Salivary Hormone Testing

Policy Number: AHS – G2120 – Salivary Hormone Testing	Prior Policy Name and Number, as applicable: G2120 – Salivary Hormone Testing for Menopause and Aging
Initial Presentation Date: 09/18/2015 Revision Date: 03/03/2021	

I. Policy Description

Testing of saliva has been proposed as a noninvasive 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 (ACOG & ASRM, 2012).

Hypercortisolism can occur in several disorders, including Cushing's syndrome (pituitary hypersecretion of corticotropin/ACTH), or as a result of glucocorticoid administration resulting in obesity, hypertension, menstrual irregularity, and glucose intolerance (Lacroix, Feelders, Stratakis, & Nieman, 2015; Nieman et al., 2008; L. K. Nieman, 2019a; Quddusi, Browne, Toivola, & Hirsch, 1998).

II. Related Policies

Policy Number	Policy Title
AHS-G2161	Hormonal Testing in Adult Females
AHS-G2013	Hormonal Testing in Adult Males

III. 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. Late Night Salivary Cortisol testing **MEETS COVERAGE CRITERIA** for diagnosing Cushing's Syndrome.

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 a patient's illness.

2. Salivary hormone testing 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 **DOES NOT MEET COVERAGE CRITERIA**. Salivary hormone tests include but are not limited to the following:

a. Estrogen, including estrone (E1), estradiol (E2), and estriol (E3)

b. Melatonin

c. Progesterone

d. Testosterone

e. DHEA

f. Cortisol

IV. Scientific Background

Testing of hormone levels in the saliva has been proposed as a noninvasive 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 (ACOG & ASRM, 2012). 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 (Wood, 2009).

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 (ACOG & ASRM, 2012; Conaway, 2011). 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 (Flyckt et al., 2009; Lewis, McGill, Patton, & Elder, 2002). Studies suggest that salivary assessments of hormone levels are inaccurate and do not correlate with levels determined from serum (Conaway, 2011), as there is large within-patient variability in salivary hormone concentrations, especially when exogenously administered hormones are given (Hardiman, Thomas, Osgood, Vlassopoulou, & Ginsburg, 1990; Klee & Heser, 2000; Lewis et al., 2002; Meulenberg, Ross, Swinkels, & Benraad, 1987; Wren et al., 2000). Salivary hormone levels often fluctuate with factors, such as circadian rhythm, and frequently do not correlate well with serum levels of hormones (Wood, 2009).

Salivary hormone measurement may be utilized for many purposes. Menopause occurs due to changing hormone levels, mainly estrogen. In general, women 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 women experience during the menopausal transition (Martin & Barbieri, 2020; Taylor & Manson, 2011). There are few indications for the measurement of hormone levels to evaluate success of therapy when treating a postmenopausal woman with hormones. If treatment is initiated for symptom control, therapy should be titrated to the alleviation of symptoms, not a laboratory value (ACOG & ASRM, 2012). A salivary hormone test has been developed by Genova Diagnostics, which evaluates levels of hormones in males and females during perimenopause, menopause, and andropause (male menopause) (Genova_Diagnostics, 2020).

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 (L. K. Nieman, 2019b). For example, the presence of Cushing's 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 (L. K. Nieman, 2020). 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 (Fleseriu, Hamrahian, Hoffman, Kelly, & Katznelson, 2016).

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 (Spence et al., 2018). 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 women who desire to have an assessment of hormones like estrogen, progesterone, DHEA, testosterone, estriol, and cortisol (UniKey, 2018; ZRTLAB, 2018). Moreover, another proprietary test proposes that conditions such as multiple sclerosis (MS) can be assessed through irregularities in melatonin (Genova, 2019a). 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 MS; there has been far too little published data with human subjects to draw any conclusions (Wurtman, 2017; R. Wurtman, 2019). Osteoporosis is another condition that tests may purportedly be able to screen for with

saliva (Genova, 2019b). However, this test may be of limited utility as the risks of hormone therapy may outweigh the benefits (Rossouw et al., 2002).

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 (El-Farhan, Rees, & Evans, 2017). 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, Li, and Kellermann (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 (El-Farhan et al., 2017).

Initial diagnostic tests for hypercortisolism should be highly sensitive, even if the diagnosis may be excluded later. Late night salivary cortisol (LNSC) is a first-line diagnostic test for CS as indicated by the approach outlined by the 2008 Endocrine Society (Nieman et al., 2008) and others (Hinojosa-Amaya, Varlamov, McCartney, & Fleseriu, 2019). 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 (L. K. Nieman, 2020).

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's syndrome" (Nunes et al., 2009).

Clinical Validity and Utility

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 women. Salivary measurements were collected at 0, 1, 3, 4, 7, and 8 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 1 week was 82.11 ± 104.52 nmol/L (Lewis et al., 2002); similar enormous variations were found at 3 and 7 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 8 (Lewis et al., 2002). The finding with inconsistent salivary progesterone levels was even found among premenopausal women 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 (Sakkas et al., 2020).

LNSC measurements were found to be concordant with the 24-hour urine test, with 97% concordance at ≥4 nmol/L and 69% concordance at ≥10 nmol/L. However, the tests were stated to be "equivalent" at the more sensitive cutoff of 4 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 Cushing's syndrome (Doi, Clark, & Russell, 2013). Another study found LNSC to be 100% sensitive and 98% specific at a cut-off of 2.4 nmol/L (Antonelli, Ceccato, Artusi, Marinova, & Plebani, 2015). 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 10%, 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 (Antonelli et al., 2015).

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 (Crewther, Obminski, Orysiak, & Al-Dujaili, 2018). 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 1341 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 1 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.

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.

V. Guidelines and Recommendations

American Association of Clinical Endocrinologists (AACE) (Goodman, Cobin, Ginzburg, Katz, & Woode, 2011)

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 postmenopausal women has no predictive value on what the normal levels should be. A salivary measurement cannot be used to correct the levels of sex hormones (Goodman et al., 2011).

American College of Obstetricians and Gynecologists (ACOG) and the American Society of Reproductive Medicine Practice Committee (ASRM) [(ACOG & ASRM, 2012) reaffirmed 2020]

ACOG and ASRM 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 (ACOG & ASRM, 2012).

Finally, the guideline wrote that "there is no evidence that hormonal levels in saliva are biologically meaningful." (ACOG & ASRM, 2012)

North American Menopausal Society (NAMS, 2012, 2017)

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" (NAMS, 2012).

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 inter-individual and intraindividual variability" (NAMS, 2017).

Endocrine Society (ES) (Nieman, 2015; Santoro et al., 2016)

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 hormone therapy lacks evidence, and the American College of Obstetricians and Gynecologists, the North American Menopausal Society, and the Endocrine Society all recommend against salivary hormone testing (Santoro et al., 2016).

The ES also recommends a test of at least two LNSC measurements for diagnosis of Cushing's Syndrome. If a patient has eucortisolism after a transsphenoidal selective adenomectomy (TSS), a measurement of late-night salivary or serum cortisol is recommended (Nieman, 2015; Nieman et al., 2008).

VI. State and Federal Regulations, as applicable

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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
82530	Cortisol free
82533	Cortisol; total
82626	Dehydroepiandrosterone (dhea)
82627	Dehydroepiandrosterone
82670	Estradiol; total
82671	Estrogens; fractionated
82672	Estrogens; total
82677	Estriol
82679	Estrone
82681	Estradiol; free, direct measurement (eg, equilibrium dialysis)
84144	Progesterone
84402	Testosterone; free
84403	Testosterone; total
84410	Testosterone; bioavailable, direct measurement (eg, differential precipitation)
S3650	Saliva test, hormone level; during menopause

Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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