Maternal Serum Screening
Fetal Aneuploidy and ONTD Risk

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CLINICAL BACKGROUND

Current practice guidelines recommend that screening for fetal aneuploidy should be offered to all women who present for prenatal care before twenty weeks of gestation. The screening should be done regardless of maternal age, with the option of invasive diagnostic testing when indicated by the screening results. Targeted disorders include Down syndrome, Trisomy 18, open neural tube defects (ONTD) and Smith-Lemli-Opitz syndrome (SLOS).

CLINICAL APPLICATION

Results of maternal serum screening tests are risk assessments, which give a statistical likelihood of the targeted disorders. The risk calculations are based on patient-specific risk factors combined with the laboratory test results.

Our laboratory uses standard cut-off values that estimate risk at mid-term for the various targeted disorders. Patients with risk estimates higher than the cut-off values may elect to undergo further testing.

RESULT INTERPRETATION

Our laboratory provides a patient-specific report for all maternal serum prenatal risk testing. The report includes complete demographic and obstetric information on the patient, graphical representations of the calculated risk factors with cutoffs and a narrative interpretation of the clinical significance of the results.

Quick Facts

- The targeted disorders for prenatal risk screens are Down Syndrome, Trisomy 18, Open Neural Tube Defects (ONTD) and Smith-Lemli-Opitz syndrome (SLOS).

- Results for this testing are risk assessments, which give a statistical likelihood of a certain disorder.

- Risk calculations are based on patient-specific pre-test risk and comparison of the measured markers with expected values.

- Follow-up diagnostic tests include chorionic villus sampling and amniocentesis.
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TEST INFORMATION

First Trimester Screen (FTSNT)

- This early gestation screen combines the results of maternal serum markers, pregnancy associated plasma protein A (PAPP-A), total human chorionic gonadotropin (THCG) with ultrasound nuchal translucency (NT) measurements to calculate risk. The targeted disorders for the First Trimester Screen are Down syndrome (detection rate 82 – 87%) and Trisomy 18 (detection rate 80%).
- The specimen must be drawn in the first trimester, between 11 weeks 0 days and 13 weeks 6 days gestation. Crown rump length must be between 40.5 mm and 84 mm.
- The First Trimester Screen does not screen for open neural tube defects or Smith-Lemli-Opitz syndrome.

### DETECTION AND SCREEN POSITIVE RATES

<table>
<thead>
<tr>
<th></th>
<th>First Trimester Only</th>
<th>First &amp; Second Trimester</th>
<th>Second Trimester Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Trimester Screen</td>
<td>SEQUENTIAL Screen With NT</td>
<td>INTEGRATED Screen With NT</td>
</tr>
<tr>
<td>Down Syndrome Detection Rate</td>
<td>82-87%</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Down Syndrome Cut-offs*</td>
<td>1/270</td>
<td>1st trimester 1/50</td>
<td>2nd trimester 1/270</td>
</tr>
<tr>
<td>Down Syndrome Screen Positive Rate</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Trisomy 18 Detection Rate</td>
<td>80%</td>
<td>90%**</td>
<td>90%</td>
</tr>
<tr>
<td>Open Neural Tube Detection Rate</td>
<td>-</td>
<td>80%**</td>
<td>80%</td>
</tr>
<tr>
<td>SLOS Detection Rate</td>
<td>-</td>
<td>60%**</td>
<td>60%</td>
</tr>
<tr>
<td>Markers</td>
<td>NT, PAPP-A, hCG (1st trimester)</td>
<td>AFP, hCG, Estriol, Inhibin A (2nd trimester)</td>
<td>NT, PAPP-A (1st trimester)</td>
</tr>
<tr>
<td>Timing</td>
<td>11w, 0d – 13w, 6d</td>
<td>11w, 0d – 13w, 6d, 14w, 0d – 22w, 6d</td>
<td>11w, 0d – 13w, 6d, 14w, 0d – 22w, 6d</td>
</tr>
<tr>
<td>Turnaround Time</td>
<td>2-5 days</td>
<td>2-5 days; Preliminary report after 1st trimester; final report after 2nd trimester sample</td>
<td>2-5 days; Interpretive report only after 2nd trimester sample</td>
</tr>
</tbody>
</table>

*Down syndrome risk calculation is based on a cutoff of 1/270 unless otherwise noted. A screen positive interpretation is provided if the calculated risk is equal to or greater than 1/270.

** When second trimester testing is performed.

Second Trimester Alpha Fetoprotein Screen (MSSI)

- This screen tests for alpha fetoprotein only to calculate a risk factor for open neural tube defects (detection rate 80%).
- The specimen must be drawn in the second trimester, between 14 weeks 0 days and 22 weeks 6 days gestation.
- The Second Trimester Alpha Fetoprotein Screen is often ordered when a First Trimester Screen has been done earlier in the pregnancy.
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Prenatal Risk Quad Screen (MSS4)
• The Prenatal Risk Quad Screen is performed in the second trimester. It combines the results of four maternal serum markers, alpha fetoprotein (AFP), total human chorionic gonadotropin (ThCG), dimeric inhibin A (DIA) and unconjugated estriol (uE3) to calculate risk. The targeted disorders are Down syndrome (detection rate 81%), Trisomy 18 (detection rate 60%), SLOS (detection rate 60%) and ONTD (detection rate 80%).
• The specimen must be drawn in the second trimester, between 14 weeks 0 days and 22 weeks 6 days gestation.

Sequential Screen (SEQN1 AND SEQN2)
• The Sequential Screen can provide results in two stages. The first sample (SEQN1) is drawn in the first trimester, between 11 weeks 0 days and 13 weeks 6 days gestation. Crown rump length must be between 40.5 mm and 84 mm. Maternal serum markers, pregnancy associated plasma protein A (PAPP-A) and total human chorionic gonadotropin (ThCG) are combined with ultrasound nuchal translucency (NT) to calculate risk. The targeted disorder in the first trimester is Down syndrome.
• If the calculations from the first sample indicate a high probability for Down syndrome, a final report is issued to the caregiver and the screening is complete. No second trimester sample is required in these cases.
• If the results from the first sample do not indicate increased risk, a preliminary report will be issued to the caregiver and an additional blood draw in the second trimester is required.
• The second sample (SEQN2) is collected between 14 weeks 0 days and 22 weeks 6 days gestation. Results for maternal serum markers, alpha fetoprotein (AFP), total human chorionic gonadotropin (ThCG), dimeric inhibin A (DIA) and unconjugated estriol (uE3) are combined with the pregnancy associated plasma protein A (PAPP-A) and nuchal translucency results from the first trimester to calculate risk. The targeted disorders in the second trimester are Down syndrome (detection rate 95%), Trisomy 18 (detection rate 90%), SLOS (60% detection rate), and ONTD (detection rate 80%).
• The Sequential Screen is recommended for potentially high-risk pregnancies in which early-gestation risk estimates are desired, along with the higher detection rate of the second specimen calculations.

SUMMARY OF TEST CODE CHANGES

<table>
<thead>
<tr>
<th>OLD TEST CODE</th>
<th>NEW TEST CODE</th>
<th>TEST NAME</th>
<th>CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFPMS</td>
<td>MSS1</td>
<td>AFP, Maternal Serum</td>
<td>Test Code</td>
</tr>
<tr>
<td>QDSCR</td>
<td>MSS4</td>
<td>Prenatal Risk Quad Screen</td>
<td>Test Code and SLOS reported</td>
</tr>
<tr>
<td>MSSFT</td>
<td>FTSNT</td>
<td>1ST Trimester Screen</td>
<td>Performed at PAML</td>
</tr>
<tr>
<td>MSINT1</td>
<td>ITG1</td>
<td>Integrated Screen, specimen 1</td>
<td>Performed at PAML</td>
</tr>
<tr>
<td>MSINT2</td>
<td>ITG2</td>
<td>Integrated Screen, specimen 2</td>
<td>Performed at PAML</td>
</tr>
<tr>
<td>MSINT1</td>
<td>ITGN1</td>
<td>Integrated Screen with NT, specimen 1</td>
<td>Performed at PAML</td>
</tr>
<tr>
<td>MSINT2</td>
<td>ITGN2</td>
<td>Integrated Screen with NT, specimen 2</td>
<td>Performed at PAML</td>
</tr>
<tr>
<td>MSSEQ1</td>
<td>SEQN1</td>
<td>Sequential Screen with NT, specimen 1</td>
<td>Performed at PAML</td>
</tr>
<tr>
<td>MSSS2</td>
<td>SEQN2</td>
<td>Sequential Screen with NT, specimen 2</td>
<td>Performed at PAML</td>
</tr>
</tbody>
</table>

Smith-Lemli-Opitz syndrome (SLOS) screening is now included on all screening panels evaluating maternal estriol levels.
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Integrated Screen with NT (ITGN1 and ITGN2)

• The first sample (ITGN1) is drawn in the first trimester between 11 weeks 0 days and 13 weeks 6 days gestation. Crown rump length must be between 40.5 mm and 84 mm. The maternal serum marker, pregnancy associated plasma protein A (PAPP-A) and ultrasound nuchal translucency (NT) are measured for risk calculations to be done in the second trimester.

• There is no report for first trimester testing.

• The second sample (ITGN2) is collected between 14 weeks 0 days and 22 weeks 6 days gestation. Results for maternal serum markers, alpha fetoprotein (AFP), total human chorionic gonadotropin (ThCG), dimeric inhibin A (DIA) and unconjugated estriol (uE3) are combined with the pregnancy associated plasma protein A (PAPP-A) and nuchal translucency results from the first trimester to calculate risk. The targeted disorders are Down syndrome (detection rate 96%), Trisomy 18 (detection rate 90%), SLOS (detection rate 60%), and ONTD (detection rate 80%).

• Results from the first and second trimester are combined in a single report.

• The integrated screen with NT is a great option for patients that decline CVS and/or CVS is unavailable. It offers the highest detection rate, preserves AFP screening for ONTD, and provides a single result.

NEW – SLOS Screening Now Included in Sequential, Integrated and Quad Screen

Our laboratory now includes screening for Smith-Lemli-Opitz syndrome (SLOS) on screening panels that evaluate maternal estriol levels. Studies of pregnancies affected with SLOS have reported decreased unconjugated estriol (uE3) levels. The levels of AFP and/or hCG may be normal or decreased. Our laboratory uses a screen positive cut off of 1/50 for SLOS. The cut off of 1/50 will detect approximately 60% of affected pregnancies with a screen positive rate of less than 1%. SLOS is an autosomal recessive condition associated with multiple birth defects caused by an abnormality in cholesterol metabolism due to a deficiency of the enzyme 7-dehydrocholesterol (7-DHC) reductase. Features of SLOS include prenatal and postnatal growth restriction, moderate to severe mental retardation, microcephaly, and multiple malformations. Birth prevalence of SLOS is approximately 1/20,000 to 1/40,000.

For more information, please contact your local sales representative.

REFERENCES

2. Wald, NJ, et al: First and second trimester antenatal screening for Down’s Syndrome: The results of the Serum, Urine and Ultrasound Screening Study