Salivary Hormone Testing AHS – G2120

Description of Procedure or Service

**Definition**
Testing of saliva has been proposed as a noninvasive method to measure free (unbound to carrier proteins and thus active) 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) or as a result of glucocorticoid administration (Quddusi, Browne, Toivola, & Hirsch, 1998) resulting in obesity, hypertension, menstrual irregularity, and glucose intolerance (Lacroix, Feelders, Stratakis, & Nieman, 2015; L. Nieman, 2017a; Nieman et al., 2008; Quddusi, Browne, Toivola, & Hirsch, 1998).

**Related Policy:**
- Hormonal Testing in Females
- Hormonal Testing in Males

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

BCBSNC will provide coverage for salivary hormone testing when it is determined the medical criteria or reimbursement guidelines below are met.

**Benefits Application**

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**When salivary hormone testing is covered**

Reimbursement for Late Night Salivary Cortisol testing is allowed for diagnosing Cushing’s Syndrome.

**When salivary hormone testing is not covered**
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Reimbursement is not allowed for 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.

Salivary hormone tests include but are not limited to the following:
- Estrogen
- Melatonin
- Progesterone
- Testosterone
- DHEA
- Cortisol

Policy Guidelines

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 concentration of an unconjugated steroid hormone well as unconjugated steroids diffuse 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 a hormone such as DHEA to represent concentrations poorly (Wood, 2009).

Salivary hormone level testing is often recommended by bioidentical hormone vendors as a means of providing individualized 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 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).

In general, women have 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, 2017; 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).

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 ELISA or
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EIA to assess the concentration of hormones such as estradiol or progesterone. The concentrations 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 such as estrogen, progesterone, DHSA, testosterone, estriol, and cortisol (UniKey, 2018; ZRTLAB, 2018). Moreover, another proprietary test proposes that they can assess conditions such as multiple sclerosis through irregularities in melatonin (Genova, 2019a). However, not only is melatonin not widely measured through saliva, there is currently no compelling data whether administering melatonin has any utility with dealing with MS; there has been far too few data with human subjects to draw any conclusions (R. Wurtman, 2017; Richard Wurtman, 2017). 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).

One of the primary hormones that diffuses freely into saliva and can be well-approximated by salivary measurements is cortisol. 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, 2017). 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. Nieman, 2017b).

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 as indicated by the approach outlined by the 2008 Endocrine Society (Nieman et al., 2008) 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. Nieman, 2017b).

Clinical Validity and Utility
A study by Lewis et al 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. 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). 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. 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, Ceccato, Artusi, Marinova, & Plebani, 2015).

Applicable State/Federal Regulations
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
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Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

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 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, Cobin, Ginzburg, Katz, & Woode, 2011).

American College of Obstetricians and Gynecologists (ACOG) and the American Society of Reproductive Medicine Practice Committee (ASRM, 2012)
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).

The American College of Gastroenterology (ACG) (Rubio-Tapia, Hill, Kelly, Calderwood, & Murray, 2013)
The ACG published guidelines regarding celiac disease (CD) and stated that “Stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD (Strong recommendation, weak level of evidence) (Rubio-Tapia et al., 2013).”

North American Menopausal Society (NAMS, 2012)
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).

Endocrine Society
The Endocrine Society 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 Endocrine Society also recommends a test of at least two late-night salivary cortisol 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)

Billing/Coding/Physician Documentation Information
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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

 Appliesable service codes: 82350, 82353, 82626, 82627, 82670, 82671, 82672, 82677, 82679, 84144, 84402, 84403, 84410, S3650

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Specialty Matched Consultant Advisory Panel review 3/20

**Policy Implementation/Update Advisory Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>1/1/19</td>
<td>New policy developed. BCBSNC will provide coverage for salivary hormone testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)</td>
</tr>
<tr>
<td>5/14/19</td>
<td>Reviewed by Avalon 1st Quarter 2019 CAB. Minor changes to Description Section. Revised NonCovered statement to read: “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 is considered not medically necessary.” Added Cortisol to list of NonCovered tests. Policy Guidelines section and References updated. Medical Director review 4/2019. <strong>Policy noticed 5/14/2019 for effective date 7/16/2019.</strong> (an)</td>
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<tr>
<td>10/29/19</td>
<td>Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)</td>
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<tr>
<td>03/31/20</td>
<td>Specialty Matched Consultant Advisory Panel 3/18/20. No change in policy statement. (eel)</td>
</tr>
<tr>
<td>5/12/20</td>
<td>Reviewed by Avalon for 1st Quarter 2020 CAB. Updated Description and Policy Guidelines section. Added references. No change to policy statement. Medical Director review 4/2020. (eel)</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.