Salivary Hormone Testing

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I. Policy Description

Testing of saliva has been proposed as a non-invasive method to measure free (unbound to carrier proteins) steroid hormones, including estrogen, progesterone, androgens, and cortisol, for diagnosis of hormonal imbalance and administration of individualized hormone replacement therapy.[1]

Hypercortisolism can occur in several disorders, including Cushing syndrome (pituitary hypersecretion of corticotropin/ACTH), or glucocorticoid administration resulting in obesity, hypertension, menstrual irregularity, and glucose intolerance.[2-5]

Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1) For individuals with signs and symptoms of Cushing syndrome, late night salivary cortisol testing **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

2) For the screening, diagnosis, **and/or** monitoring of menopause, infertility, endometriosis, polycystic ovary disease (PCOS), premenstrual syndrome, osteoporosis, sexual dysfunction, seasonal affective disorder, depression, multiple sclerosis, sleep disorders, **or** diseases related to aging, salivary hormone testing **DOES NOT MEET COVERAGE CRITERIA**.

III. Table of Terminology

Term	Definition
AACE	American Association of Clinical Endocrinologists
ACOG	American College of Obstetricians and Gynecologists
ACTH	Adrenocorticotropic hormone
AI	Adrenal Insufficiency
ASRM	American Society of Reproductive Medicine Practice Committee
CLIA '88	Clinical Laboratory Improvement Amendments of 1988

CMS	Centers for Medicare and Medicaid Services
CS	Cushing syndrome
DHEA	Dehydroepiandrosteron
E1	Estrone
E2	Estradiol
E3	Estriol
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
ERCUSYN	European Registry on Cushing's Syndrome
ES	Endocrine Society
FDA	Food and Drug Administration
HT	Hormone therapy
IVF	In vitro fertilization
LC-MS	Liquid chromatography with tandem mass spectrometry
LDTs	Laboratory-developed tests
LNSC	Late night salivary cortisol
MHT	Menopausal hormone therapy
MP	Micronized progesterone
MS	Multiple sclerosis
NAMS	North American Menopausal Society
PCOS	Polycystic ovary disease
RIA	Radioimmunoassay
TSS	Transsphenoidal selective adenomectomy

IV. Scientific Background

Testing of hormone levels in the saliva has been proposed as a non-invasive method to measure free (unbound to carrier proteins and thus active) steroid hormones (estrogen, progesterone, androgens, cortisol, etc.) for diagnosis of hormonal imbalance and administration of individualized hormone replacement therapy.[1] Saliva measurements are thought to represent the concentrations of unconjugated steroid hormones as well as unconjugated steroids that have diffused freely into saliva. Conjugated steroids will often show significant decreases in concentration because their filtration process into the saliva is limited. This is what causes hormones, such as cortisol, estradiol, and testosterone to approximate concentrations well and the hormone dehydroepiandrosterone (DHEA) to represent concentrations poorly.[6]

Salivary hormone level testing is often recommended by bioidentical hormone vendors as a means of providing personalized therapy. However, individualized testing and monitoring is only useful when a narrow therapeutic window exists for a drug or a drug class. Steroid hormones, such as estrogen and progesterone, do not meet these criteria and do not require individualized testing.[1,7] Furthermore, there is no evidence that hormonal levels in saliva are biologically meaningful. Saliva is an ultra- filtrate of the blood and in theory, should be amenable to testing for free concentrations of hormones; however, salivary testing does not appear to be an accurate or precise method of hormone testing.[8,9] Studies suggest that salivary assessments of hormone levels are inaccurate and do not correlate with levels determined from serum,[7] as there is large within-patient variability in salivary hormone concentrations,

especially when exogenously administered hormones are given.[9-13] Salivary hormone levels often fluctuate with factors, such as circadian rhythm, and frequently do not correlate well with serum levels of hormones.[6]

Salivary hormone measurement may be utilized for many purposes. Menopause occurs due to changing hormone levels, mainly estrogen. In general, [individuals] experience menopause at a mean age of 51 years, with most becoming menopausal between 45 and 55. Menopausal hormone therapy (MHT, estrogen alone or combined with a progestin) is used for management of menopausal symptoms and is highly effective for symptoms, such as hot flashes and vaginal atrophy. In some cases, MHT may be used for the mood lability that many [individuals] experience during the menopausal transition.[14,15] There are few indications for the measurement of hormone levels to evaluate success of therapy when treating a post-menopausal [individual] with hormones. If treatment is initiated for symptom control, therapy should be titrated to the alleviation of symptoms, not a laboratory value.[1] A salivary hormone test has been developed by Genova Diagnostics, which evaluates levels of hormones in [individuals] during perimenopause, menopause, and andropause.[16,17]

One of the primary hormones that diffuses freely into saliva and can be well-approximated by salivary measurements is cortisol. Cortisol is a steroid hormone that is produced due to stress. Salivary flow rate does not affect cortisol concentration, and salivary cortisol correlates well with serum-free cortisol. This property can be used to identify adrenal insufficiencies and other related disorders.[18] For example, the presence of Cushing syndrome (CS) is suggested by signs of hypercortisolism, such as proximal myopathy, facial plethora, and wide purplish striae. However, none of these are pathognomonic, and many are nonspecific (such as obesity or hypertension). As a result, the diagnosis must be confirmed by biochemical tests, one of which is a salivary cortisol measurement.[19] The recurrence of hypercortisolemia after an initial treatment for CS seems to be predicted earlier by late night salivary cortisol (LNSC) testing compared to urinary free cortisol excretion.[20]

Proprietary Testing

Saliva testing measures the amount of hormone available to target tissues and is a good option for monitoring hormonal therapy. ZRT Laboratories developed a Saliva Steroid Profile using liquid chromatography/tandem mass spectrometry (LC-MS/MS) which tests a broad range of bioavailable hormones and hormone metabolites in one saliva sample collection. LC-MS/MS testing accurately reports levels of estrogen, such as those seen in men, children, and people using aromatase inhibitors, and includes a test for ethinyl estradiol, three hormone blockers, and melatonin. “Testing the levels of both upstream precursors and downstream metabolites of these parent active steroids [estrogens, progestogens, androgens, glucocorticoids, mineralocorticoids, melatonin, synthetic estrogen ethinyl, estradiol, anastrozole, letrozole, and the 5α-reductase inhibitor finasteride] will help determine which steroid synthesis enzymes are low, overactive, blocked by natural or pharmaceutical inhibitors, or defective due to metabolic dysfunctions (e.g., Polycystic Ovarian Syndrome (PCOS), Premenstrual Dysphoric Disorder (PMDD), luteal dysfunction, overexpression of aromatase, and estrogen dominance) and inborn errors of metabolism such as Congenital Adrenal Hyperplasia (CAH).”[21] ZRT is one of the first labs to measure hormones in saliva and helped establish the method that made saliva hormone testing commercially viable for health care providers and patients around the globe.

UnikeyHealth developed a saliva hormone testing panel to assess six hormone levels with an at-home test. The hormones tested are progesterone, estradiol, estriol, testosterone, DHEA, and cortisol. This at-home test provides recommendations and is purported to identify underlying causes of hormonal imbalance issues based on the individualized hormone assessment.[22]

Genova Diagnostics has developed several saliva hormone tests including The Rhythm™ hormone test,[23] Menopause Plus™,[24] The Comprehensive Melatonin Profile,[25] and The Adrenocortex Stress Profile.[26] The Rhythm™ hormone test is a comprehensive assessment of estradiol, progesterone, and testosterone which can help assess underlying causes of disorders such as premenstrual syndrome (PMS), infertility, and menstrual irregularities.[23] Menopause Plus™ is Genova's most comprehensive salivary hormone profile and is designed to provide insight into the impact that shifting hormone levels may play in men (andropause or male menopause) and women (peri/menopause). This test collects eight saliva samples every other day over six days for estrone (E1), estradiol (E2), estriol (E3), progesterone, progesterone/estradiol ratio (P/E2), and testosterone.[24] The Comprehensive Melatonin Profile analyzes the circadian secretion patterns of melatonin by analyzing three saliva samples taken in the morning, afternoon, and midnight. This test is purported to determine underlying causes of melatonin imbalances in sleep disorders, depression, and seasonal affective disorder.[25] Lastly, The Adrenocortex Stress Profile provides an assessment of the Hypothalamic-Pituitary-Adrenal (HPA) axis using carefully timed salivary samples of cortisol and DHEA. This may help reveal HPA axis imbalances which could be a contributing factor in cardiovascular disease, immune dysregulation, diabetes, chronic fatigue, persistent pain, or cognitive decline.[26]

Analytical Validity

Multiple proprietary tests are available for salivary hormone testing. Tests such as ZRT and UnikeyHealth ask the user to submit saliva samples and send the specimen to the proprietary lab where it can be analyzed. Labs will typically use an immunoassay-based method, such as an enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay (EIA), to assess the concentration of hormones, such as estradiol or progesterone. Others may use an automated competitive electrochemiluminescence immunoassay for LNSC measurement.[27] The results are compiled into a report listing the concentrations of each hormone as well as comments on abnormal amounts. These tests are often marketed to post-menopausal [individuals] who desire to have an assessment of hormones like estrogen, progesterone, DHEA, testosterone, estriol, and cortisol.[21,22] Moreover, another proprietary test proposes that conditions such as multiple sclerosis can be assessed through irregularities in melatonin.[25] However, not only is melatonin not widely measured through saliva, but there is currently no compelling data for whether administering melatonin has any utility with dealing with multiple sclerosis; there has been far too little published data with human subjects to draw any conclusions.[28] Osteoporosis is another condition that tests may purportedly be able to screen for with saliva.[23] However, this test may be of limited utility as the risks of hormone therapy may outweigh the benefits.[29]

Salivary cortisol was first measured by direct radioimmunoassay (RIA) in 1978, but more accurate cortisol immunoassays have now been developed; however, these assays are often limited due to poor specificity.[31] Further, late at night, cortisol levels may fall below detection limits for some RIA testing methods. Liquid chromatography with tandem mass spectrometry (LC-MS-MS) has also been used for the detection of salivary cortisol. Schiffer, et al. (2019) developed a novel LC-MS/MS assay to identify androgens in saliva samples with appropriate sensitivity. Prior, Li, et al. (2018) was able to utilize the same technique (LC-MS/MS) to accurately quantify three estrogens (estrone E1, estradiol E2, and estriol E3) in an assay with an accuracy of 98.9-112.4% and precision of (≤7.4%) as a hopeful alternative to blood samples. However, this field continues to face limitations due to poorly standardized assays and a lack of a single, validated reference range.[31]

Initial diagnostic tests for hypercortisolism should be highly sensitive, even if the diagnosis may be excluded later. LNSC is a first-line diagnostic test for CS as indicated by the approach outlined by the 2008 Endocrine Society[2] and others.[33] LNSC measurements are obtained at least twice because the hypercortisolism in CS may be variable. Two measurements must be abnormal for the test to be considered abnormal; this may be especially difficult for patients with fluctuating disease. The diagnosis of CS is established when at least two different first-line tests (such as LNSC and 24-hour urinary cortisol excretion) are abnormal. Once the diagnosis is established, additional evaluation is done to identify the cause of the hypercortisolism.[19]

A locally modified RIA assay was developed by Nunes, et al. (2009) and measured LNSC in obese patients with a current or past diagnosis of CS. The assay was able to diagnose a recurrence of CS with a sensitivity of 90% and a specificity of 91.8%; it was also reported that "a threshold of 12 nmol/liter yielded 100% sensitivity and specificity in overt [Cushing] syndrome."[34]

Ueland, et al. (2021) studied the analytical validity of LNSC as a screening test for CS. Bedtime and morning salivary samples were collected from 54 children in the obesity clinic and three children with pituitary CS using liquid chromatography tandem mass spectrometry (LC-MS/MS). These levels were compared to 320 salivary samples from healthy children to set cut-off values. Bedtime cut-off levels for cortisol and cortisone were 2.4 and 12.0 nmol/L, respectively. By "Applying these cut-off levels on the verification cohort, one child from the obesity clinic had bedtime salivary cortisol exceeding the defined cut-off level, but normal salivary cortisone. All three children with pituitary CS had salivary cortisol and cortisone far above the defined bedtime cut-off levels. Healthy subjects showed a significant decrease in salivary cortisol from early morning to bedtime."[35] The authors conclude that bedtime salivary cortisol levels with a diagnostic threshold above 2.4 nmol/L can be applied as a screening test for CS in children.

Clinical Utility and Validity

A study by Lewis, et al. (2002) focusing on salivary progesterone measurements found major variation when a progesterone cream was applied to several post-menopausal [individuals]. Salivary measurements were collected at zero, one, three, four, seven, and eight weeks. The average baseline for the 20 mg/g cream group was found to be 0.25 ± 0.12 nmol/L, but the measurement at one week was 82.11 ± 104.52 nmol/L;[9] similar enormous variations were found at three and seven weeks, as well as the 40 mg/gm cream group. In contrast, the placebo group's baseline was 0.43±0.21 and 0.38±0.20 in week eight.[9] The finding with inconsistent salivary progesterone levels was even found among premenopausal [individuals] obtaining in vitro fertilization (IVF); on the other hand, salivary estradiol was found to be correlative to serum-based assessment and could be a less invasive alternative to blood draws for ovarian stimulation during IVF cycles.[36]

Late night salivary cortisol measurements were found to be concordant with the 24-hour urine test, with 97% concordance at ≥ four nmol/L and 69% concordance at ≥ 10 nmol/L. However, the tests were stated to be "equivalent" at the more sensitive cut-off of four nmol/L. The authors concluded that due to the concordance of the salivary test with the urine test, the salivary test should replace the urinary test as the frontline test for CS.[37] Another study found LNSC to be 100% sensitive and 98% specific at a cut-off of 2.4 nmol/L.[38] Both cortisol and its metabolite cortisone were tested as cortisone is a significant source of interference in certain immunoassays. The variation between and within runs were both under ten percent, the method was linear up to 55.4 nmol/L for cortisol, and the lower of limit of quantification was 0.51 nmol/L for cortisol.[38]

A study measured the utility of salivary testosterone and cortisol concentrations in 71 junior athletes (26 females and 45 males) in response to stress. The researchers compared results of salivary samples to capillary blood samples taken at the same time; while blood samples showed an increase in both testosterone and cortisol concentrations in both sexes, salivary samples showed no change in testosterone or cortisol levels.[39] This may suggest that salivary hormone testing in these populations is not as efficient as other methods.

Valassi, et al. (2017) analyzed diagnostic data from 1,341 CS patients in the European Registry on Cushing's syndrome (ERCUSYN) and noted that of the three main first-line CS diagnostic tests, the urinary free cortisol test was performed in 78% of patients as a first-line testing method, overnight one mg dexamethasone suppression test was performed in 60% of patients, and LNSC was performed in only 25% of patients. This shows that LNSC may not be used as frequently as other testing methods for a first-line diagnosis of CS.[40]

Salivary testing for cortisol could also prove useful in occupational settings as a parameter for stress. Oldenburg and Jensen (2019) conducted a study on merchant ship crew, and found that after adjustment, average salivary cortisol level was positively associated with "acute shipboard stressors, namely the average current working time (p=.050) and the average number of terminals that had been served during the last 7 days (p=0.008)." This laboratory data is essential in all fields wherein professionals experience high levels of stress, so that measures can be taken to create a positive working environment.[41]

Kim, et al. (2020) studied the diagnostic utility of stimulated salivary cortisol as a non-invasive diagnostic tool for adrenal insufficiency (AI). One hundred and twenty subjects were measured for stimulated cortisol levels and these levels were compared to those obtained from the short Synacthen test (SST). AI was defined as a cortisol level of <496.8 nmol/L during the SST. Thirty-four of 120 patients were diagnosed with AI according to SST results. "Basal and stimulated salivary cortisol levels were positively correlated with basal (r=0.538) and stimulated serum cortisol levels (r=0.750), respectively (all P<0.001)." The cut-off level of morning basal salivary cortisol was 3.2 nmol/L, and the cut-off value of stimulated salivary cortisol was 13.2 nmol/L. Subjects with a stimulated salivary cortisol level above 13.2 nmol/L but a stimulated serum cortisol level below 496.8 nmol/L (n= 2) had lower serum albumin levels than those showing a concordant response. The authors conclude that "The diagnostic performance of stimulated salivary cortisol measurements after the SST was comparable to serum cortisol measurements for diagnosing AI."[42]

Kvam Hellan, et al. (2024) aimed to establish diagnostic cut-off levels for salivary cortisol (sa-cortisol) and cortisone using liquid chromatography tandem mass spectrometry (LC-MS/MS) after cosyntropin stimulation to evaluate AI. The study involved 128 healthy individuals (16 on oral estrogens) and 59 patients with suspected AI, among whom 26 were diagnosed with it based on conventional serum cortisol criteria. The results indicated that an sa-cortisol level of greater than or equal to 12.6 nmol/L at 60 minutes post-cosyntropin was optimal for ruling out AI, showing 89% diagnostic accuracy, 85% sensitivity, and 90% specificity. The study found a strong correlation between sa-cortisol and serum cortisol but noted better performance for sa-cortisol over salivary cortisone. Salivary testing was particularly advantageous for women on oral estrogen and individuals for whom venous sampling posed challenges. The study highlighted sa-cortisol as a reliable, non-invasive biomarker for AI diagnosis.[43]

Recent methodological research highlights critical limitations in commonly used salivary hormone assays. Brouillard, et al. (2025) conducted a comparative study evaluating immunoassay and mass spectrometry techniques for salivary sex hormone analysis, ELISA-based immunoassays, which are

widely used in commercial saliva hormone panels, demonstrated poor validity, particularly for estradiol and progesterone, when compared with LC-MS/MS. They concluded that LC-MS/MS remains the more reliable method of quantifying salivary sex steroids. These findings indicate that salivary sex hormone testing lacks clinical validity unless performed with mass spectrometry and restricted to evidence-supported clinical indications.[44]

V. Guidelines and Recommendations

American Association of Clinical Endocrinologists (AACE)

The AACE has noted salivary hormone level testing as recommended by certain proponents to provide individualized therapy. However, these methods are not FDA or CLIA approved, and factors such as hydration and circadian rhythm may influence the concentration of hormones within a subject. Standardization is difficult, and even though standardized blood tests do exist; it is of limited clinical utility because measuring hormone levels in post-menopausal [individuals] has no predictive value on what the normal levels should be. A salivary measurement cannot be used to correct the levels of sex hormones.[45] This was reaffirmed in 2017.[46]

American College of Obstetricians and Gynecologists (ACOG) and the American Society of Reproductive Medicine Practice Committee (ASRM)

American College of Obstetricians and Gynecologists and the American Society of Reproductive Medicine Practice Committee released joint guidelines on compounded hormone therapy that stated salivary hormone testing had no evidence to support its biological utility and that testing the hormone levels were neither accurate nor precise. The guidelines stated that salivary hormone testing had large intra-patient variability depending on factors such as diet and that saliva did not provide a reasonable representation of serum hormone levels. Saliva may be contaminated with other cell types, contains lower concentration of hormones than serum, and impossible to reliably test for a representative result. The guidelines concluded that evidence is inadequate to support an individualized hormone therapy based on salivary, serum, or urine testing.[1]

Finally, the guideline wrote that "there is no evidence that hormonal levels in saliva are biologically meaningful. In addition, whereas saliva is an ultrafiltrate of the blood and in theory should be amenable to testing for ''free'' (unbound) concentrations of hormones, salivary testing does not currently offer an accurate or precise method of hormone testing."[1] This guideline was reaffirmed in 2023.

The ACOG and ASRM published a clinical consensus stating that "although proponents claim that salivary testing can help tailor hormone therapy, salivary testing does not offer accurate or precise assessment of hormone levels. Steroid hormones mostly are bound to albumin, with less than five percent circulating in free form. Estrogen levels are extremely low in saliva, which make it methodologically challenging to measure. Progesterone is present in the saliva at higher levels but circulating levels do not necessarily reflect the levels present in the tissue." Currently, there are no FDA-approved salivary or urinary tests for steroid hormone measurement.[47]

North American Menopausal Society (NAMS)

The NAMS addressed salivary hormone testing with regards to MHT, stating that salivary hormone testing is "inaccurate and unreliable." The NAMS further notes that the levels in serum, saliva, and tissue

are "markedly different" and alludes to the FDA's statement that there is "no scientific basis for using saliva testing to adjust hormone levels."[48]

The NAMS also addressed salivary hormone testing in the context of compounded HT (hormone therapy), which would include estradiol, estrone, and micronized progesterone (MP), but corroborates that salivary testing for HT is considered "unreliable because of differences in hormone pharmacokinetics and absorption, diurnal variation, and interindividual and intraindividual variability."[49] Their recommendations also state "Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed" (Level II/III).[49]

Endocrine Society (ES)

The ES states that "salivary hormone assays are not standardized, do not have independent quality control programs, and lack an accepted reference range." The Society further mentions that there is no scientific evidence that a correlation exists between symptoms and salivary hormones. Assessment or monitoring of HT lacks evidence, and the ACOG, the NAMS, and ES all recommend against salivary hormone testing to assess or monitor hormone levels because "they lack a rationale and therefore lead to unnecessary expense of treatment."[50]

The ES also recommends a test of at least two LNSC measurements for diagnosis of CS. If a patient has eucortisolism after a transsphenoidal selective adenomectomy (TSS), a measurement of late night salivary or serum cortisol is recommended.[2,51]

VI. Applicable State and Federal Regulations

Food and Drug Administration (FDA)

Salivary hormones may be measured by multiple tests. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDT's are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

CPT	Code Description
82530	Cortisol; free
82533	Cortisol; total
S3650	Saliva test, hormone level; during menopause
0462U	Melatonin levels test, sleep study, 7 or 9 sample melatonin profile (cortisol optional), enzyme-linked immunosorbent assay (ELISA), saliva, screening/preliminary Proprietary Test: Salimetrics® Salivary Melatonin Profile (Circadian Phase Assessment) Lab/Manufacturer: Salimetrics® Clinical Laboratory, Salimetrics®, LLC

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VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
07/19/2022	Updated background, guidelines, and evidence-based scientific references.

	Literature review did not necessitate any modifications to the coverage criteria. Revised code disclaimer statement
06/28/2023	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modifications to the coverage criteria. Committee approved: 06/28/2023
05/14/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity and consistency: CC1, changed “the diagnosis of” to “individuals with signs and symptoms of” Cushing syndrome. Committee approved: 05/14/2024
05/21/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Removed CPT code 82626, 82627, 82670, 82671, 82672, 82677, 82679, 82681, 84144, 84402, 84403, 84410 Added CPT code 0462U Committee approved: 05/21/2025
06/17/2026	CAB Review Q2 2026: Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Committee Approved: 06/17/2026