Maternal Serum Screening

Indications for Ordering

Low-risk individuals
Maternal Serum Screen, First Trimester
- First-trimester screening test for Down syndrome (trisomy 21 [T21]) and trisomy 18 (T18)

Maternal Serum Screen, Sequential
- Combined first- and second-trimester screening tests for T21, T18, and open neural tube defects (ONTD)

Maternal Serum Screen, Integrated
- Combined first- and second-trimester screening tests for T21, T18, and ONTD

Maternal Serum Screen, Quad
- Second-trimester (>14 weeks) screening test for T21, T18, and ONTD for individual who did not have first-trimester screening performed

High-risk individuals
All high-risk pregnant women should consider noninvasive prenatal testing (NIPT), chorionic villus sampling (CVS), or amniocentesis instead of the tests listed above
- High risk defined as
  - Women ≥35 years at delivery
  - Previous pregnancy with chromosome aneuploidy
  - Either parent is a known carrier of a chromosomal translocation or inversion
  - Abnormal fetal ultrasound
  - Increased risk of ONTD due to family history, patient use of specific medications (eg, valproic acid or carbamazepine), or diabetic status

Test Description
Methodology depends on test components
- Alpha fetoprotein (AFP) and human chorionic gonadotropin (hCG)
  - Noncompetitive (sandwich) immunoassay
    - Antibodies — capture protein to a solid phase and detect presence of protein
    - External calibrators used
- Unconjugated estriol (uE3)
  - Solid phase competitive immunoassay
    - Antiestriol polyclonal antibody (labeled estriol)
    - Solid phase antibody directed against the estriol antibody
    - External calibrators
- Dimeric Inhibin-A (DIA)
  - Noncompetitive (sandwich) microtiter immunoassay
    - Capture antibody to inhibin subunit βA
    - Detection antibody to subunit α
    - External calibrators
- Pregnancy-associated plasma protein-A (PAPP-A)
  - Sequential immunoenzymatic assay
  - Measures protein using monoclonal antibodies and external calibrators
- Post-test risks — calculations by a multivariate log Gaussian model
  - Risk estimates for T21 and T18 are strongly influenced by maternal age
  - Refer to table for first- and second-trimester screening options

Tests to Consider
Primary tests
Maternal Serum Screen, First Trimester, hCG, PAPP-A, NT 3000145
- First-trimester screening test for T21 and T18
- Does not include AFP for ONTD screening
- Requires NT measurement performed by an ultrasonographer certified by the Fetal Medicine Foundation (FMF) or the Nuchal Translucency Quality Review (NTQR)

Maternal Screening, Sequential, Specimen #1, hCG, PAPP-A, NT 3000146
- First-trimester screening test for T21 and T18
- Requires NT measurement performed by an ultrasonographer certified by the FMF or NTQR
- Risks provided in both first and second trimesters

Maternal Screening, Sequential, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A 3000148
- Second-trimester screening test for T21, T18, and ONTD
- Requires a previously submitted first-trimester specimen, Maternal Screening, Sequential, Specimen #1, hCG, PAPP-A, NT (3000146)
- Requires NT measurement performed by an ultrasonographer certified by the FMF or NTQR
- Risks provided in both first and second trimesters
**Disease Overview**

- **Incidence**
  - ONTD – 1/900 pregnancies
  - T21 – 1/600 births
  - T18 – 1/3,000 births

- **Background**
  - **ONTD**
    - Most common ONTDs include
      - Spina bifida
        - Often results in some degree of paralysis of lower limb, loss of bowel and bladder control, ventriculomegaly
      - Anencephaly
      - Incompatible with life
      - Risk – independent of maternal age
  - **T21**
    - Extra copy of chromosome 21
    - Features
      - Moderate intellectual disability
      - Characteristic facial features
      - Variety of medical conditions (e.g., cardiac abnormalities)
    - Risk – increases with maternal age
      - ~50% of babies with T21 are born to women <35 years
  - **T18**
    - Extra copy of chromosome 18
    - Most newborns die within their first year of life
    - Features
      - Severe to profound intellectual disability
      - Small size at birth/poor growth
      - Variety of medical conditions (e.g., cardiac abnormalities) which are generally more severe than those seen in T21
    - Risk – increases with maternal age

**Screening/detection**

- Maternal serum screening helps to identify pregnancies at risk for ONTD, T21, or T18
- Most families who have a child with ONTD, T21, or T18 have no obvious risk factor for the condition (e.g., advanced maternal age, previous history)
- Refer to table for first- and second-trimester screening options
- Abnormal results for any screen requires followup
  - Targeted ultrasound (US)
  - Other prenatal diagnostic procedures
  - Genetic counseling

**Test Interpretation**

**Results**

- T21 cutoffs listed below are ARUP default cutoffs
  - Clients may request a different T21 cutoff

**Maternal Serum Screen, First Trimester**

- T21 screen – 1/230 or worse, reported as abnormal
- T18 screen – 1/100 or worse, reported as abnormal

**Maternal Serum Screen, Sequential**

- First trimester
  - T21 and T18 screen – 1/25 or worse, reported as abnormal
  - Second-trimester specimen not required if first-trimester result is abnormal
- Second trimester
  - T21 screen – 1/110 or worse, reported as abnormal
  - T18 screen – 1/100 or worse, reported as abnormal
  - ONTD screen
    - AFP <2.5 MoM – increased risk for ONTD
    - AFP <2.5 MoM – screen will be reported as abnormal when the ONTD risk is 1/250 or worse
    - uE3 <0.15 MoM – increased risk for congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome
    - hCG ≥3.5 MoM – increased risk for poor fetal outcome
Maternal Serum Screen, Integrated  
- See maternal serum screen sequential for second trimester

Maternal Serum Screen, Quad  
- See maternal serum screen sequential for second trimester

**Limitations**
- A screen interpreted as "normal" misses approximately 15-20% of ONTD cases, 10-20% of T21 cases, and 10-20% of T18 cases, depending on the test and maternal age
- AFP false positives occur with multiple gestation pregnancies, fetal ventral wall defects, fetal demise, and underestimated gestational age

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### First- and Second-Trimester Prenatal Screening Options

<table>
<thead>
<tr>
<th>Specimen(s) collected</th>
<th>First Trimester Only</th>
<th>Serum Integrated (without NT)</th>
<th>Full Integrated (with NT)</th>
<th>Sequential Screen</th>
<th>Quad</th>
</tr>
</thead>
<tbody>
<tr>
<td>US – CRL, NT Blood – PAPP-A, total hCG</td>
<td>Blood – 43-83.9 mm (11w0d–13w6d)</td>
<td>32.4-83.9 mm (10w0d-13w6d) by US or LMP</td>
<td>Blood – 32.4-83.9 mm (10w0d-13w6d)</td>
<td>US – CRL, NT Blood – PAPP-A</td>
<td>Blood – 43-83.9 mm (11w0d-13w6d)</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Second-trimester measurements</td>
<td>N/A</td>
<td>AFP, hCG, uE3, DIA</td>
<td>AFP, hCG, uE3, DIA</td>
<td>AFP, hCG, uE3, DIA</td>
<td>AFP, hCG, uE3, DIA</td>
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<tr>
<td>Gestational age</td>
<td>N/A</td>
<td>14w0d-24w6d (by previous CRL or LMP)</td>
<td>14w0d-24w6d (by previous CRL)</td>
<td>14w0d-24w6d (by previous CRL)</td>
<td>14w0d-24w6d</td>
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<tr>
<td>Down syndrome (T21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Detection rate</td>
<td>85%</td>
<td>85%</td>
<td>87%</td>
<td>86% (63% – first draw; 23% – second draw)</td>
<td>81%</td>
</tr>
<tr>
<td>Screen-positive rate</td>
<td>6%</td>
<td>3-4%</td>
<td>1%</td>
<td>1.6% (0.6% – first draw; 1% – second draw)</td>
<td>4-5%</td>
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<tr>
<td>Trisomy 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection rate</td>
<td>~80%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>~80%</td>
</tr>
<tr>
<td>Screen-positive rate</td>
<td>&lt;1%</td>
<td>0.01%</td>
<td>0.01%</td>
<td>0.01%</td>
<td>&lt;0.5%</td>
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<tr>
<td>Open neural tube defect</td>
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<tr>
<td>Detection rate</td>
<td>N/A</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
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<tr>
<td>Screen-positive rate</td>
<td>N/A</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
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<tr>
<td>Results reported</td>
<td>First trimester</td>
<td>Second trimester</td>
<td>Second trimester</td>
<td>Both first and second trimesters</td>
<td>Second trimester</td>
</tr>
</tbody>
</table>