3652

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
09/15/2024	Document updated with literature review. The following changes were made to Coverage: Added chronic kidney disease, laryngopharyngeal reflux disease (LPRD) or gastro-esophageal reflux disease (GERD); cancer, including but not limited to, oral cancer, head and neck cancer, breast cancer; and periodontal disease to the list of indications considered experimental, investigational and/or unproven. Added Home saliva cancer screening and saliva-based DNA kits, included but not limited to the following, are considered experimental, investigational and/or unproven: Viome Cancer Detect-Oral & Throat Test for diagnosis of oral cancer; ZRT; 23andMe; Ancestry. NOTE 1: Laboratory tests are not covered unless they are ordered by a physician or other qualified health care professional. References 1,2, 5-11, 22-28, 33 were added; others revised, and some removed. Title changed from Salivary Hormone Testing.
05/01/2023	Reviewed. No changes.
12/01/2022	Document updated with literature review. Coverage unchanged. Reference 18 added; some updated and others removed.
09/15/2021	Reviewed. No changes.
02/01/2021	Document updated with literature review. The following change was made to Coverage: A medically necessary statement was added for late night salivary cortisol testing for diagnosing Cushing's Syndrome. References 2-4, 11-12, 15, and 21-22 were added and others updated.
10/15/2019	Reviewed. No changes.
04/01/2018	Document updated with literature review. Coverage unchanged.
01/15/2017	Reviewed. No changes.

06/15/2016	Document updated with literature review. The following was added to the experimental, investigational and/unproven coverage statement: 1) Serial monitoring of estradiol and progesterone levels to detect/predict ovulation during the menstrual cycle; and 2) Diagnosing or monitoring for the evaluation and management of menopause and aging. Title changed from Salivary Testing.
02/01/2015	Reviewed. No changes.
11/01/2013	Document updated with literature review. Coverage unchanged.
10/01/2008	Policy reviewed without literature review; new review date only.
11/15/2006	Revised/updated entire document
07/01/2004	New medical document