LEGACY HEALTH | LEGACY LABORATORY SERVICES

PRENATAL SCREENING PROGRAM
Importance of Patient Demographics to Assessing Risk

Complete information is required to produce the most accurate risk assessment possible for open neural tube defects (NTD), Trisomy 21 (Down syndrome), and Trisomy 18 (Edward Syndrome) for both First and Second Trimester Screening. **Inaccurate or missing Information will lead to both false negative and false positive screens.**

<table>
<tr><th>QUESTION/
POSSIBLE ANSWERS</th><th>REASON FOR IMPORTANCE</th></tr>
<tr><td colspan="2">INFORMATION REQUIRED FOR ALL SCREENS</td></tr>
<tr><td>Mother's date of birth[1]
• mm/dd/yyyy</td><td>As a woman ages, her a priori risk increases for Down syndrome. For example, if age was the only marker for Down Syndrome, risk would be as shown in the table below.
<table>
<tr><th>Maternal Age (years)</th><th>Risk of Down Syndrome</th></tr>
<tr><td>25</td><td>1/1296</td></tr>
<tr><td>35</td><td>1/368</td></tr>
<tr><td>45</td><td>1/29</td></tr>
</table></td></tr>
<tr><td>Mother's ethnicity[2,3]
• Asian
• Black
• Caucasian
• Other</td><td>Both serum AFP and hCG values in black women are approximately 10% to 15% higher than in Caucasian women. Both serum markers are used to calculate risk assessments for birth defects. Data suggests that the prevalence of Down syndrome is unaffected by race. However, birth prevalence of neural tube defects is 50% lower in African Americans than Caucasians. Therefore, it is recommended to adjust for differences in races before assessing risk. If woman is partially black, then choose black as race.</td></tr>
<tr><td>Weight in pounds[4]
• Weight (lbs)</td><td>The average weight for women is approximately 135-165 pounds depending on race (from lightest to heaviest: Asians, Caucasians, and African Americans). As the weight decreases, the serum concentration of estriol, hCG, AFP, inhibin A, and PAPP-A increases at varying degrees. As the weight increases, these serum marker concentrations decrease. These changes are likely due to maternal blood volume and not associated with the child's health. Changes in concentrations can lead to both false screen positive and screen negative results, especially for Trisomy 18 and neural tube defects. Weight is not required for amniotic fluid testing.</td></tr>
<tr><td>Estimated date of delivery (EDD)[5]
• mm/dd/yyyy</td><td>The gestational age is calculated from the estimated date of delivery. Analyte concentrations change depending on the gestational age of the fetus. The table below illustrates how changing only the gestational age can affect the risk for each of the diseases. Other patient demographics and serum marker concentrations remained the same.
<table>
<tr><th rowspan="3">Gestational Age*</th><th colspan="6">Risk Assessment</th></tr>
<tr><th colspan="2">Down Syndrome</th><th colspan="2">Trisomy 18</th><th colspan="2">Open Neural Tube Defects (ONTD)</th></tr>
<tr><th>Risk</th><th>Interpretation</th><th>Risk</th><th>Interpretation</th><th>Risk</th><th>Interpretation</th></tr>
<tr><td>15 w, 0 d</td><td>1:2,560</td><td>Negative</td><td>~1:31,000</td><td>Negative</td><td>1:293</td><td>Positive</td></tr>
<tr><td>15 w, 5 d</td><td>1:266</td><td>Positive</td><td>~1:31,000</td><td>Negative</td><td>1:512</td><td>Negative</td></tr>
<tr><td>16 w, 5 d</td><td>1:13</td><td>Positive</td><td>~1:6,440</td><td>Negative</td><td>1:1080</td><td>Negative</td></tr>
<tr><td>17 w, 5 d</td><td>~1:6</td><td>Positive</td><td>~1:3,120</td><td>Negative</td><td>1:2170</td><td>Negative</td></tr>
</table>
*w = weeks, d = days</td></tr>
<tr><td>EDD determined by[5]
• LMP
• Ultrasound</td><td>Gestational age is the most important demographic for accurate risk assessment. Ultrasound, particularly crown rump length in the first trimester, will provide the most accurate method for dating.</td></tr>
<tr><td>Number of fetuses[6]
• 1
• 2
• >2</td><td>The concentration of each serum marker relates to the entire pregnancy, while the nuchal translucency (see below) measurement is specific to each fetus. Serum markers can only be used to obtain a pregnancy specific pseudo-risk since the concentration cannot be associated with a specific fetus. Since the concentration of each marker will most likely be increased compared to a singleton pregnancy, knowing the number of fetuses is important.

Legacy sends testing for multiple fetus pregnancies to a referral lab.</td></tr>
<tr><td>If fetus # is >1, chorion?
• Dichorionic
• Monochorionic</td><td>For twin pregnancies, selecting dichorionic or monochorionic is required. The chorion is the membranous structure that encloses the fetus. Monochorionic twins are usually identical twins that share the same chorion as well as the same genetic code. Dichorionic twins are usually fraternal twins, each having their own chorion and are not genetically identical. Since identical twins are genetically equal, both fetuses will have the same chromosomal abnormality or neural tube defect. For fraternal twins, one fetus may be healthy while the other fetus is affected by disease.</td></tr>
<tr><td>Repeat test during same pregnancy?[7,8]
• No
• Yes</td><td>The interpretation of a repeat maternal serum sample may differ from the interpretation of an initial serum specimen. Repeat testing is not recommended for Down syndrome screening unless an initial sample is drawn too early for reliable interpretation. If a test on a second sample is performed, it is essential that the revised risk be calculated using the results from both samples. This will minimize false positive results.</td></tr>
</table>

Importance of Patient Demographics to Assessing Risk

QUESTION/ POSSIBLE ANSWERS	REASON FOR IMPORTANCE
Medication dependent diabetic at conception[9,10] • No • Yes • Unknown	In order to prevent lowering the detection rate or increasing the false positive rate, the serum marker results are adjusted in diabetic mothers. Pregnant women who have diabetes prior to conception have a 12% lower serum AFP levels but have a higher birth prevalence of neural tube defects than non-diabetics of the same gestation age. Differences are slight for the other analytes. For example, estriol is 8% lower, second trimester hCG is 5% lower, and inhibin A is 9% lower in pregnant women with diabetes. Insulin Dependent Diabetes Mellitus does not affect the prevalence of Down syndrome.
Smoker at conception[11] • No • Yes • Unknown	First Trimester: Smoking can decrease serum PAPP-A concentrations by ~19% and increase nuchal translucency by ~6%. These changes may lead to a slight increase in Down syndrome and neural tube defect risk. The risk for Trisomy 18 will be even more significantly increased. Second Trimester: Smoking can decrease hCG concentrations by ~25% and increase inhibin A concentrations by ~54%. These changes to concentration may lead to a slight increase in Down syndrome and neural tube defect risk, and a large increase in Trisomy 18 risk.
IVF pregnancy[12] • No • Yes	If the pregnancy was the result of *in vitro* fertilization (IVF) using an egg donor, then the donor's date of birth or age is required. The concentration of serum markers may change significantly when a donor egg is used.
Previous pregnancy with chromosome abnormality?[13] • No • T21 (Down) • T18 • T13 • Other	A woman with a previous Down syndrome, Trisomy 18 or Trisomy 13 pregnancy has an increased risk for having the current pregnancy with the same chromosomal abnormality. For example, the table below summarizes the risks for a 35.5 year old woman in second trimester. **CONDITION** / **RISK FOR CURRENT PREGANCY IF PREVIOUS PREGNANCY WAS …** **… healthy** / **… with chromosomal abnormality** **Down syndrome**: 1/270 / 1/110 **Trisomy 13 or 18**: 1/270 / 1/164 Legacy sends testing with a family history of chromosomal abnormality to a referral lab.
ADDITIONAL INFORMATION REQUIRED FOR SECOND TRIMESTER SCREENING	
Mother had previous pregnancy with NTD? • No • Yes • Unknown	A woman who has one child with a neural tube defect has a slightly higher chance of having another baby with the same defect. Legacy sends testing with a family history of neural tube defect to a referral lab.
Either parent has an NTD? • No • Yes • Unknown	If one of the parents was born with a neural tube defect, the mother has a greater chance of giving birth to a child with a neural tube defect. Legacy sends testing with a family history of neural tube defect to a referral lab.
Any grandparents have an NTD? • No • Yes • Unknown	If any of the grandparents was born with a neural tube defect, the mother has a greater chance of giving birth to a child with a neural tube defect. Legacy sends testing with a family history of neural tube defect to a referral lab. neural tube defect
ADDITIONAL INFORMATION REQUIRED FOR FIRST TRIMESTER SCREENING	
Ultrasound date [5,12] • mm/dd/yyyy	Date of ultrasound is required to process the sonography results below.
Sonographer Name Certification Number Certifying Agency • Choose from list of names	Legacy only accepts results from sonographers who have been trained by one of the two agencies: 1.) Fetal Medicine Foundation (FMF) or 2.) Nuchal Translucency Quality Review Program (NTQR). **Each sonographer should be set up with Legacy Prenatal Screening Program before sending patients to the lab.** Allow one week before submitting patient specimens for Legacy to set up new sonographer parameters.
Nuchal Translucency (NT) (mm) [5,12] • NT (mm)	Combined with the serum markers, nuchal translucency is required to assess Trisomy 21 and 18 risks in the first trimester. The acceptable range for nuchal translucency measurements is 0.1 – 4.0 mm.
Crown Rump Length (CRL) (mm) [5,12] • CRL (mm)	Crown rump length measurement is required to calculate the gestational age. The acceptable range for crown rump length measurements is 40.6 – 84.0 mm.
Twin B NT (mm) Twin B CRL (mm)[6] • NT (mm) • CRL (mm)	Risk must be assessed for each fetus. Since Legacy does not perform testing on multiple fetus pregnancies, we send the specimen and information to our referral laboratory.

References:

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3. Spencer K, Heath V, El-Sheikhah A, Ong CY, Nicolaides KH, Ethnicity and the need for correction of biochemical and ultrasound markers of chromosomal anomalies in the first trimester: a study of Oriental, Asian and Afro-caribbean populations, *Prenat Diagn*, 2005, 25: 365-369.
4. Watt HC, Wald NJ, Alternative of methods of maternal weight adjustment in maternal serum screening for Down syndrome and neural tube defects. *Prenat Diagn*, 1998, 18: 842-845.
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7. Hackshaw AK, Wald NH, Repeat testing in antenatal screening for Down syndrome using dimeric inhibin-A in combination with other maternal serum markers, *Prenat Diagn*, 2001, 21: 58-61.
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12. Lambert-Messerlian G, Dugoff L, Vidaver J, Canick JA, Malone FD, Ball RH, Comstock CH, Nyberg DA, Saade G, Eddleman K, Klugman S, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, D'Alton ME, First- and second-trimester Down syndrome screening markers in pregnancies achieved through assisted reproductive technologies (ART): a FASTER trial study, *Prenat Diagn*, 2006, 26: 672-678.
13. Arbuzova S, Cuckle H, Mueller R, Shmi I, Familial Down syndrome: evidence supporting cytoplasmic inheritance, *Clin Genet*, 2001, 60: 456-462.

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