Saliva Hormone Tests

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This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

DESCRIPTION

Saliva is produced primarily by the parotid, sublingual, and submandibular glands. Salivary fluid may contain various amounts of hormones, depending on the ability of these hormones to leave the blood, penetrate through or around the salivary cell membranes, and diffuse into the saliva. Lipid-soluble hormones can pass directly through cell membranes via passive diffusion and are commonly found in the saliva. Small, water-soluble hormones may be able to enter the saliva through the tight junctions between salivary cells in a process called ultrafiltration. Salivary cells do not appear to use active transport to place hormones into the saliva.

Salivary tests may help to identify hormonal imbalances in individuals which can occur at any age and effects how a person feels daily. The slightest dysfunction of an individual’s hormones can result in weight gain, mood changes, low libido, poor memory or concentration, depression, bone loss, migraines or headaches and sleep disorders. Salivary testing can also be used to monitor the outcomes of hormonal replacement therapy.

Several laboratory tests are now being offered to consumers as home-based testing. Among these tests, saliva testing for certain hormones (e.g., estrogen (estradiol), progesterone, testosterone, dehydroepiandrosterone (DHEA) and cortisol) has been proposed for the screening, diagnosis, and/or monitoring of menopause, preterm labor, and other conditions.

The saliva used for hormone testing may be collected in the clinic setting or by the individual at home. The sample is then sent to a laboratory for evaluation.

Menopause
The results of the test may then be used to determine the need for vitamins, herbs, and phyto-hormones (e.g., phytoestrogen and phytotestosterone). These may be manufactured products (e.g., vitamins, topical creams) or products compounded specifically for the individual.

Pre-Term Labor
Preterm birth is a major complication of pregnancy and remains a leading cause of neonatal morbidity and mortality worldwide. Improvements in the understanding of the pathophysiology of preterm labor have led to the development of novel diagnostic tools of use to identify women at greatest risk for preterm birth. Currently two FDA-approved biochemical tests are available in the United States:

- Fetal fibronectin (This is not a salivary test and not applicable to this medical policy)
- Salivary estriol

A practice bulletin from ACOG issued in 2002 (no updated bulletin found in 2021) on preterm saliva testing states the following:

- **Salivary Estriol**
  - Observational studies have shown that maternal levels of serum estradiol and salivary estriol increase before the onset of spontaneous term and preterm labor. A test using salivary estriol levels was designed to predict preterm delivery, but maternal estriol levels peak at night and may be suppressed by betamethasone administration. The test carries a high percentage of false-positive results and can add significantly to the cost of prenatal care if used in the low-risk population. Trials with salivary estriol testing have failed to establish its usefulness for anything more than investigational purposes.

Patients
The relevant population(s) of interest are patients presenting with hormone changes due to preterm labor or menopause.

Interventions
The intervention includes saliva hormone tests including but not limited to estrogen (estradiol), progesterone, testosterone, melatonin, and/or dehydroepiandrosterone (DHEA) which can be used to monitor the outcomes of hormonal replacement therapy.

Comparators
The comparators of interest are standard of care: serum specimen for measurement of hormones.

Outcomes
The outcomes of interest are to diagnose and treat the underlying condition correctly.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Summary of Evidence
Serum is the standard specimen used for measurement of hormones. Because saliva is similar to a blood ultrafiltrate, it has been theorized that salivary hormone concentrations may correlate with free/unbound serum concentrations. However, the promotion of saliva testing has been criticized. Critics site a lack of scientific evidence supporting the use of salivary hormone levels for determining and monitoring hormone therapy. They also claim that hormone concentrations in saliva are highly variable and may not correlate with biological or clinical response to treatment, that salivary hormone levels may not reflect free hormone levels in blood, and that the large variability associated with salivary hormone assays makes them unreliable. Therefore, the medical literature fails to demonstrate that salivary tests are appropriate for screening, diagnosing, or monitoring patients with menopause, preterm labor, and other conditions and therefore is considered investigational.

Practice Guidelines and Position Statements

The American College of Obstetricians and Gynecologists (ACOG)
(2012, Reaffirmed 2020) Committee Opinion Number 532, Compounded Bioidentical Menopausal Therapy

- 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 amendable to testing for “free” (unbound) concentrations of hormones, salivary testing does not currently offer an accurate or precise method of hormone testing. There are several problems with salivary testing and monitoring of free hormone levels.
    - Salivary levels do not consistently provide a reasonable representation of endogenous, circulating serum hormones. There is within patient variability in

salivary hormone concentrations, especially when exogenously administered hormones are given. Salivary hormone levels vary depending on diet, time of testing, and the specific hormone being tested.
    - The pharmacokinetics of exogenously administered compounded hormones cannot be known, it is not possible to estimate with reliability how and when to test saliva to obtain a representative result.
    - Saliva contains far lower concentrations of hormone than serum and its prone to contamination with blood, infectious agents, and epithelial cells all of which may affect the level of hormone to be measured.

Although more sensitive testing is becoming available using mass spectrometry, there are few indications for the measurement of hormone levels to ascertain success of therapy when treating postmenopausal woman with hormones. If treatment is initiated for symptom control, subjective improvement in symptoms is the therapeutic end point, and there is no need to assess hormone levels. Hormone therapy should not be titrated to hormone levels (serum, urinary or salivary). (*Accessed August 2022*)

North American Menopause Society (NAMS)
(2022) The NAMS provided a position statement on hormone therapy which stated:

- Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed. (Level II/III). (*Accessed August 2022*)

American Association of Clinical Endocrinologists (AACE)
(2011) Medical guidelines for clinical Practice for the Diagnosis and Treatment of Menopause Salivary hormone level testing is recommended by many bioidentical hormone proponents as a means of providing patients with "individualized" therapy. Yet these methods are not approved by either the FDA or the Clinical Laboratory Improvement Amendments (the US Health and Human Services agency regulating laboratory standards). Accurate studies have revealed large intra-subject variability in salivary hormone concentrations, which fluctuate depending on numerous variables, including diet, hydration, and circadian rhythm. These conditions are difficult to standardize. Standardized blood tests, which are available for sex steroids, are well established but have limited clinical value in evaluating menopausal hormone therapy (MHT). (Evidence Level: 4 no evidence (theory, opinion, consensus, or review)). (*Accessed August 2022*)

PRIOR APPROVAL

Not applicable.

POLICY

Menopause

The use of salivary testing for individuals with menopause is considered **investigational** for all indications.

Preterm Labor Risk
The use of salivary testing to assess preterm labor risk is considered **investigational** for all indications.

Based on the peer reviewed literature there is lack of clinical evidence to indicate the treatment decisions made based on the results of salivary testing for menopause and preterm labor risk can be used to enhance patient management and improve beneficial health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- S3650 Saliva test, hormone level; during menopause
- S3652 Saliva test, hormone level; to assess preterm labor risk

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POLICY HISTORY

Date	Reason	Action
August 2022	Annual Review	Policy Renewed
August 2021	Annual Review	Policy Revised
August 2020	Annual Review	Policy Renewed
August 2019	Annual Review	Policy Renewed
August 2018	Annual Review	Policy Renewed
August 2017	Annual Review	Policy Renewed
August 2016	Annual Review	Policy Renewed
September 2015	Annual Review	Policy Renewed
October 2014	Annual Review	Policy Revised
December 2013	Annual Review	Policy Renewed
May 2013	Annual Review	Policy Renewed
May 2012	Annual Review	Policy Renewed
May 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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