Prenatal Genetic Testing: Screening and Diagnosis

Congratulations on your pregnancy. While most women have healthy, uncomplicated pregnancies, about 3% of babies are born with a change in physical and/or mental development or genetic condition. Prenatal genetic testing is intended to be a way to learn during your pregnancy if your baby may have one of these conditions instead of waiting until after the baby is born. The American College of Obstetrics and Gynecology recommends that screening and invasive diagnostic testing should be available to all women, regardless of maternal age and that women should be counseled regarding the differences between screening and invasive diagnostic testing. The decision regarding whether or not to have any testing is yours. This handout will review the various screening and testing options during pregnancy as well as decision-making factors and is meant to be an extra resource in addition to the Prenatal Genetic Testing Overview class and/or discussion with your regular OB provider.

Chromosome Conditions

The pieces of genetic information that carry our genetic instructions (genes) are called chromosomes; most people have 46 total. One copy of each chromosome is inherited from a person’s mother and the other copy is inherited from the father.

Conditions like Down syndrome, Trisomy 18 and Trisomy 13 occur when an egg or sperm cell divides unequally, allowing an extra or missing chromosome to be present in the first fertilized cell at conception. This can occur for anyone of any age or background and is typically a random event; there is nothing a parent does to cause this to happen. Likewise, there is nothing anyone can do to prevent these events from occurring. Down syndrome is caused by a baby having an extra chromosome 21 (trisomy 21), which has a wide range in how it affects physical and mental development, spanning from mild to moderate intellectual disability, and may involve possible heart defects, intestinal blockage, or decreased muscle tone leading to developmental delay. There are also many babies with Down syndrome who do not have significant medical problems at birth, and the average life expectancy is in the sixties.

Trisomy 18 is caused by a baby having an additional copy of chromosome 18; trisomy 13 happens when a baby has an extra chromosome 13. These conditions tend to be more severe in terms of the effects on physical and mental development, including heart problems, cleft lip and/or palate, kidney problems, and seizures among others. There is a greatly increased chance for a pregnancy loss, even in the second or third trimester; less than 10% of babies with these conditions survive to or beyond one year of age.

Babies may also have different numbers of sex chromosomes that determine if a baby is male or female. Most females have two X chromosomes; most males have one X and one Y chromosome. Females with Trisomy X have an extra X chromosome (47,XXX) and may have no symptoms or any of a very wide range of symptoms; these may include tall stature, mildly low muscle tone, absence or of change in kidney, urinary tract, or reproductive organs, congenital hip dysplasia, seizures, hand tremors, chronic constipation, gastroesophageal reflux, or increase in autoimmune disorders. Developmental delays may affect language and motor development. IQ is typically in the average to low-average range, about 85; up to 10% may have mild intellectual disability. Challenges may include attention difficulties, executive function deficits, anxiety and sensory processing difficulties. Maturity often lags chronological age. Fertility may be affected by premature ovarian failure.

Females with Turner syndrome have just one X chromosome and are missing the second sex chromosome (45,XO), which may cause puffy hands and feet at birth, heart defects, height less than 5 feet, kidney problems, thyroid problems, liver concerns, hearing loss, scoliosis, infertility, and possible learning disabilities or social problems. When identified early in pregnancy, especially when significant extra fluid is seen in certain areas for the baby, the chance for a natural pregnancy loss is significantly increased.

Males with Klinefelter syndrome who have an extra X chromosome (47,XXY) may also have a wide range of things that may be different, including changes in kidney development, hypospadias, cryptorchidism, small penis, small testes, infertility, sparse facial and body hair, enlarged breasts, low muscle tone, speech delay, fine and gross motor delays, learning disabilities, social skill difficulties (shyness, withdrawal), expressive language (writing) may be a lifelong challenge, ADHD, mood disorders, anxiety, reduced IQ (by about 15 points compared with siblings) and less than 10% have intellectual disability.
Males with Jacob’s syndrome who have an extra Y chromosome (47,XYY) may have no identifiable symptoms or may have tall stature, low muscle tone, tremors, tics, seizures, speech delay, developmental delay, attention difficulties, possible learning disabilities and normal IQ.

The chance to conceive a baby with an extra or missing chromosome increases with age. The following chart outlines the chance for chromosome conditions to occur.

<table>
<thead>
<tr>
<th>MATERNAL AGE AT DELIVERY</th>
<th>CHANCE FOR DOWN SYNDROME AT BIRTH</th>
<th>ALL CHROMOSOME CONDITIONS AT BIRTH</th>
<th>% CHANCE TO OCCUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1 in 1923</td>
<td>1 in 526</td>
<td>Less than 0.5%</td>
</tr>
<tr>
<td>25</td>
<td>1 in 1205</td>
<td>1 in 476</td>
<td>0.5 to 1%</td>
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<tr>
<td>30</td>
<td>1 in 885</td>
<td>1 in 384</td>
<td>1 to 2%</td>
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<tr>
<td>35</td>
<td>1 in 365</td>
<td>1 in 178</td>
<td>2 to 7%</td>
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<tr>
<td>36</td>
<td>1 in 287</td>
<td>1 in 149</td>
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<tr>
<td>37</td>
<td>1 in 225</td>
<td>1 in 123</td>
<td></td>
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<tr>
<td>38</td>
<td>1 in 177</td>
<td>1 in 105</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>1 in 139</td>
<td>1 in 80</td>
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</tr>
<tr>
<td>40</td>
<td>1 in 109</td>
<td>1 in 63</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>1 in 85</td>
<td>1 in 48</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>1 in 67</td>
<td>1 in 39</td>
<td></td>
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<td>43</td>
<td>1 in 53</td>
<td>1 in 31</td>
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<td>44</td>
<td>1 in 41</td>
<td>1 in 24</td>
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<tr>
<td>45</td>
<td>1 in 32</td>
<td>1 in 18</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>1 in 25</td>
<td>1 in 15</td>
<td></td>
</tr>
</tbody>
</table>

Data from Hook and Chambers (1977) and Hook (1981). ***Except 47,XXX

Prenatal screening tests are available to provide a “personalized” risk assessment, which can predict the chance of a pregnancy being affected by one of these conditions. Diagnostics tests, such as chorionic villus sampling (CVS) and amniocentesis are able to create a picture of a baby’s chromosomes to determine whether or not a pregnancy has one of these most common chromosome conditions.

SCREENING

Screening tests include blood testing from the pregnant mother to assess the chance that a pregnancy has certain chromosomal conditions or open spina bifida.

The chance of having a child with an Open Spina Bifida (OSB) does not typically increase with age. OSBs are one of the most common birth defects for which screening is offered to all women in pregnancy. OSBs also have a wide range of severity, from fatal to a small change detected incidentally later in life; mid-range often involves decreased control of leg muscles and possible bowel or bladder problems. Blood test screening identifies up to 80% of OSBs and 95% of the most severe type, anencephaly. Ultrasound is expected to directly identify most open spina bifida, over 95%. Open spina bifida is one of the few conditions for which fetal surgery to repair the opening during pregnancy would be considered.

**Serum Integrated Screening (SIS)**

SIS is available to all women in pregnancy and is a two-part, combined blood test screen. It is currently the accepted screening in pregnancy for all multiples (twins or more), regardless of maternal age. Part 1 must be drawn from 10 to 13 weeks in pregnancy. Part 2 can be performed from 15 to 21 weeks and provides full final results with specific probabilities. After Part 2, patients are notified if the chance for Down syndrome is at least 1 in 270 (<0.5%) or the chance for trisomy 18 is at least 1 in 100 (1%). If Part 1 is not drawn before 14 weeks in pregnancy, a patient is offered a Quad screen, which is part 2 by itself. It is important to ensure that the laboratory uses the correct due date for the pregnancy, ethnicity for the mother, weight, and number of babies. If any information is not correct, the results should be recalculated.

Based on the pattern of the protein and hormone levels produced by the pregnancy, results are provided in the form of a probability, such as 1 in 200 (1/200), which equals ½ of one percent (0.5%). The larger the second number or bottom of the risk fraction (1 in 5,000 = 1/5,000 = .02%), the less likely the pregnancy will have that condition. The smaller the second number (1 in 10 = 1/10 = 10%), the more likely the pregnancy will have that condition. **It is important to note that this test will not determine for sure whether a pregnancy will or will not**
have that condition, it will only provide a probability (chance) that the baby has the condition. The chance for Down syndrome or trisomy 18 in a particular pregnancy starts with the chance by the patient/mother’s age at delivery and is adjusted according to the levels measured in her blood. Therefore, the chance that a concern is identified (screen positive) increases with maternal age. However, if a baby truly has one of these conditions, testing is more likely to find it for patients at later ages compared to younger ages.

If concerns are raised with either part of the testing, this is called a screen positive result. A screen positive can be a true positive, where the baby is later confirmed to be affected with the condition of concern. More often, these results are falsely positive, where the baby is later confirmed not to have the condition of concern. Overall, SIS identifies about 88% of pregnancies affected with Down syndrome in which about 6% will screen positive for this condition. SIS identifies about 90% of pregnancies affected with trisomy 18 in which about 0.1% will screen positive. It also identifies about 80% of pregnancies with open spina bifida in which 1 to 3% will screen positive. Positive screens indicate there is a reason to look more closely at the pregnancy by ultrasound and are intended to provide additional information so that parents may consider further testing, such as non-invasive prenatal testing, chorionic villus sampling or amniocentesis.

**Non-Invasive Prenatal Testing (NIPT) - InformaSeq**

NIPT is the newest type of prenatal screening that involves a blood test which analyzes fetal and maternal DNA circulating in the pregnant mother’s blood to determine if a pregnancy is at high or low risk for Down syndrome, trisomy 18, or trisomy 13. It can also analyze the amount of X and Y chromosome material. Military clinics in the National Capital Area send testing to LabCorp who offers InformaSeq NIPT. This testing is currently available to women whose pregnancies are at increased risk for one or more of these conditions. Increased risk factors include one or more of the following: Maternal age at least 35 years at delivery, previous pregnancy with one of the above chromosome conditions, fetal ultrasound suggestive of one of the above chromosome conditions, and/or positive maternal serum screening test (i.e., SIS or Quad screen).

NIPT measures how much fragmented chromosome material is present and has a higher detection rate and lower false positive rate than SIS or Quad screening. It is expected to identify 99.9% of pregnancies affected with Down syndrome, 97.4% of trisomy 18, 87.5% of trisomy 13 and 95% of Turner syndrome. The false positive rate is 0.2% for Down syndrome, 0.4% for trisomy 18, <0/1% for trisomy 13 and about 1% for sex chromosomes. It may be ordered in any of the three following ways: to include no information about fetal sex, to include information to indicate only if the baby is male or female, or to include the number of predicted X and Y chromosomes to identify conditions such as Triple X, Turner syndrome or Klinefelter syndrome.

Results reported as “Aneuploidy Detected” or “Aneuploidy Suspected” indicate there is an increased chance the pregnancy has one or more of the screened chromosome conditions and is intended to provide additional information so that parents have increased awareness and may consider further diagnostic testing, such as CVS or amniocentesis. There is a <3% chance that the testing will be uninformative and repeat testing may be considered. NIPT is considered a screening test and does not provide the equivalent full, comprehensive information provided by traditional diagnostic testing, such as chorionic villus sampling or amniocentesis. NIPT does not screen for open spina bifida; ultrasound and/or a separate blood test can be done to screen for this.

**Ultrasound**

Ultrasound evaluation is another method of screening in pregnancy. In the first trimester, ultrasound is used primarily to confirm a baby’s due date and that a miscarriage has not occurred. A nuchal translucency (NT) ultrasound, measuring the amount of fluid beneath the skin behind a baby’s neck, is recommended to be performed for all twin pregnancies between 11 to 14 weeks. All women are offered a detailed ultrasound examination at approximately 18 to 20 weeks of pregnancy. Ultrasound is able to determine if there are any concerns in the physical development of the pregnancy. It can look for “markers” that are not physical birth defects but are physical signs that may be seen more often in pregnancies with chromosome conditions. At least half of babies with Down syndrome will have a finding on this ultrasound. At least 80% of pregnancies with more severe chromosome conditions, such as Trisomy 18, will have a finding on this ultrasound. This ultrasound can be used to gather more information following blood test screening before making any further decisions regarding diagnostic testing. However, even blood test screening combined with ultrasound can still not identify with certainty if a baby has Down syndrome or other chromosome conditions.
DIAGNOSTIC TESTING

Prenatal diagnostic tests provide a full picture of a baby’s chromosomes, which identifies whether or not whole chromosomes are extra or missing. It is able to diagnose conditions such as Down syndrome, trisomy 18, and trisomy 13. The two diagnostic procedures available in pregnancy are chorionic villus sampling (CVS) and amniocentesis. Both procedures involve insertion of an instrument into the uterus and amniotic sac to either obtain a very small sample of the placental tissue (CVS) or a few small tubes of amniotic fluid (amniocentesis). The main advantage of CVS is that it is performed earlier, at 10 to 12 weeks of pregnancy. Amniocentesis can be performed at or after 16 weeks of pregnancy. Amniocentesis can also further test for open neural tube defects. Results from either usually take 7 to 10 days. The accuracy of these tests is 99.9%, as close to 100% as we can get. Both diagnostic procedures pose risks to the pregnancy, such as infection or amniotic fluid leakage, which may result in miscarriage. The chance for miscarriage following either procedure is expected to be about 1 in 300 to 1 in 500. If a chromosome condition is identified, this testing is not very helpful in predicting how mildly or severely a particular individual would be affected. Prenatal diagnostic tests can also be used for common autosomal recessive conditions, such as cystic fibrosis, sickle cell disease, and Tay Sachs disease, when both parents are known to be carriers of the same condition. Standard fetal chromosome analysis does not assess single genes and may miss very small deletions, duplications or other rearrangements. If you are strongly considering a diagnostic test, we recommend individual genetic counseling to further review these tests in greater detail and give informed consent.

CARRIER SCREENING

Carrier screening is offered based on one’s family history or ethnic background. Most conditions for which carrier screening is offered are autosomal recessive disorders. As you may know, each person has two copies of his or her genetic instructions (genes); having received one copy from her mother and one from her father. In someone who has a recessive condition, both copies of a particular genetic instruction are changed in a way that causes it to work differently in the body. Most often, a person with a recessive condition inherited one change from each parent. Individuals who have just one gene change for a particular condition are said to be “carriers”. Carriers do not usually have symptoms of or problems from the condition and are only found to be carriers either by having a blood test to look for the most common genetic changes or by giving birth to a child with the condition. When both parents are carriers, they have a 1 in 4 (25%) chance that any child they have together will have the condition. They also have a 1 in 2 (50%) chance any of their children will be carriers like either of them, and a 1 in 4 (25%) chance their children will not be carriers nor be affected with the condition.

Carrier screening is performed by a blood test. Typically the mother is tested first; and if she is found to be a carrier, her partner would be offered testing. If both parents are found to be carriers, prenatal diagnostic testing, such as chorionic villus sampling (CVS) or amniocentesis that can determine if the baby has the condition is offered.

If you had carrier screening in a previous pregnancy it does not need to be repeated. It is important to note that most carrier screening is not able to identify 100% of the gene changes that may cause the condition. Therefore, a negative carrier screen does not eliminate the chance that someone is a carrier or will have a child with the condition, but it does significantly reduce it. The following chart outlines the chances of being a carrier of the most common autosomal recessive conditions for which carrier screening is available based on one’s ethnic background.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CHANCE TO BE A CARRIER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-Thalassemia</td>
<td>Southeast Asian, 1 in 20&lt;br&gt;Mediterranean</td>
</tr>
<tr>
<td>Beta- Thalassemia</td>
<td>Mediterranean, 1 in 25&lt;br&gt;Asian, 1 in 30&lt;br&gt;Hispanic, 1 in 30 to 50&lt;br&gt;African, 1 in 75</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>Ashkenazi Jewish, 1 in 40</td>
</tr>
<tr>
<td>Cystic Fibrosis (CF)</td>
<td>Caucasian, 1 in 25&lt;br&gt;Ashkenazi Jewish, 1 in 25&lt;br&gt;Hispanic, 1 in 65&lt;br&gt;African American, 1 in 65</td>
</tr>
<tr>
<td>Familial Dysautonomia</td>
<td>Ashkenazi Jewish, 1 in 30</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>African American, 1 in 10&lt;br&gt;Hispanic, up to 1 in 30&lt;br&gt;Mediterranean, 1 in 40&lt;br&gt;Middle-Eastern, Indian</td>
</tr>
<tr>
<td>Tay Sachs Disease</td>
<td>Ashkenazi Jewish, 1 in 30&lt;br&gt;French Canadian, French Cajun</td>
</tr>
</tbody>
</table>
MAKING A DECISION

Decisions regarding screening or diagnostic testing are very personal. When considering which or if any of this testing is right for you, it may be helpful to consider whether or not you would want to know earlier in your pregnancy if your baby has one of these conditions or wait to find out after the baby is born. Some people prefer to know early so they may prepare by reading books or talking with healthcare providers. Some may consider certain reproductive options if they did not expect their baby to survive or expected the baby to have special needs or disabilities. Knowing this information early may add to the stress and anxiety from some people where it may reduce it for others. In general, the results from these tests are not expected to significantly affect the care provided to you in your pregnancy. Any of these conditions can be tested after the baby is born. Therefore, the decision regarding testing during pregnancy depends on whether the potential benefits (reassurance, ability to prepare) received from any of these tests outweighs the potential risks (anxiety, possible miscarriage).

Individuals who need a definite answer may want to consider going straight to a diagnostic test, such as CVS or amniocentesis. Individuals who would like information but are unsure if they want to have diagnostic testing may benefit from starting with screening (blood test and ultrasound). If they are satisfied with their screening results, they may not feel the need to pursue further testing. If the screening is not reassuring, they may consider further diagnostic testing. Individuals who feel that they are not concerned about having a child with any of the above-mentioned conditions and do not feel they need the information before the baby is born may consider not having any screening or diagnostic testing in pregnancy.

We hope this information is helpful. If you have any questions or concerns, please feel free to contact a genetic counselor or request a referral from your OB provider for an individual genetic counseling appointment.

Erica Sturm, MS, Certified Genetic Counselor, 301.295.2170; Erica.L.Sturm.civ@mail.mil
Prenatal Assessment Center Front Desk/ Appointments, 301.319.5050 (ultrasound and genetic counseling)

ADDITIONAL RESOURCES

- Relay Health – https://app.relayhealth.com
  Further discussion with your OB provider
- March of Dimes
  www.marchofdimes.com
- National Institutes of Health – Health Information
  http://health.nih.gov
- Association for X and Y Variations
  www.axysinfo.org
- Cooley’s Anemia Foundation
  www.thalassemia.org
- Cystic Fibrosis Foundation
  www.cff.org
- Jewish Genetic Disease Consortium
  www.jewishgeneticdiseases.org/jewish-genetic-diseases/
- National Down Syndrome Society
  www.ndss.org
- Sickle Cell Disease Association of America
  www.sicklecelldisease.org/index.cfm?page=about-scd
- Spina Bifida Association of America
  www.spinabifidaassociation.org
- Support Organization for Trisomy 18, 13 and Related Disorders
  trisomy.org
- Turner Syndrome Society of the United States
  www.turnersyndrome.org