# Salivary Hormone Testing

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**INSTRUCTIONS FOR USE:** Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

**SCOPE:** Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

## *PLAN PRODUCT AND BENEFIT APPLICATION*

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

*Oregon*: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Salivary Hormone Testing: PHP members must also meet the testing criteria governed by the Oregon Health Plan (OHP) Prioritized List of Health Services and the OHP Diagnostic Procedure Codes / Procedure Group 1119. Diagnostic services needed to establish a diagnosis are covered regardless of where the ultimate diagnosis appears on the Prioritized List. Once the diagnosis is determined, coverage of further treatment is reimbursed if the service appears in the funded region of the list for that condition.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

## COVERAGE CRITERIA

I. The use of salivary cortisol testing (e.g., late night salivary cortisol) may be considered **medically necessary** when **both** of the following criteria (A. and B.) are met:

   A. To diagnose suspected endogenous Cushing's syndrome; **and**
   B. The sample is analyzed in a Clinical Laboratory Improvement Amendments (CLIA) approved laboratory.

II. The use of salivary cortisol testing is considered **not medically necessary** when criterion I. above is not met.

III. The use of salivary hormone tests for the evaluation of preterm labor are considered **not medically necessary.**

IV. The use of salivary hormone tests including but not limited to, dehydroepiandrosterone (DHEA), estrogen, melatonin, progesterone, or testosterone are considered **not medically necessary** for

the screening, diagnosis, or monitoring of menopause or diseases related to aging, or any other indications

## POLICY CROSS REFERENCES

None

**The full Company portfolio of current Medical Policies is available online and can be accessed here.**

## POLICY GUIDELINES

**BACKGROUND**

**Salivary Hormone Testing**

Salivary hormone testing is a diagnostic medium that uses saliva as an analyte for measuring hormone levels in the body.[1] Hormones, when imbalanced, can cause various diseases (e.g. over exposure of cortisol leading to Cushing's syndrome). Saliva testing has several advantages:

- saliva is readily available
- the collection of saliva is less invasive than other bodily fluids (e.g., blood)
- saliva can be collected by the patient in an ambulatory setting (e.g., at home)
- the patient can also collect multiple saliva samples, if needed, to aid in the diagnostic process
- saliva samples can remain stable at room temperature for several weeks

**Late Night Salivary Cortisol (LNSF) to Diagnose Cushing's Syndrome**

LNSF is a salivary hormone test for Cushing's syndrome. Cushing's syndrome, also known as hypercortisolism, results from chronic exposure to the hormone cortisol.[2] Cortisol is one of the steroid hormones, and most cells within the body have cortisol receptors; therefore, overexposure to cortisol can affect many different bodily functions. There are two different types of Cushing's syndrome: endogenous and exogenous.[3] Endogenous Cushing's syndrome is the result of an adrenal gland tumor producing an unregulated amount of cortisol. Exogenous Cushing's syndrome, the most common type, results from taking excessive amounts of corticosteroid drugs (e.g., medications for severe allergies, asthma, or arthritis).[4] Typically, exogenous Cushing's syndrome can be promptly diagnosed by evaluating a patient's long-term corticosteroid drug use and noticeable clinical symptoms (significant weight gain in the trunk, fat pad on the mid-back, moon-shape face, and muscle weakness). Conversely, the clinical features of endogenous Cushing's syndrome can change often and appear similar to other diseases, especially in mild cases; therefore, a diagnosis may be very difficult.

Normally, a person's cortisol levels are elevated in the morning and decrease late at night. In patients with hypercortisolism, their cortisol levels are significantly elevated between 11:00 p.m. and 12:00 a.m.[5] This late night elevated cortisol level is one of the earliest detectable abnormalities in patients with Cushing's syndrome.[6] The sample is collected using a saliva collection kit that consists of a cotton swab

and plastic tube (e.g., Salivette made by the Sarstedt Company). The kit is sent home with the patient, and between 11:00 p.m. and midnight the patient places the cotton swab in their mouth and allows it to soak up saliva for 2-3 minutes. The cotton swab is then placed in the plastic tube and mailed to the lab for analysis.

Untreated, Cushing's syndrome is associated with significant morbidity and mortality.[5] A population-based study by Lindholm and colleagues showed that patients with completely uncontrolled Cushing's syndrome have a five-fold excess mortality[7]; therefore, the prompt and accurate diagnosis of suspected Cushing's syndrome is crucial.

**Salivary Hormone Tests for Menopause**

Salivary hormone tests have been proposed as a diagnostic medium for menopause. Rather than blood, plasma, or urine these diagnostic tests use saliva samples to elucidate the presence or absence of hormones during menopause. Salivary testing to diagnose menopause is usually done using hormone panels (testing several different hormones in one test at the same time) that measure dehydroepiandrosterone (DHEA), estrogen, melatonin, progesterone, and testosterone (e.g., Diagnos-Techs Peri- and Post-Menopausal Hormone Panels). The patient collects the saliva sample at home, freezes the sample, and mails it to the diagnostic lab for analysis.[8]

**Salivary Hormone Tests for the Evaluation of Preterm Labor (PTL)**

Salivary hormone tests have also been proposed for the evaluation of PTL, defined as regular contractions associated with cervical change before 37 weeks gestation.[9] PTL is the primary cause of preterm delivery (the birth of a baby before 37 weeks gestation). There are major risks and co-morbidities associated with preterm delivery, including but not limited to death, respiratory distress, jaundice, and infection; therefore, identifying preterm labor and preventing preterm delivery is crucial.[58] Levels of the hormone estriol have been shown to significantly increase 2-4 weeks before the onset of PTL.[10] Typically, estriol levels would be measured through blood or 24-hour urine collections; however, salivary estriol tests (e.g., SalEst by Adeza Biomedical Corp.) have been proposed as a diagnostic alternative to standard testing methods.

**Saliva Tests for Other Conditions**

Other salivary-based hormone tests have recently become available for the diagnosis of other diseases related to aging and/or hormonal imbalances. Male salivary hormone panels (e.g., Diagnos-Techs Male Hormone Panel and Expanded Male Hormone Panel) have been proposed as a diagnostic test for various disease related to aging in men; for example, andropause (i.e., hypogonadism or low testosterone), benign prostatic hyperplasia, and alopecia.[11] The male hormone panel measures levels of progesterone, dehydroepiandrosterone (DHEA), androstenedione, estrone, and testosterone. The Adrenal Stress Index (ASI) (e.g., Diagnos-Techs ASI Panel) has been developed for the evaluation of chronic stress and fatigue, dysglycemia, and chronic pain and inflammation.[12] The ASI panel measures cortisol, DHEA, 17-Hydroxyprogesterone, insulin, secretory IgA, and gliadin antibodies. A salivary hormone panel has also been proposed for the evaluation of diseases related to bone health (e.g., Bone Health Panel Diagnos-Techs); for example, osteopenia, osteoporosis, rheumatoid arthritis, and Paget's disease.[13] The bone health hormone panel detects salivary levels of progesterone, estradiol, testosterone, cortisol, follicle stimulating hormone, and DHEA.

## REGULATORY STATUS

### U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

The U.S. Food and Drug Administration (FDA) regulates laboratory tests under the Clinical Laboratory Improvement Act (CLIA). The CLIA, "requires clinical laboratories to be certificated by their state as well as the Centers for Medicare & Medicaid Services (CMS) before they can accept human samples for diagnostic testing."[14]

## CLINICAL EVIDENCE AND LITERATURE REVIEW

### EVIDENCE REVIEW

### Late Night Salivary Cortisol (LNSF)

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of late night salivary cortisol testing for diagnosing Cushing's syndrome. Below is a summary of the available evidence identified through July 2023.

Systematic Reviews

- A 2008 systematic review and meta-analysis conducted by Elamin and colleagues summarized the evidence on the accuracy of common tests for diagnosing Cushing's syndrome (CS).[15] The authors searched electronic databases from 1975 through September 2007, and included cross-sectional and longitudinal studies that enrolled participants with suspected CS. Eligible studies evaluated the accuracy of urinary free cortisol (UFC), serum bedtime cortisol, salivary bedtime cortisol (e.g., late night salivary cortisol), 1-mg overnight dexamethasone suppression test (DST), or the 2-day 2mg DST for diagnosing CS. The quality of selected articles was reviewed and data was extracted by two independent reviewers. The accuracy of the various tests was measured using sensitivity and specificity or likelihood ratios (LR).

  After full text review, the authors identified 27 studies eligible for inclusion giving a sample size of 8,631 patients. The results indicated similar diagnostic accuracy between all five tests included in the meta-analysis. Specifically, salivary midnight cortisol had a LR positive of 8.8 (high LR positive indicates a test that can help rule in CS) and a LR negative of 0.07 (a very low LR negative indicates a test that can help rule out CS). A similar diagnostic accuracy between tests was also shown in studies that used more than 1 testing strategy.

  There are several strengths of this systematic review, including the review of evidence by two independent authors following a strict protocol, quality rating of each selected study, data extraction by two independent reviewers, assessment of heterogeneity of the included studies, and conducting a

random effects meta-analysis. Another significant strength of this systematic review is the attempted contact of all authors of the selected studies to verify the extracted data or complete any missing data (70% successfully contacted and 90% of those contacted confirmed data or contributed missing data). A significant limitation of this systematic review is the broad range in prevalence of CS between studies. The authors acknowledge this limitation and suggest there is some degree of selection or referral bias in the included studies. Another limitation is the small number of included studies specifically evaluating late night salivary cortisol testing (n=4) and poor methodological quality of some included studies. Ultimately, the authors concluded "commonly used tests to diagnose CS appear highly accurate, particularly when used in combination."[15]

- In 2009, Carroll et al conducted a systematic review and meta-analysis to evaluate late-night salivary cortisol testing for the diagnosis of Cushing's syndrome (CS).[16] The authors searched electronic databases from January 1950 through December 2007. Eligible studies included adult patients referred for diagnosis of possible CS, patients with a diagnosis of CS made by clinical or biochemical testing other than late-night salivary cortisol, and studies with sufficient data to calculate the clinical utility of late-night salivary cortisol. Two independent authors assessed the methodological quality and extracted data of the selected studies. The accuracy of late-night salivary cortisol was assessed using pooled sensitivity, specificity, likelihood ratio (LR) positive, LR negative, and diagnostic odds ratios.

  After full text review, 7 articles met eligibility and quality criteria giving a sample size of 937 patients. All patients in the included studies had a previously confirmed diagnosis of CS by biochemical and pathological testing. The pooled sensitivity for diagnosing CS was 92% and specificity was 96%. The diagnostic odds ratio was 311 while the LR positive was 21 and LR negative was 0.08.

  Strengths of this systematic review include the identification of literature, quality assessment, and data extraction by two independent reviewers. The assessment of heterogeneity between studies and the use of random effects meta-analysis are also strengths of this study. The use of the diagnostic odds ratio is a significant strength of this systematic review because it is the best indicator for diagnostic test performance when using pooled data. A significant limitation of this study is the high degree of heterogeneity (87%) found between studies when calculating the $I^2$ statistic. This could indicate some degree of selection or referral bias in the selected studies. Limitations were also seen in the poor methodological quality of some included studies, and the potential for publication bias due to the exclusion of studies based on study design. The authors concluded, "late-night salivary cortisol has excellent diagnostic characteristics and as such, is a robust, convenient test for screening and diagnosis of Cushing syndrome."[16]

<u>Randomized Controlled Trials (RCTs)</u>

No RCTs were identified for the use of late-night salivary cortisol testing in the diagnosis of CS; however, RCTs are rarely performed to evaluate diagnostic tests. More commonly, diagnostic cohort studies are used to evaluate the diagnostic accuracy of a test (e.g., sensitivity and specificity).[17]

<u>Nonrandomized Studies</u>

- A 2014 prospective diagnostic cohort study by Elias and colleagues was conducted to evaluate the variability, reproducibility, and diagnostic performance of late-night salivary cortisol (LNSF) and

urinary free cortisol (UFC) using concurrent and consecutive samples in CS patients.[18] A total of 75 patients were enrolled between 2005 and 2012 who had clinical features of hypercortisolism but were undiagnosed. Patients collected saliva samples using Salivette saliva kits at 9:00 a.m. and 11:00 p.m. on three consecutive days. On these same days, urine collection for UFC was also obtained. Saliva samples were analyzed using radioimunnoassay (RIA) and urine samples were analyzed using liquid chromatography. The diagnostic efficiency of each test was evaluated using a receiver operating curve (ROC) and positive/negative likelihood ratios (LRs).

The results indicated no significant difference between LNSF and UFC among the 3 samples obtained for each patient. In 17.3% of patients, LNSF confirmed the diagnosis of CS after a normal UFC result. Conversely, UFC did not confirm the diagnosis of CS in patients with normal LNSF results. In evaluating the ROCs, the ratio between the area under the curves (AUC) for LNSF and UFC was 0.928; therefore, indicating a better performance of LNSF than UFC in diagnosing CS. The analysis of LRs also proved LNSF to be superior to UFC (LNSF LR +17.5, UFC LR +4.5). Strengths of this study include the extended recruitment period and comparison of LNSF to another diagnostic test. Another significant strength is the use of ROCs and LRs for evaluating diagnostic efficiency. These analyses, unlike sensitivity and specificity, are independent of disease prevalence. Limitations of this study include the prospective cohort design, small sample size, and recruitment based on referrals from one hospital. The authors concluded, "LNSF has superior diagnostic performance than UFC and should be used as the primary biochemical diagnostic test for CS diagnosis."[18]

- In 2008, Cardoso et al. conducted a diagnostic case-control study to evaluate the reproducibility and diagnostic value of lane-night salivary cortisol (LNSF) testing in patients with CS.[19] A total of 21 patients with confirmed CS and 121 healthy controls were enrolled. All subjects collected a 24-hour urine free cortisol (UFC) and LNSF on the same day. Some participants were also randomly selected (n=26 healthy controls and n=21 CS patients) to obtain two nonconsecutive LNSF samples in order to assess the reproducibility of the test. Diagnostic performance was evaluated by receiver operating curves (ROCs) and reproducibility was assessed using intraclass coefficients of correlations (ICCs).

  The LNSF test was found to be highly reproducible. The values obtained from consecutive samples in healthy controls were not statistically significantly different from those obtained in CS patients. The calculated ICC was 0.83 for healthy controls and 0.89 for CS patients; therefore indicating 17% or less variation in each subject. Late-night salivary cortisol levels were statistically significantly higher in CS patients than in healthy controls. LNSF was also able to diagnose CS with a sensitivity of 100% and specificity of 97.5%.

  Strengths of this study included the use of a comparison healthy control group, evaluation of reproducibility, and the use of ROCs to evaluate diagnostic performance. Limitations include the case-control study design, small sample sizes, and exclusion of participants due to noncompliance. Ultimately, authors concluded late-night salivary cortisol testing was a good screening tool based on the "noninvasive nature, remarkable reproducibility, and diagnostic perfomances."[19]

- In 1998, Raff et al. conducted a diagnostic case-control study to evaluate the accuracy of late-night salivary cortisol in patients with proven CS (n=39), patients referred for possible CS (n=39), and in normal patients (n=73).[20] The patients collected saliva samples at 11:00 p.m. and 7:00 a.m. the following morning using the Salivette saliva kit. All patients also underwent urinary free cortisol (UFC) testing within 1 month of saliva sampling. Patients with proven CS had a statistically significantly

higher 11:00 p.m. salivary cortisol as compared with normal subjects or patients with possible CS. Salivary cortisol at 7:00 a.m. was also significantly elevated in patients with proven CS compared to normal subjects or patients with possible CS. The late-night salivary cortisol test exhibited 92% sensitivity and 100% specificity in patients with proven CS. The combination of late-night salivary cortisol and UFC produced 100% sensitivity in patients with proven CS. Strengths of this study included the recruitment of participants from three different medical centers and the inclusion of proven CS patients, potential CS patients, and normal patients. Limitations are seen in the diagnostic cohort design and the small sample sizes. The authors concluded late-night salivary cortisol is a reliable test for the evaluation of spontaneous Cushing's syndrome (a.k.a. endogenous Cushing's syndrome).

A number of observational studies continue to be published that demonstrate that late-night salivary cortisol has high clinical validity and utility for diagnosing CS. [21,22]

**Salivary Hormone Tests for Menopause**

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of salivary hormone testing for the screening, diagnosis, or monitoring of menopause. Below is a summary of the available evidence identified through July 2023.

Systematic Reviews

- A 2013 Hayes systematic review (archived in 2018) evaluated salivary hormone testing for menopausal women.[23] The literature search identified eight studies evaluating salivary hormone testing in postmenopausal women. The included study designs varied (2 placebo-controlled, 3 randomized, 2 within subject/repeated measures design, 1 prospective cohort, and 1 case-control) and sample sizes ranged from 12 to 76 patients. The studies also had variations in follow-up time (ranging from 0 days to 1 year) and in the specific hormones measured. All studies compared salivary hormone levels with serum hormone levels, and six studies also evaluated various treatments for menopause symptoms (e.g., hormone replacement therapy).

  Of the included studies, only two compared hormone levels in saliva and blood using statistical analyses. One study found significant correlations between estrogen levels in saliva and in blood in the treatment group, but not in the control group. The other study found a "significant modest relationship" between salivary and blood levels of testosterone. The other studies reported hormone levels in saliva versus blood or urine but did not report any statistical analyses. None of the selected studies examined the role of salivary hormone testing in diagnosing perimenopause or menopause. Also, no studies evaluated the impact of salivary hormone testing on treatment decisions for menopausal women. No adverse events related to saliva collection were reported by any studies.

  Overall, Hayes gave a "D2 rating for salivary hormone testing in postmenopausal women for determination of menopausal state or for guidance of treatment decisions."[23] This rating is based on the limited and very low quality body of evidence.

Randomized Controlled Trials (RCTs)

- In 2009, Flyckt et al. conducted a double-blinded phase III trial to evaluate salivary testosterone levels versus serum testosterone levels in postmenopausal women who received a transdermal

testosterone patch or placebo patch for the treatment of hypoactive sexual desire disorder.[24] A total of 56 postmenopausal women were recruited and randomized to receive the testosterone patch or placebo patch. In naturally postmenopausal women, serum and saliva samples were collected concurrently at baseline, 24 week follow-up, and 52 week follow-up. In surgically postmenopausal women, serum and saliva samples were collected concurrently at baseline, 12 week follow-up, 24 week follow-up, and 52 week follow-up.

The results indicated no correlation for salivary testosterone levels with any of the serum testosterone levels. Only after performing a log transformation of the data were modest correlations were found between saliva testosterone and serum testosterone. Strengths of this study include the randomized, controlled design, double blinding, and use of a placebo comparator. Limitation include the lack of patient information provided (e.g., age and previous or current hormone treatment), lack of outcome variables (only evaluated testosterone levels), and very limited inclusion criteria with no exclusion criteria. The authors concluded the, "results do not support the routine use of salivary testosterone levels in postmenopausal women".

- In 2002, Lewis et al. conducted a double-blind placebo controlled study to determine the levels of progesterone in plasma, red cells, and saliva in postmenopausal women using transdermal progesterone (P4) creams.[25] A total of 24 postmenopausal women were recruited to receive a 20mg P4 cream, 40mg P4 cream, or placebo cream. Patients were instructed to apply a specific amount of the cream morning and evenings and were followed-up for 8 weeks. Morning samples of blood, urine, and saliva were collected at baseline, 1 week, 3, weeks, 4 weeks, 7 weeks, and 8 weeks.

  Results indicated small increases in plasma and red cell P4 levels compared to the placebo group. Saliva P4 levels also increased throughout the 8 week follow-up, but were very high and varied significantly between measurements (ranging from 0.25 nmol/L to 82.11 nmol/L). Due to the high variability of salivary hormone levels across groups, the authors "caution against the use of saliva measurements to monitor progesterone absorption".[25] Strengths of this study include the double-blinded design and use of a placebo comparison group. Limitations are evident in the very small sample size, lack of data reported for the groups (age and sample size of each group was not reported), and limited outcome data (only reported the P4 measurement).

Nonrandomized Studies

Five nonrandomized studies were also identified that evaluated the use of salivary hormone testing in peri- and post-menopausal women.[26-30] All of these studies had significant methodological limitations including but not limited to the following:

- Small sample sizes
- Lack of control groups
- Lack of randomization
- Lack of statistical comparisons between diagnostic tests
- Lack of clinical outcomes data (e.g., sensitivity and specificity)

These significant methodological limitations do not permit conclusions to be drawn; furthermore, these nonrandomized studies were included in the Hayes review discussed above.

**Salivary Hormone Tests to Evaluate Preterm Labor**

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of salivary estriol testing for the evaluation of preterm labor. Below is a summary of the available evidence identified through July 2023.

Heine and colleagues (1999) conducted a randomized controlled trial (n=601) to compare the accuracy of predicting preterm labor (PTL) using salivary estriol testing versus the Creasy score (scoring instrument to predict preterm labor).[31] Salivary estriol testing correctly predicted PTL in 91% of cases versus 75% of cases for the Creasy score. Salivary estriol testing had a sensitivity of 44%, specificity of 92%, positive predictive value of 19%, and a negative predictive value of 98%. Although these results suggest salivary estriol testing may be diagnostically accurate for identifying preterm labor, this study did not evaluate the impact of this test on the management of preterm labor and patient outcomes.

Ramsey and Andrews (2003) evaluated two biochemical predictors of preterm labor: fetal fibronectin (glue-like protein that leaks into the birth canal if a preterm delivery is likely to occur) and salivary estriol.[32] Their study indicated that positive salivary estriol tests were more closely associated with the identification of late preterm birth (birth between 34 and 37 weeks gestation); therefore limiting the use of salivary estriol testing in clinical practice, because late preterm birth has low rates of neonatal morbidity and mortality.

Ultimately, there was not enough evidence to support the diagnostic utility of salivary hormone testing for the evaluation of preterm labor. Further studies of salivary estriol testing are needed to evaluate the diagnostic accuracy, reliability, and the clinical impact on the prevention of preterm delivery.

**Other Conditions**

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of salivary hormone testing for other conditions related to aging and/or hormone imbalances. There was not enough evidence to support the diagnostic utility of salivary hormone testing for all other conditions, including but not limited to, chronic fatigue and stress, hypogonadism, benign prostatic hyperplasia, osteoporosis, and rheumatoid arthritis.

**CLINICAL PRACTICE GUIDELINES**

No clinical practice guidelines were identified regarding the use of salivary hormone tests for the evaluation of preterm labor or salivary hormone tests for diseases related to aging and other conditions.

**Late Night Salivary Cortisol (LNSF)**

<u>American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons (AACE/AAES)</u>

The 2009 AACE/AAES evidence-based clinical practice guideline for the management of adrenal incidentalomas recommended the use of late-night salivary cortisol test as a biochemical evaluation for adrenal Cushing syndrome (a.k.a. endogenous Cushing syndrome).[33]

The Endocrine Society

The 2008 Endocrine Society evidence-based clinical practice guideline for the diagnosis of Cushing's syndrome recommended the late-night salivary cortisol test in patients with multiple symptoms of the syndrome and in which exogenous glucocorticoid use had been excluded.[34] The guideline suggested two saliva collections on separate evenings (between 11:00 p.m. and 12:00 a.m.), and patient's with abnormal results should see an endocrinologist to undergo further testing.

**Salivary Hormone Tests for Menopause**

American Association of Clinical Endocrinologists (AACE)

The 2011 AACE evidence-based clinical practice guidelines for menopause stated, "salivary hormone level testing is not approved by either the FDA or the Clinical Laboratory Improvement Amendments."[35] The guidelines also acknowledge that, "accurate studies have revealed large intrasubject variability in salivary sex hormone concentrations, which fluctuate depending on numerous variables."[35]

North American Menopause Society

The 2017 North American Menopause Society position statement on menopause and hormones stated, "the use of salivary hormone testing has been proven to be inaccurate and unreliable."[36] The position statement also acknowledged the difficulty of assessing hormones (specifically progesterone) due to significantly different levels in serum, saliva, or tissue. Although this is not a clinical practice guideline, the position statement was published in a peer-reviewed journal (The Journal of the North American Menopause Society).

American College of Obstetricians and Gynecologists (ACOG)

The 2012 (reaffirmed in 2023) ACOG committee opinion stated, "there is no evidence that hormonal levels in saliva are biologically meaningful and that saliva testing is not an accurate or precise method for measuring hormones."[37]The committee also agreed that saliva contains a much smaller concentration of hormones than serum, and salivary hormone tests do not reliably provide accurate levels of hormones due to several external influences (e.g., diet, time of testing, hormone being tested).

Food and Drug Administration (FDA)

A 2015 FDA consumer update regarding menopausal hormone therapy acknowledged a lack of evidence and scientific basis for salivary hormone testing. The FDA also stated, "saliva hormone levels do not accurately reflect a woman's hormone levels."[38]

## *BILLING GUIDELINES AND CODING*

| CODES* | | |
|---|---|---|
| **CPT** | 0462U | Melatonin levels test, sleep study, 7 or 9 sample melatonin profile (cortisol optional), enzyme-linked immunosorbent assay (ELISA), saliva, screening/preliminary |

| | | |
|---|---|---|
| | 82530 | Cortisol; free |
| | 82533 | Cortisol; total |
| | 82626 | Dehydroepiandrosterone (DHEA) |
| | 82627 | Dehydroepiandrosterone-sulfate (DHEA-S) |
| | 82670 | Estradiol |
| | 82671 | Estrogens; fractionated |
| | 82672 | Estrogens; total |
| | 82677 | Estriol |
| | 82679 | Estrone |
| | 82681 | Estradiol; free, direct measurement (eg, equilibrium dialysis) |
| | 83516 | Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method |
| | 83520 | Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified |
| | 84144 | Progesterone |
| | 84402 | Testosterone; free |
| | 84403 | Testosterone; total |
| | 84436 | Thyroxine; total |
| | 84439 | Thyroxine; free |
| | 84443 | Thyroid stimulating hormone (TSH) |
| | 84479 | Thyroid hormone (T3 or T4) uptake or thyroid hormone binding ratio (THBR) |
| | 84480 | Triiodothyronine T3; total (TT-3) |
| | 84999 | Unlisted chemistry procedure |
| | 86316 | Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each |
| | 88341 | Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure) |
| | 88342 | Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure |
| | 88344 | Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure |
| | | |
| **HCPCS** | S3650 | Saliva test, hormone level; during menopause |
| | S3652 | Saliva test, hormone level; to assess preterm labor risk |

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**

- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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## *POLICY REVISION HISTORY*

| DATE | REVISION SUMMARY |
|---|---|
| 2/2023 | Converted to new policy template. |
| 12/2023 | Annual review. Changed denial language from “investigational” to “not medically necessary”. |
| 7/2024 | Q3 2024 code set update. |