MATERNAL SERUM SCREENING

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INSTRUCTIONS FOR USE

Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

BeaconLBS recommends that maternal serum screening to identify pregnancies at risk of aneuploidy/fetal chromosome abnormalities or structural abnormalities should be performed on:

- All women, regardless of maternal age, who present before 20 weeks of gestation.
  - If the woman seeks prenatal care in the first trimester (14 weeks or less), a strategy that incorporates both first- and second-trimester screening should be offered (i.e., first trimester, integrated, or sequential screening).
  - Neural tube defect screening [i.e., open spina bifida (OSB)] should be offered in the second trimester to women who elect only first-trimester screening for aneuploidy by the use of a second trimester alpha fetoprotein (AFP) test.
  - If the woman presents for prenatal care after the first trimester for screening, the Quadruple Marker testing strategy recommended at 15-20 weeks gestation.
These recommendations are based upon guidelines from the American College of Obstetricians and Gynecologists (ACOG).

**BACKGROUND**

Maternal serum screening is a noninvasive way in the first or second trimester in pregnancy to identify pregnancies at high risk for fetal chromosomal and structural abnormalities (i.e., Down syndrome, trisomy 18, open spina bifida(OSB), and other serious fetal abnormalities). Clinical use of maternal serum screening to evaluate risk of fetal abnormalities began in the 1970s, when high maternal serum alpha fetoprotein (AFP) levels were shown to be correlated with increased risk of OSB. The goals of early identification of risk for fetal abnormalities include:

- To decrease the likelihood that patients will undergo invasive diagnostic procedures such as amniocentesis and chorionic villus sampling, unless such procedures are appropriate;
- To assist families to make informed reproductive choices;
- To provide information to guide clinical and other decisions about prenatal care, delivery, and neonatal care.

By definition, screening tests often have a higher rate of false negative results or false positive results when compared to diagnostic tests. Laboratories will often combine multiple screening analytes in order to simultaneously maximize detection rates and minimize false positive rates.

Accurate estimation of gestational age is important for all screening tests, and is best obtained with ultrasound measurements. Additionally, imaging studies may be particularly useful in multiple gestational pregnancies. Maternal serum levels increase with each additional fetus and therefore, Down syndrome risks are not typically provided when there are more than 2 fetuses.

Maternal serum markers and ultrasound measurements during pregnancy must be assessed in the context of multiple other factors, including maternal age, race, weight, family history, gestational age, and presence of insulin dependent diabetes. Therefore, the laboratory should have access to this demographic and clinical information. The choice of screening tests to be performed is dependent on several factors including gestational age at presentation, availability of follow-up diagnostic testing, and patient preference.

**Screening Panels**

Table 1 presents the combinations currently in widespread use with gestational timing, and detection and false positive rates.

*Quadruple Marker Screening*

The Quadruple Marker Screen or “Quad” screen is available for women who present between 15 and 20 weeks gestation. It combines measurements of maternal serum AFP, human chorionic gonadotropin (hCG), dimeric inhibin A (DIA), and unconjugated estriol (uE3) with maternal age risk. Historically, the second-trimester Quad Marker Screen supplanted a combination of maternal serum AFP, hCG, and uE3 (Triple Test; not shown in Table 1) because it improved the detection rate for Down syndrome from 70% to 80%.
The Quadruple Marker screen has an estimated detection rate of 75-80% for Down syndrome (with a 5% false-positive rate) and 73% for trisomy 18 (with a 0.5% false-positive rate). A risk assessment for OSB is also provided with an estimated detection rate of 80% (with a 1-3% false-positive rate).

First Trimester Screening

The First Trimester screening approach includes ultrasound measurement of nuchal translucency (NT) and/or nasal bone, pregnancy-associated plasma protein A (PAPP-A), and hCG. Some laboratories include dimeric inhibin A (DIA) in order to increase Down syndrome detection. This approach is available for women who present in the first trimester for screening and who wish to complete their aneuploidy screening in the first trimester. The detection rates for Down syndrome and trisomy 18 are 86% (with a 5% false-positive rate) and 75% (with a 0.5% false-positive rate), respectively.

Screening for OSB cannot be performed in the first trimester, therefore patients receiving first trimester screening are recommended to have serum AFP testing in the second trimester.

Integrated Screening

Integrated screening combines first- and second-trimester screening test results to determine a pregnant woman’s risk of Down syndrome and trisomy 18. This approach requires measurements from two blood specimens, one collected in the first trimester and one collected in the second trimester. The Integrated screening approach includes maternal age risk, first trimester NT and PAPP-A screening measurements, and second trimester AFP, uE3, hCG, and DIA (Quad screen) measurements. The results of the first trimester portion of the Integrated screening tests are reported only after the second trimester test results are available.

This approach achieves higher detection rates for Down syndrome and trisomy 18 than the First Trimester screening approach. The detection rate for Down syndrome with this approach is 92.4% (with a 3.3% false-positive rate). For trisomy 18, the detection rate is 90% and for OSB the rate is 80%.

Serum Integrated Screening

Serum Integrated screening is identical to Integrated screening, except that a NT measurement is not used in the risk assessment. Serum Integrated Screening combines maternal age risk and first trimester maternal serum PAPP-A measurement with second trimester measurements of AFP, uE3, hCG, and DIA (Quad screen). This test may be beneficial for women without access to an NT measurement or for women in whom an NT measurement cannot be obtained for technical reasons.

This approach achieves detection rates higher than those with the first trimester or second trimester Quadruple Marker screening (see Table 1). The estimated detection rate for Down syndrome is 88.1% (with a false-positive rate of 6.0%). For trisomy 18 and OSB the detection rates are 90% and 80%, respectively.

Sequential Screening

The Sequential approach to screening is a refinement of the Integrated approach that makes testing in the second trimester dependent on the results of first trimester screening tests. For most patients, Sequential Screening will require measurements from two blood specimens, one collected during the first trimester and the other in the second trimester.
In the first stage of Sequential Screening, an initial Down syndrome risk assessment is performed using maternal age, first trimester NT, PAPP-A, and hCG. Women with an exceptionally high Down syndrome risk are reported as screen positive with the recommendation to refer them for genetic counseling and diagnostic testing. Women whose Down syndrome risk assessment is below the cut-off proceed with the second stage of Sequential Screening (second trimester maternal serum AFP, uE3, hCG, and DIA analysis), at which time a final risk assessment for Down syndrome is provided based on NT, PAPP-A, and the four second trimester markers. Sequential Screening provides an estimated Down syndrome detection rate of 92.3% (with a 3.5% false-positive rate).  

A screening result is provided for OSB, and the screening markers are also used to identify pregnancies at high risk of trisomy 18. The estimated detection rate for trisomy 18 is 90% (with a 0.1% false-positive rate).  

Table 1. Accuracy of maternal serum and ultrasound screening approaches in pregnancy

<table>
<thead>
<tr>
<th>Screening Approach</th>
<th>Gestational Age&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Down syndrome</th>
<th>Trisomy 18</th>
<th>Open Spina Bifida (OSB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Trimester</td>
<td>Second Trimester</td>
<td>Detection Rate</td>
<td>False-positive Rate</td>
</tr>
<tr>
<td>Quadruple Screen</td>
<td>None</td>
<td>AFP, uE3, hCG, DIA&lt;sup&gt;*&lt;/sup&gt;</td>
<td>75-80%&lt;sup&gt;8&lt;/sup&gt;</td>
<td>5%&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>First Trimester</td>
<td>NT, PAPP-A, hCG, DIA&lt;sup&gt;*&lt;/sup&gt;</td>
<td>None</td>
<td>86%&lt;sup&gt;8&lt;/sup&gt;</td>
<td>5%&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Integrated</td>
<td>NT, PAPP-A</td>
<td>AFP, uE3, hCG, DIA</td>
<td>92.4%&lt;sup&gt;11&lt;/sup&gt;</td>
<td>3.3%&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum Integrated</td>
<td>PAPP-A</td>
<td>AFP, uE3, hCG, DIA</td>
<td>88.1%&lt;sup&gt;11&lt;/sup&gt;</td>
<td>6%&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sequential</td>
<td>NT, PAPP-A, hCG</td>
<td>AFP, uE3, hCG, DIA</td>
<td>92.3%&lt;sup&gt;11&lt;/sup&gt;</td>
<td>3.5%&lt;sup&gt;11&lt;/sup&gt;</td>
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<sup>a</sup> Screen positive result indicates diagnostic testing should be offered.  
*Some laboratories include DIA in order to increase Down syndrome detection.  
Abbreviations: AFP, alpha fetoprotein; DIA, serum dimeric inhibin A; hCG, serum human chorionic gonadotropin; NA, not applicable; NR, not reported; NT, nuchal translucency; PAPP-A, serum pregnancy-associated plasma protein A; uE3, serum unconjugated estriol.

**Screening Panel Components (Analytes)**

**Alpha Fetoprotein (AFP)**

AFP is an albumin-like fetal protein that enters the maternal circulation via the placenta and amnion. Low maternal serum AFP, in the second trimester, is correlated with increased risk of Down syndrome and trisomy 18, and high maternal serum AFP is correlated with increased risk of OSB.<sup>2, 6</sup>

**Dimeric Inhibin A (DIA)**

DIA is a dimeric glycoprotein hormone secreted by both the placenta and maternal gonads. Elevations of maternal serum DIA levels in the first and second trimesters are correlated with risk of fetal Down syndrome. DIA is not used to evaluate the risk of trisomy 18 or OSB.<sup>3</sup>

**Human Chorionic Gonadotropin (hCG)**

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hCG is a glycoprotein hormone involved in maintaining the corpus luteum and occurs as a heterodimer with alpha and beta subunits. Serum tests may measure levels of intact hCG (alpha and beta subunits) or free beta hCG. Serum hCG levels increase on average in women who are carrying a fetus with Down syndrome and are decreased for a fetus with trisomy 18.1 hCG is not used to evaluate the risk of OSB.

**Pregnancy-associated Plasma Protein A (PAPP-A)**

PAPP-A is a metalloproteinase that was originally identified as a placental protein in maternal serum.1 Maternal serum levels of PAPP-A are low in the first trimester in women carrying a fetus with Down syndrome or trisomy 18. PAPP-A is not used to evaluate the risk of OSB.

**Unconjugated Estriol 3 (uE3)**

uE3 is a steroid hormone expressed at high levels during pregnancy. Maternal serum uE3 levels in the second trimester are low in women carrying a fetus with Down syndrome or trisomy 18.6 uE3 is not used to evaluate OSB.

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**CLINICAL EVIDENCE**

Maternal serum screening to identify risk of fetal abnormalities is still evolving. For example, use of the first trimester screening approach has been increasing in the US. The first trimester screening approach is the most sensitive and selective screening approach available for pregnant women who do not wish to undergo screening in the second trimester.1

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**GUIDELINES AND RECOMMENDATIONS**

**American College of Obstetricians and Gynecologists (ACOG)1**

The current guidelines for clinical use of maternal serum screening from the American College of Obstetricians and Gynecologists (ACOG) are evidence-based.1 In 2007, ACOG issued a practice bulletin to describe the available clinical evidence concerning maternal serum markers levels and ultrasound studies as screening tests for fetal chromosomal abnormalities, and to make recommendations for screening for Down syndrome. The group noted that clinicians should consider factors such as gestational age at presentation, availability of follow-up diagnostic testing, and patient preference when deciding among first trimester, integrated, sequential, or quadruple marker screening tests for their pregnant patients.

In summary ACOG recommends1:

- All women, regardless of maternal age, who present before 20 weeks of gestation should be offered maternal serum screening to identify risk of aneuploidy, and should be educated concerning the meaning of screening versus diagnostic testing.
  - If the woman seeks prenatal care in the first trimester a strategy that incorporates both first- and second-trimester screening should be offered (i.e., First trimester, integrated, or sequential screening).
  - Quadruple Marker screening is recommended for women who present after first trimester for screening.
  - Neural tube defect screening should be offered in the second trimester to women who
elect only first-trimester screening for aneuploidy.

In addition ACOG made several recommendations related to ultrasonography, however those are beyond the scope of laboratory testing and are not noted in this document. Regarding laboratory testing, the Practice Guidelines also concluded the following:

- First-trimester screening using both NT measurement and biochemical markers is an effective screening test for Down syndrome in the general population. At the same false-positive rates, this screening strategy results in a higher Down syndrome detection rates than does the second-trimester maternal serum triple screen and is comparable to the quadruple screen.
- Measurement of NT alone is less effective for first-trimester screening than is the combined test (NT and biochemical markers)
- Integrated first- and second-trimester screening is more sensitive with lower false-positive rates than first-trimester screening alone.
- Serum integrated screening is a useful option in pregnancies where NT measurement is not available or cannot be obtained.
- Down syndrome risk assessment in multiple gestation using first- or second- trimester serum analytes is less accurate than in singleton pregnancies.
- After first-trimester screening, subsequent second trimester Down syndrome screening is not indicated unless it is being performed as a component of the integrated test, stepwise sequential, or contingent sequential test.

As part of these guidelines, ACOG also recommends that women found to have an increased risk of aneuploidy with first-trimester screening should be offered genetic counseling and the option of CVS or second-trimester amniocentesis.¹

**US FOOD AND DRUG ADMINISTRATION (US FDA)**

Many of the kits used for maternal serum screening are US Food and Drug Administration (FDA) approved for certain uses. Currently, there are no kits approved for clinical use in screening for Down syndrome or trisomy 18.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

For Medicare populations, CMS does not pay for screening procedures (tests) performed in the absence of signs or symptoms. (Section 1862(a)(7) of the Social Security Act)

There are several CMS policies that apply to prenatal screening. Physicians should consult their state’s regulations.

Medicare does not have a National Coverage Determination (NCD) for Maternal Serum Screening but it does on Alpha-fetoprotein Testing. CPT 82105 is addressed in the National Coverage Determination and compliance with this policy is required where applicable.
### APPLICABLE CODING

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<td>82677</td>
<td>Unconjugated Estriol (uE3)</td>
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<td>84702</td>
<td>Gonadotropin, chorionic (hCG); quantitative</td>
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<td>86336</td>
<td>Inhibin A</td>
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<td>84163</td>
<td>Pregnancy-associated plasma protein-A (PAPP-A)</td>
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REFERENCES


POLICY HISTORY/REVISION HISTORY

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