02.04.05 Saliva Hormone Tests

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Related Policies
None

Summary

Description
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, sleep disorders, and effect pregnancy. Salivary tests may help to identify hormonal changes in individuals and have been purposed to diagnose and monitor hormonal changes with menopause and preterm labor which are discussed in this evidence review.

Summary of Evidence
For individuals who have menopause who receive saliva hormone testing the evidence includes 1 systematic review and 1 observational study. Relevant outcomes include change in health status and morbid events. The lack of clinical studies do not permit conclusions in the clinical utility of salivary hormonal testing to manage menopause or imbalances of hormones in aging. Some association studies have been identified in the literature; however, there are no published clinical trials or adequately powered

reviews/studies that demonstrate how the results of salivary hormone testing can be used clinically to direct patient treatment of menopause. Therefore, the use of diagnosing or monitoring for the evaluation and management of menopause have not been proven. Further well powered-randomized controlled trials with long term outcomes need to be completed to determine the technology improves net health outcomes. The evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

For individuals who are at risk for preterm labor who receive saliva hormone testing the evidence includes 2 systematic reviews. Relevant outcomes include change in health status and morbid events. Some studies have shown that maternal levels of serum estradiol and salivary estriol increase before the onset of 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 certain medications. The test carries a high percentage of false-positive results. There are no clinical utility studies that examined the influence of saliva hormone testing on treatment decisions for preterm labor. Trials with salivary estriol testing have failed to establish its improvement in the net health outcomes. Further well powered-randomized controlled trials with long term outcomes need to be completed to determine the technology improves net health outcomes. The evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

Additional Information

None

OBJECTIVE

The objective of this evidence review is to evaluate the net health outcome of the use of salivary hormone to assess and aid in the diagnosis and monitoring of preterm labor and menopause.

PRIOR APPROVAL

Not applicable.

POLICY

Menopause

The use of salivary testing for individuals with menopause is considered **investigational** for all indications because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

Preterm Labor Risk

The use of salivary testing to assess preterm labor risk is considered **investigational** for all indications because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes.

POLICY GUIDELINES

Note:
Iowa House File 2668 (Iowa Code section 514C.36) requires that certain health plans issued or renewed on or after January 1, 2025 “provide coverage for biomarker testing for the purposes of diagnosing, treating, appropriately managing, or monitoring a disease or condition in a covered person when the biomarker testing has demonstrated clinical utility.” Iowa House File 2668 defines clinical utility

as ”sufficient medical and scientific evidence indicating that the use of a biomarker test will provide meaningful information that affects treatment decisions and guides improvement of net health outcomes, including an improved quality of life or longer survival.” Wellmark has reviewed this Medical Policy in light of Iowa House File 2668.

Coding

See the Codes table for details.

BACKGROUND

Salivary hormone measurement may be utilized for many purposes. Saliva testing for certain hormones (e.g., estrogen (estradiol), progesterone, testosterone, dehydroepiandrosterone (DHEA) and cortisol) has been purposed for the screening, diagnosis, and/or monitoring of menopause, preterm labor, and other conditions. Testing of hormone levels in the saliva has been suggested 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 imbalances and administration of individualized replacement therapy. 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. Salivary hormone levels may vary according to the time of day, diet, or hydration and saliva flow rate; therefore, the timing of saliva collection may affect results.

In 2008 Groschl provided an overview of the current applications of salivary hormone analysis. The author noted that although saliva has not yet become a mainstream sample source for hormone analysis, it has proven to be reliable and, in some cases, even superior to other body fluids. Nevertheless, much effort will be needed for this approach to receive acceptance over the long-term, especially by clinicians. Such effort entails the development of specific and standardized analytical tools, the establishment of defined reference intervals, and implementation of round-robin trials. One major obstacle is the lack of compliance sometimes observed in outpatient saliva donors. Moreover, the author stated that there is a need for standardization of both collection and analysis methods to attain better comparability and evaluation of published salivary hormone data.

Individualized testing and monitoring are only useful when a narrow therapeutic window exists for a drug or a drug class. Steroid hormones, such as estrogen and progesterone, do not require individualized testing (ACOG & ASRM, 2012). Furthermore, there is no evidence that hormonal levels in saliva are biologically meaningful. Salivary hormone levels often fluctuate with factors, such as circadian rhythm, and frequently do not correlate well with serum levels of hormones. Saliva is an ultra- filtrate of the blood and in theory, should be amenable to testing for free concentrations of hormones. Studies suggest 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 within-patient variability associated with salivary hormone assays makes them inaccurate and unreliable, especially when exogenously administered hormones are given. Different laboratories may require different testing methods, such as obtaining several samples over a couple of weeks at specific times of the day. 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. Several laboratory tests are now being offered to consumers as home-based testing.

Menopause

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. Hormone therapy (HT) (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. Salivary hormone tests have been purposed to measure the number of free hormones (dehydroepiandrosterone [DHEA], estrogen, melatonin, progesterone and/or testosterone) found in the saliva. A salivary hormone test has been developed by Genova Diagnostics, which evaluates levels of hormones during perimenopause, menopause,

Evidence-based clinical practice guidelines from the American Association of Clinical Endocrinologists outline the appropriate methods of screening and diagnosing menopause. The primary test for menopause screening is serum follicle-stimulating hormone, for thyroid dysfunction serum thyroid-stimulating hormone, and bone density measurement is the primary method of screening for osteoporosis. These guidelines indicate salivary testing as an appropriate method of screening, diagnosing, or monitoring these disorders.

Pre-Term Labor

Preterm labor that leads to preterm birth is considered a healthcare problem worldwide. It is a major complication of pregnancy and remains a leading cause of neonatal morbidity and mortality worldwide. The National Center for Health Statistics (National Vital Statistics System) in 2024 (published in May 2025) reports that the birth rate was 3,622,673 and the preterm birth rate was 10.41% in the United States. Improvements in the understanding of the pathophysiology of preterm labor have led to the development of novel diagnostic tools of use to identify individuals at greatest risk for preterm birth. Therefore, identification of individuals at risk for preterm labor has been a research focus for many years, with the hope that early intervention can prevent the progression from preterm labor to preterm birth. Current techniques include a scoring system based on an individual's past medical history (the Creasy system), home uterine activity monitoring, and measurements of fetal fibronectin collected on a cervical swab. It has also been observed that salivary estriol levels surge several weeks before the onset of spontaneous preterm labor.

Measurement of salivary estriol has been explored as a risk predictor for preterm labor. Salivary hormone tests are purported to predict spontaneous premature labor by measuring salivary estriol, an estrogen hormone. A surge in the levels of salivary estriol typically occurs several weeks prior to the onset of spontaneous labor.

Regulatory Status

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.

- 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.
- Genova Diagnostics has developed several saliva hormone tests including Menopause Plus™, Menopause Plus™ is Genova's most comprehensive salivary hormone profile and is designed to provide insight into the impact that shifting hormone levels. 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.

- Salivary estriol - (i.e., SalEst™) is a laboratory technique approved by the FDA for measuring salivary estriol as a risk assessment marker of preterm labor and delivery. The SalEst system is indicated for use every 1 to 2 weeks in pregnant women with singleton pregnancies between their 22nd and 36th weeks of pregnancy.

Note: This section is not intended to be all inclusive.

RATIONALE

This evidence review was created in May 1998 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 2025.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Menopause

Clinical Context and Test Purpose

The purpose of salivary hormone testing is to assess and aid in the diagnosis, treatment and monitoring of menopause.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals presenting with hormone changes due to menopause.

Interventions

The intervention includes saliva hormone tests including but not limited to estrogen (estradiol), progesterone, testosterone, melatonin, cortisol, 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 include survival, test accuracy, test validity, morbid events.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

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).

Review of Evidence

Systematic Reviews
In July of 2013 Hayes, a symplr company, completed a Health Technology Assessment (HTA) which was last reviewed in June of 2017 on salivary hormone testing for menopausal individuals. The HTA only identified 2 studies that used statistical analyses to evaluate the correlation between hormone levels in saliva and blood. These studies reported significant relationships between estrogen and testosterone levels in saliva and blood in individuals receiving hormone therapy, but neither study reported sensitivity or specificity statistics. The HTA did not identify any clinical utility studies that examined the influence of saliva hormone testing on treatment decisions for postmenopausal individuals. The HTA rated salivary hormone testing in postmenopausal individuals for determination of menopausal state or for guidance of treatment decisions a D^2 rating. A D^2 rating indicates, “insufficient evidence. There is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management."

Observational Studies
In addition to the 2 studies evaluated in the HTA, Geoffroy (2012) published a large cohort study assessing the relationship between cortisol levels and cognitive deficits with aging, in 4655 patients. A total of four salivary samples were obtained from each patient; two at 45 years: one taken 45 minutes after waking and another three hours later, and then two at 50 years using the same sampling method. Authors reported an association between increased cortisol levels and a reduction in verbal memory and fluency tests at 50 years compared to initial scores. Although these results suggest an association between increased salivary cortisol measurements and some cognitive deficits over time, the evidence does not demonstrate that salivary hormone testing reliably improves clinical decision-making or health outcomes related to age-related cognitive function. In addition, it is unclear if the same results would have been reached if cortisol levels had been measured using some other method, such as blood sampling.

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, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No evidence is available from randomized or nonrandomized controlled studies in which outcomes from groups of well-matched patients managed using salivary testing were compared with those managed using serum specimens for measurement of hormones.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Due to insufficient evidence of clinical validity, no inferences can be drawn about the clinical utility of salivary testing in menopause.

Section Summary: Salivary Testing in Menopause

The lack of clinical studies do not permit conclusions in the clinical utility of salivary hormonal testing to manage menopause or imbalances of hormones in aging. Some association studies have been identified in the literature; however, there are no published clinical trials or adequately powered reviews/studies that demonstrate how the results of salivary hormone testing can be used clinically to direct patient treatment of menopause. Therefore, the use of diagnosing or monitoring for the evaluation and management of menopause have not been proven. Further well powered-randomized controlled trials with long term outcomes need to be completed to determine the technology improves net health outcomes.

Preterm Labor

Clinical Context and Test Purpose

The purpose of salivary hormone testing is to assess and aid in the diagnosis and monitoring of preterm labor.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals presenting with hormone changes due to preterm labor.

Interventions

The intervention includes saliva hormone tests including but not limited to estrogen (estradiol), progesterone, testosterone, cortisol, and/or dehydroepiandrosterone (DHEA) which can be used to monitor the risk of preterm labor.

Comparators

The comparators of interest are standard of care: scoring system based on an individual past medical history (the Creasy system), home uterine activity monitoring, measurements of fetal fibronectin collected on a cervical swab, hormones serum specimen measurement.

Outcomes

The outcomes of interest include test accuracy, test validity, reduction in the incidence of preterm labor or birth, or both; decrease in the incidence of hospitalization in the neonatal intensive care unit (NICU); or degree of cervical dilation at the time of diagnosis of preterm labor, morbid events.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

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).

Review of Evidence

Systematic Reviews
In October of 2025 Hayes, a symplr company, completed a Health Technology Assessment (HTA) which was last reviewed in October of 2009 on salivary estriol test for preterm labor. The HTA identified 2 studies that “have investigated the diagnostic performance of salivary estriol testing to predict preterm labor and birth (McGregor et al., 1995; Heine et al., 1999; Heine et al., 2000); the results of one of the studies were reported in two journal articles (Heine et al., 1999; Heine et al., 2000). Both studies were prospective, blinded, and multicenter. All studies were performed by or with support of the manufacturer of SalEst, which is the only salivary estriol test commercially developed for this indication. While manufacturer involvement always raises concern about investigator bias, both studies were blinded. There are 2 issues utilizing salivary estriol to identify the preterm delivery risk. The sample group (singleton pregnancies with a preterm delivery risk) is small, “and the sensitivity of the test is approximately 42% to 64%, which results in low positive predictive value for the test, even for women with known risk factors.” Additionally there are no proven treatments “to prevent the onset of labor or to significantly prolong gestation; thus, even accurate detection of individuals at high risk for preterm delivery would be unlikely to alter pregnancy outcome.” A negative salivary estriol test may provide reassurance and could potentially reduce unnecessary tocolytic therapy, it is also possible it would lead to increased unnecessary surveillance and use of tocolytic drugs, without change in the net health outcome.

The HTS did not identify any clinical utility studies that examined the influence of saliva hormone testing on treatment decisions for the prediction of preterm labor and birth. The HTS rated the salivary estriol test “as an aid in predicting risk of preterm delivery in women with known risk factors for preterm labor and delivery and singleton pregnancies” a C rating. A C rating indicates, “Potential but unproven benefit. Some published evidence suggests that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, substantial uncertainty remains about safety and/or impact on health outcomes because of poor-quality studies, sparse data, conflicting study results, and/or other concerns." The HTS rated the salivary estriol test”in women with no known risk factors for preterm delivery” a D rating. The HTS also rated the salivary estriol test “in women with multiple gestations a D rating. A D rating indicates, “No proven benefit. Published evidence shows that the technology does not improve health outcomes or patient management for the reviewed application(s) or is unsafe.”

In addition to the studies evaluated in the HTA, Klebanoff et al (2008) completed a secondary analysis of a clinical trial that examined if salivary progesterone (P) or estriol (E3) concentration at 16 to 20 weeks' gestation predicts preterm birth or the response to 17alpha-hydroxyprogesterone caproate (17OHPC). Baseline saliva was assayed for P and E3. Weekly salivary samples were obtained from 40 women who received 17OHPC and 40 who received placebo. Both low and high baseline saliva P and E3 were associated with a slightly increased risk of preterm birth. However, 17OHPC prevented preterm birth

comparably, regardless of baseline salivary hormone concentrations. Thus, salivary P or E3 does not appear to predict preterm birth.

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, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No evidence is available from randomized or nonrandomized controlled studies in which outcomes from groups of well-matched patients managed using salivary testing were compared with those managed using serum specimens for measurement of hormones.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Due to insufficient evidence of clinical validity, no inferences can be drawn about the clinical utility of salivary testing in menopause.

Section Summary: Preterm Labor

Some studies have shown that maternal levels of serum estradiol and salivary estriol increase before the onset of 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 certain medications. The test carries a high percentage of false-positive results. Trials with salivary estriol testing have failed to establish its improvement in the net health outcomes. Further well powered-randomized controlled trials with long term outcomes need to be completed to determine the technology improves net health outcomes.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists (ACOG)

In 2012, ACOG Committee published Opinion Number 532, Compounded Bioidentical Menopausal Therapy that waswhich stated, “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. There are several problems with salivary testing and monitoring of free hormone levels.

- First, salivary levels do not consistently provide a reasonable representation of endogenous, circulating serum hormones. There is large 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.
- Second, because 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.
- Third, saliva contains far lower concentrations of hormone than serum and is prone to contamination with blood, infectious agents, and epithelial cells—–all of which may affect the level of hormone to be measured."

In November 2023 the ACOG issued a Clinical Consensus Number 6, Compound Bioidentical Menopausal Therapy, that replaced the committee opinion Number 532. The updated publication states "salivary testing does not offer accurate or precise assessment of hormone levels. 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."

American Association of Clinical Endocrinologists (AACE)

In 2011 the AACE published Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause which noted 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 sex 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)).

North American Menopause Society (NAMS)

In 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).

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	No code(s)	
HCPCS		
	S3650	Saliva test, hormone level; during menopause
	S3652	Saliva test, hormone level; to assess preterm labor risk
Type of Service	Laboratory	
Place of Service	Outpatient/ Inpatient	

POLICY HISTORY

Date	Reason	Action
August 2025	Annual Review	Policy Renewed
August 2024	Annual Review	Policy Renewed
August 2023	Annual Review	Policy Revised
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:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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