MEDICAL POLICY

Premature Rupture of Membranes (PROM) Testing

Effective Date: 9/1/2019

Section: LAB  Policy No: 107

Technology Assessment Committee Approved Date: 2/2011; 2/12; 6/13; 5/14; 5/15; 7/15; 4/16

Medical Policy Committee Approved Date: 6/17; 6/18; 8/19

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

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

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid 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.

POLICY CRITERIA

Tests for the evaluation of premature rupture of fetal membranes are considered investigational and are not covered. Tests include, but are not limited to:

1. Actim® ROM
2. AmniSure® ROM
3. PartoSure™
4. ROM Plus® Fetal Membrane Rupture Test

CPT CODES

All Lines of Business
Not Covered

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>84112</td>
<td>Evaluation of cervicovaginal fluid for specific amniotic fluid protein(s) (e.g., placental alpha microglobulin-1 [PAMG-1], placental protein 12 [PP12], alpha-fetoprotein), qualitative, each specimen</td>
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Unlisted Codes

All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be denied as not covered.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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</table>

DESCRIPTION

During pregnancy, the fetal membrane protects the developing fetus and its surrounding fluid from infection. Although tearing or rupture of membranes (ROM) normally occurs during labor, in approximately 12% of pregnancies that are at term (≥ 37 weeks of development), the membrane ruptures before initiation of labor, which is called premature ROM (PROM). PROM that occurs at < 37 weeks of development is referred to as preterm premature ROM (PPROM), which complicates approximately 3% of all pregnancies in the United States. Early detection of PROM and PPROM is important, since physicians must respond quickly to the substantial increase in risks after these conditions.

The optimal approach to clinical assessment and treatment of women with term and preterm PROM remains controversial. Management hinges on knowledge of gestational age and evaluation of the relative risks of delivery versus the risks of expectant management (e.g., infection, abruptio placentae, and umbilical cord accident). Standard methods for detection of PROM include the following: visual pooling of amniotic fluid, sterile speculum examination, nitrazine test to assess the pH of vaginal secretions, microscopic evaluation of crystallization of amniotic fluid into fernlike patterns, ultrasonographic examination to assess amniotic fluid levels, and ultrasonographically guided transabdominal instillation of indigo carmine dye. However, a speculum examination can cause patient discomfort and standard vaginal fluid analysis techniques may give inaccurate results.

There are three commercially available tests intended to detect rupture of fetal membranes:

- Actim® PROM test (manufactured by Medix Biomedica, Espoo, Finland, and distributed in the United States by Cooper Surgical, Inc., Trumbull, CT) is a rapid, point-of-care, qualitative immunoassay intended to detect premature rupture of fetal membranes in pregnant women with symptoms suggestive of fetal membrane rupture. The test detects the presence of human IGFBP-1 in cervicovaginal secretions.
- AmniSure® ROM (rupture of membrane) test (AmniSure International, LLC, Boston, MA, a Qiagen Sciences company) is a noninvasive immunoassay intended to detect premature rupture of fetal membranes in pregnant women with symptoms suggestive of fetal membrane rupture. The test detects the presence of human PAMG-1 (Placental Alpha Microglobulin-1, a protein found in amniotic fluid) in vaginal secretions.
• PartoSure™ (Parsagen Diagnostics, Inc.) is a noninvasive test for predicting preterm birth by detecting levels of PAMG-1 in patient vaginal discharge. According to the company, "the PartoSure Test is intended to be used as an aid to rapidly assess the risk of preterm delivery in ≤ 7 or ≤ 14 days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilation (≤3 cm) sampled between 20 weeks, 0 days and 36 weeks, 6 days gestation."¹¹

• ROM Plus® test (Clinical Innovations, LLC, Murray, UT) is a rapid, noninvasive, immunochromatographic, point-of-care test intended to detect premature rupture of fetal membranes (PROM) in pregnant women with symptoms suggestive of membrane rupture. The test detects the presence of alpha-fetoprotein (AFP) and insulin-like growth factor binding protein-1 (IGFBP-1) in vaginal secretions using monoclonal antibodies.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of tests for the evaluation of premature membrane rupture. Below is a summary of the available evidence identified through April of 2017.

Comparison of Tests

Systematic Reviews

In late 2017, Hayes published a systematic review which evaluated the use of the Actim PROM-POC PROM Test, AmniSure ROM Test, and the ROM Plus Test.¹² The evidence review did not find any head-to-head comparative studies. The review did include 7 studies, including prospective comparative studies, a meta-analysis, and comparative in vitro studies. The Hayes review concluded there continues to be, insufficient evidence to inform definitive conclusions about the superiority of any of the requested tests for premature rupture of membranes (PROM) during pregnancy. “

AmniSure

Of all the commercially available tests for PROM, AmniSure was the first to be approved by the U.S. Federal Drug Administration (FDA) and there have been a large number of studies published on the accuracy of AmniSure. Therefore, the evidence section below for this test is limited to systematic reviews that evaluated the test performance of AmniSure on its own, or compared to clinical tests or other commercially available PROM tests. Importantly, no studies were identified that reported on the clinical utility of this test. Studies are needed to determine if the use of the AmniSure test impacts health outcomes and changes in management.

Systematic Reviews

In 2012, Hayes published a systematic review of the published studies on the AmniSure test, including two large prospective studies that evaluated the test on its own, and eight studies (n=40-206 patients) which compared the AmniSure test other methods for detection of fetal membrane rupture.² In the three large studies comparing the AmniSure ROM Test with a battery of standard clinical tests, the
AmniSure ROM Test had high sensitivity and specificity. However, in one of the three studies the false-positive rate was high (12.5%). The review reported that the overall quality of the evidence was considered low and the majority of the included studies had design flaws that made it difficult to assess the diagnostic ability of the AmniSure test. These design flaws included using inappropriate controls leading to bias, enrolling participants in patient populations known to be associated with highly variable amniotic fluid index, and heterogeneity in the comparators (the Actim PROM test, nitrazine testing and various combinations of clinical tests). In addition, the review was unable to identify RCTs that evaluated the impact of the AmniSure ROM Test on clinical decision making or health outcomes. The review concluded that the accuracy of the AmniSure test was not support its use as a stand-alone method for diagnosing PROM and that additional studies evaluating the AmniSure in women with equivocal PROM are needed to confirm the utility of the test as an adjunct to standard tests, warranting a rating of “C”. The review indicated that future studies should compare AmniSure with the currently used suite of complete suite of clinical tests as the reference standard for diagnosis of PROM.

In 2013, Ramsauer et al. published a meta-analysis that evaluated the accuracy of the Actim® PROM test compared to AmniSure®. Of the 12 studies that met inclusion criteria, four studies utilized Actim PROM (N=648), six utilized AmniSure (N=501), and two studies compared both biomarker tests (N=261). Pooled analysis included only those women with suspected ROM who had later confirmation of the diagnosis through standard clinical tests. When the two tests were compared with respect to their test performance in similar groups (i.e., patients presenting with suspected ROM but for whom leakage from the cervical os could not be visualized = unknown membrane status), AmniSure performed better than Actim PROM, with significantly higher sensitivity (96.0 % vs. 73.9%) and specificity (98.9% versus 77.8%). The studies included in this meta-analysis were heterogeneous in terms of study protocols, the clinical characteristics of included patients, and the gold standard used for confirming PROM diagnosis. In addition, women with bleeding were excluded from most of the included studies, making it unclear whether the findings were representative of the broader population of women presenting with suspected PROM. Lastly, clinical utility was not reported and, therefore, it remains unclear whether the use of these tests resulted in improved health outcomes for the mother or baby.

In 2014, Palacio et al. published a meta-analysis that compared the accuracy of Actim PROM and AmniSure tests including 17 studies; 10 for Actim PROM (N = 1,066), four for AmniSure (n = 1,081) and three studies in which both biomarker tests were compared directly. Analysis included women with suspected ROM who were later diagnosed through standard clinical tests. Among women whose membrane rupture status was known, AmniSure was not significantly different from Actim PROM in terms of test performance (Actim PROM: sensitivity: 98.2%, specificity: 95.8%, PPV: 96%, NPV 98%; AmniSure: sensitivity: 96.5%, specificity: 98.2%, PPV: 98.2%, NPV 96.5%). Among women whose rupture status was unknown, AmniSure performed significantly better than Actim PROM (Actim PROM: sensitivity: 92.1%, specificity: 90.5%, PPV: 87.9%, NPV 93.9%; AmniSure: sensitivity: 96.8%, specificity: 93.3%, PPV: 94.8%, NPV 96.7%). Pooled showed no significant differences in sensitivity or NPV between tests, but AmniSure had superior specificity and PPV compared with Actim PROM. The reviewers concluded that there was no difference in test performance in studies where they were used under the same clinical conditions or in women with known membrane status, and that further studies were needed, since the exclusion of bleeding patients may not be representative of women clinically presenting with suspected PROM.
In 2018, Hayes published a systematic review of the AmniSure test to evaluate the sensitivity, specificity, negative/positive predictive value, accuracy, and clinical utility of testing to detect fetal membrane rupture.13 A total of 18 tests were included in the review; 17 studies evaluated the capacity of AmniSure to detect PROM and 1 study assessed the clinical utility of testing. The review found the sensitivity of testing to be 89-100% and specificity to be 88-100%. However, the Hayes review noted, “(w)hen comparing the results of diagnostic tests, it is essential to remember that overall test accuracy relies on both the sensitivity (correct detection of patients who do have the condition) and the specificity (correct exclusion of patients who do not have the condition). Although some of these studies found that the AmniSure test is somewhat better than the usual combined methods for diagnosis of PROM, the available studies have not provided consistent evidence that the AmniSure test is more accurate than the nitrazine test or ferning test, which are often combined with sterile speculum examination for detection of PROM. In addition, the available studies have not demonstrated that the AmniSure test is more accurate than other available immunoassays for diagnosis of PROM.” In addition the review indicated there was insufficient evidence to evaluate the clinical utility of testing. Hayes issued a “C rating” to the AmniSure test, stating, “additional studies are needed to determine the accuracy of the AmniSure test relative to established testing methods.”

No studies regarding the efficacy of the AmniSure test were identified since the publication of the 2018 Hayes systematic review noted above.

Actim PROM

Since the systematic reviews described were published, several studies have been published which have evaluated the Actim PROM test. These studies are summarized below. Importantly, no studies were identified that reported on the clinical utility of this test, in that health outcomes and changes in management as a result of the Actim PROM test have not been addressed.

Randomized Controlled Trials

In 2014, Liang et al. conducted an RCT that compared the accuracy of placental α-microglobulin-1 (PAMG-1, AmniSure), insulin-like growth factor binding protein-1 (IGFBP-1, Actim PROM) and nitrazine test to diagnose PROM, including 120 pregnant women between 11 and 42 weeks with signs/symptoms of PROM.6 The authors reported that AmniSure was the most accurate test to diagnose premature rupture of membranes with the highest sensitivity, specificity, positive predictive value and negative predictive value. However, statistical analyses were not reported, making it difficult to draw conclusions.

Nonrandomized Studies

In 2013, Abdelaizm and Makhouf published a study that compared the performance of placental alpha microglobulin-1 (PAMG-1, AmniSure) versus insulin-like growth factor binding protein-1 (IGFBP-1, Actim PROM) to diagnose PROM, including 150 women who were divided into two groups according to presence or absence of PROM.7 In this study, no significant differences in sensitivity, specificity, NPV, PPV or accuracy were found between the two tests.

In 2014, Abdelazim published a case-control study which evaluated the accuracy of the Actim PROM test, compared to nitrazine testing and the ferning test in diagnosing PROM in 150 pregnant women
The women were divided into two groups according to presence or absence of premature rupture of the membranes (PROM); 75 patients with PROM were included in group I and 75 patients without PROM were included in group II as controls. In this study, the sensitivity and the specificity of IGFBP-1 (Actim PROM test) in diagnosing PROM were 89.3% and 82.7%, respectively, as compared with 84% sensitivity and 78.7% specificity for the Ferning test, and 86.7% sensitivity and 81.3% specificity for the Nitrazine test. The positive predictive value (PPV) and negative predictive value (NPV) of IGFBP-1 were 83.8% and 88.6%, respectively, as compared with 79.7% PPV and 83.1% NPV for the Ferning test, and 82.2% PPV and 85.9% NPV for the Nitrazine test. Although the authors stated that the Actim PROM test was more accurate than the two standard clinical tests it was measured against, it was unclear if the test performance parameters reported were significantly different between the tests.

Nonrandomized Studies

In 2013, Thomasino et al. published a multicenter prospective observational comparative study that evaluated the accuracy of the PROM Plus test compared to current conventional clinical assessment for diagnosis of ROM. The study included 285 patients (15-42 weeks of gestation) presenting with signs or symptoms of ruptured amniotic membranes. The false positive rate for the ROM Plus test was 9% and the false negative rate was 0.5%. The sensitivity and specificity were 99% and 91%, respectively; and the positive and negative predictive values were 95% and 99%, respectively. Although the author’s stated that the ROM Plus test detects PP12 and AFP with an efficacy comparable to conventional testing and better than the individual components of conventional testing (ferning, nitrazine), statistical analyses were not reported, making it difficult to draw conclusions.

In 2016, Rogers et al. published a study which compared the diagnostic performance characteristics between the ROM Plus test and the ferning test as measured in the same patient. Both tests were run on 75 pregnant patients who presented to labor and delivery with complaints of leaking amniotic fluid. The ROM Plus test performance measures were higher than that of the fern test: sensitivity (100% vs. 77.8%), specificity (94.8% vs. 79.3%), PPV (75% vs. 36.8%), NPV (100% vs. 95.8%), and accuracy (95.5% vs. 79.1%). Although the author’s stated that the ROM Plus test provides improved diagnostic accuracy for the detection of ROM compared to fern testing, statistical analyses were not reported, making it difficult to draw conclusions.

CLINICAL PRACTICE GUIDELINES

American College of Obstetricians and Gynecologists (ACOG)

In 2016, ACOG updated their Practice Bulletin on Premature Rupture of Membranes, stating that the
optimal approach to clinical assessment and treatment of women with term and preterm PROM remains controversial. According to ACOG, most cases of PROM can be diagnosed on the basis of the patient’s history and physical examination. The guideline further states that several tests for amniotic proteins are currently available with high reported sensitivity for PROM. However, these tests should be considered ancillary to standard diagnostic methods due to reported false-positive rates of 19%–30% in patients with clinically intact membranes and symptoms of labor.

In 2018, ACOG updated the practice bulletin on premature rupture of membranes which continued to note the false-positive test rate and indicated PROM testing should not replace standard testing techniques.\textsuperscript{14}

**CENTERS FOR MEDICARE & MEDICAID**

As of May 2018, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses PROM testing for any indication.

**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 Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days’ notice of policy changes that are restrictive in nature.

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.

**REGULATORY STATUS**

**Mental Health Parity Statement**

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.

**REFERENCES**


11. ECRI Institute; PartoSure Test (Parsagen Diagnostics, Inc.) for Predicting the Risk of Preterm Labor; Custom Product Brief; Published: 4/27/2017; Accessed: 5/15/2018; link.

12. Hayes; Tests for Premature Rupture of Fetal Membranes; Product Comparison; Published 12/26/2017; Accessed: 5/15/2018; link.

13. Hayes; AmniSure ROM Test for Detection of Fetal Membrane; Medical Technology Directory; Published 3/20/2018; Accessed: 5/15/2018; link.