Sequential Screening

*To the Point-* Sequential Screening is a 2-part prenatal screening test that can evaluate your chances of having a baby with Down syndrome, Trisomy 18 or open neural tube defects, such as spina bifida; results are not yes or no. Part 1 is performed in the first trimester and involves a blood draw and ultrasound. If part 1 is normal, you will have a second blood draw in the 2\textsuperscript{nd} trimester. If part 1 is abnormal, you will not have part 2 but will be offered other testing, such as, cell-free DNA (cfDNA), CVS, or amniocentesis.

**Results**

**How to Decide**

**FAQs**

**THE BASICS**

Sequential screening is a 2-part test (btw, part 1 is very similar to First trimester Screening and part 2 is very similar to second trimester maternal serum screening), which allows for a higher detection rate of Down syndrome and Trisomy 18 than either part alone. Part 1 of the sequential screen involves a blood draw and ultrasound on mom between 11-14 weeks gestation; results will tell you the chances that your baby has Down syndrome or Trisomy 18.

If part I of the sequential screen comes back high risk or abnormal, your doctor will not perform the 2\textsuperscript{nd} half of it, but rather discuss with you the option of diagnostic testing, such as, CVS or amniocentesis and/or further screening tests such as, cell-free DNA (cfDNA) and/or level II ultrasound.

If part I of the sequential screen is normal/low risk, you go on to part 2, a blood draw at 15-20 weeks gestation. Results from part 1 and 2 of the sequential screen are then combined and your final risk figures are generated. If your final result is abnormal, your doctor will discuss with you the option of diagnostic testing, such as, amniocentesis and/or further screening tests such as, cell-free DNA (cfDNA) and/or level II ultrasound.

Like other prenatal screening tests, there is no physical risk to mom or baby, however, there is a chance of increasing mom’s and/or father of baby’s anxiety depending on the results.

Sequential screening will tell you the chances that your baby has one of these conditions; results are not yes or no. Most people who have an “abnormal” or “high risk” sequential screen result have typically developing, healthy babies. This test is designed to identify
individuals who are at increased chance of these conditions and offer them further, more definitive testing. People choose to have screening tests such as sequential screening for various reasons, however, this is not a mandatory test and it is up to you!

HOW IT WORKS

Sequential screen has 2 parts. Part 1 of sequential screening has 2 components that are performed at 11-14 weeks gestation; ultrasound to measure the nuchal translucency of the baby and blood draw to measure two proteins in mom’s blood.

**Sequential screening PART 1**

**Sequential Screening Part 1 Ultrasound**

Sequential screening part 1 ultrasound can be performed by various providers (perinatologist, OB, radiologist, sonography technician), however, they should be certified as the nuchal translucency (NT) measurement requires specific measurements. Nuchal translucency is a term that describes the fluid filled space in the back of the baby’s neck. If there is extra or more fluid than normal (some fluid is normal) in the back of the baby’s neck, this measurement will be wider or bigger than usual. Extra fluid and hence a wider NT increases the chance for Down syndrome, Trisomy 18 and other birth defects.

Besides taking the NT measurement, your doctor will also determine the dating of your pregnancy (gestational age) by measuring the fetus/baby. Since the fetus is still very small, it is too early to get a good look at the other physical structures. Some doctors may be able to give you a pretty good “guess” regarding the gender at the time of your sequential screening part 1 ultrasound, but many will qualify the guess with telling you not to go home and paint the nursery blue or pink just yet.

**Sequential screening part 1- Blood draw**

There are proteins produced naturally during pregnancy by the placenta that cross over into mom’s blood stream. Research studies have shown that babies who have Down syndrome or Trisomy 18 will sometimes have levels of these proteins that are higher or lower than usual. So, sequential screening part 1 blood draw measures these proteins and looks for certain “patterns” of higher or lower levels and then using a computer algorithm which includes your age, gestational age of the pregnancy (based upon the length of the fetus), number of fetuses, your weight, race, smoking status and diabetic status, a risk figure is calculated for each of these conditions.
The most common proteins measured in sequential screening part 1 blood draw are:

**Pregnancy-associated plasma protein A (PAPP-A)**- PAPP-A is produced by the placenta and crosses over into mom’s blood stream. Lower levels of PAPP-A increase the chances of Down syndrome or Trisomy 18. Lower levels of PAPP-A can also be associated with poor pregnancy outcomes, such as, miscarriage, low birth weight and high blood pressure during the pregnancy (gestational hypertension). However, keep in mind that healthy pregnancies can have low PAPP-A levels. So, don’t panic if your PAPP-A level is a bit low.

**Human chorionic gonadotropin (hCG)**- various forms of hCG are measured for sequential screen part 1 blood draw depending on the laboratory that is used (eg. free beta hCG vs. total hCG). hCG is produced by the placenta and crosses over into mom’s blood stream. hCG tends to be higher in babies with Down syndrome and lower in babies with Trisomy 18.

**Sequential screening PART 2**

Sequential screening part 2 involves a blood draw on mom at 15-20 weeks gestation. As in the first trimester, there are also proteins produced naturally by baby or placenta during the pregnancy that cross into mom’s blood stream during the second trimester. Again, research has shown that babies who have Down syndrome, Trisomy 18 or an open neural tube defect, may have levels of these proteins that are higher or lower than usual. So, sequential screening part 2 measures these proteins and looks for certain “patterns” (higher or lower protein levels) and then using a computer algorithm which includes your age, gestational age of the pregnancy (based upon the length of the fetus), number of fetuses, your weight, race and diabetic status, a risk figure is calculated for each of these conditions.

The most common proteins that are measured in sequential screening part 2 include:

**AFP, or alpha-fetoprotein**, is a protein produced in the fetal liver during the second trimester of pregnancy and increases throughout the pregnancy. AFP tends to be higher in mom’s blood when the baby has an open neural tube defect (ONTD), such as spina bifida. Since there is an opening in the skin when an ONTD is present, AFP has another “escape route” out of the fetus and into the amniotic fluid. The “extra” AFP that has escaped then crosses into mom’s blood stream and makes the AFP level in mom’s blood higher. AFP tends to be lower than average in babies who have Down syndrome or Trisomy 18.

**HCG, or human chorionic gonadotropin**, which is produced by the placenta and crosses into mom’s blood stream. HCG levels rise in mom’s blood stream until about mid-pregnancy and then they begin to decline. Babies with Down syndrome tend to have higher than average
levels of HCG and babies with Trisomy tend to have lower than average levels of HCG.

**UE3, or unconjugated estriol**, is made by both the fetal liver and the placenta. Levels of this protein rise throughout the pregnancy. Babies with Down syndrome or Trisomy 18 tend to have lower levels of UE3.

**DIA, or dimeric inhibin A**, comes from the placenta. Levels of this protein in mom’s blood remain relatively constant through the 15th-18th week of gestation in typical pregnancies. Babies with Down syndrome tend to have higher than average levels of DIA.

**RESULTS**

Your doctor will be able to tell you the day of the ultrasound more about your NT measurement. If it is abnormal (wider), he or she may offer you further testing such as chorionic villus sampling (CVS) or cell-free DNA (cfDNA) at that time. If the NT measurement is abnormal, there is a greater chance that the baby does have a chromosome abnormality, such as Down syndrome, trisomy 18 or birth defect, such as a heart defect.

As discussed earlier, sequential screening never gives yes or no answers. For part 1 and 2 of sequential screening, results are typically given as a risk assessment, and based on how high the chance is, the lab will indicate if it is abnormal/high risk or normal/low risk. Each lab may vary a bit, but a typical cut-off for high risk for Down syndrome is 1/270, or <0.5% and 1/100 or 1% for trisomy 18. In other words, if your chance is greater than 1/270 for Down syndrome, the report would say that your results are abnormal for Down syndrome.

Let’s give an example. Let’s say you had Sequential Screening and you got a phone call from your OB or perinatologist/Maternal-Fetal Medicine office saying, “your results came back indicating an elevated chance or high risk for Down syndrome.” This may not be what you were expecting and often times it is hard to concentrate and listen to what is said beyond that statement, but hopefully the office will also tell you what the actual risk figures are for Down syndrome (if not, you should ask them). In this case, let’s just say it is 1/200 (or 0.5%). What this really means is that if they looked at 200 women who were the same age as you and had the same chemical levels and NT measurement, 1 out of those 200 babies would have Down syndrome and the other 199 would not have Down syndrome. Another way of looking at it is that the chance of having a baby without Down syndrome is 99.5%. So, even though the test results are deemed “abnormal”, the odds are the baby does not have Down syndrome.
Here’s one more example that would apply to you if you are over 35 at delivery. The sequential screen uses maternal age in its calculation, and we have already talked about the fact that the chances of things like Down syndrome increase as mom’s age increases. What this can mean is that the chance of you having a high risk or abnormal sequential screen increases a bit as you age. For example, if you are 42, your approximate background chance for Down syndrome is 1/64. This chance alone is higher than the abnormal cut-off for the both parts of the sequential screen (typically around 1/270 for Down syndrome). If a 42 year old woman with an age-related background chance of Down syndrome of approximately 1/64 has a sequential screen result of 1/200 (0.5%) for Down syndrome, the result is abnormal. However, this is actually a lower risk than her background age-related risk of 1/64 (1.6%).

Risk figures can be confusing and how they are presented can really make a difference in your perception and understanding. For example, if your chances for Down syndrome came back 1/20, this means that there is a 95% chance that the baby does NOT have the condition. So, make sure you ask your provider or genetic counselor if you have questions about the risk figures or the results in general.

**ABNORMAL RESULTS- My Sequential screen is abnormal or high risk, what should I consider?**

People choose prenatal testing for various reasons, some to find out information to simply have a heads-up and be prepared, others because they are uncertain what decisions they would make if their baby did have an abnormality. As explained above in the Sequential screen results section, most likely your baby does not have the condition at hand. However, if you are like most people, you will be at least a bit worried. It is hard to hear that something “might” be going on with your baby.

So, what happens next? Many obstetricians will refer patients with an abnormal Sequential screen to a high-risk pregnancy doctor (perinatologist or Maternal-Fetal Medicine specialist) or back to the doctor who performed the Sequential screen to discuss further testing options. Depending on your provider, you may also be referred to a genetic counselor to discuss the test results further. Genetic counselors are trained medical professionals who can explain the test results in detail, answer your questions and discuss all of the further testing options available to help you make the best decision based on your personality, beliefs, needs and values.

Further testing options that will be discussed include diagnostic options that can give you more definitive answers such as, chorionic villus sampling (CVS) and amniocentesis. Other
Sequential Screening

Screening tests include cell-free DNA (cfDNA) and level II ultrasound.

An important thing to keep in mind is that all further testing options, including level II ultrasound, noninvasive prenatal screening, CVS and amniocentesis are optional, not mandatory. See specific tests for more information on these other testing options.

NORMAL RESULTS on Sequential Screening Part 1 - Things to Consider

If your sequential screen Part 1 results are in the normal range, your doctor will schedule an appointment at 15-20 weeks gestation to come back to the office and have the sequential screen part 2 blood draw. The results from part 2 (combined with part 1) will take several days to receive and are typically called out over the phone. Part 2 will provide you with risk figures for Down syndrome, Trisomy 18 and open neural tube defects, such as, spina bifida for this particular pregnancy.

NORMAL RESULTS on Sequential Screen Part 1 and Part 2 - Things to Consider

In terms of the conditions screened for on the sequential screen, chances are decreased that your baby has one of them and many patients do not pursue further testing. However, sequential screening does not detect all cases of Down syndrome, Trisomy or open neural tube defects. Sequential screen (part 1 and part 2) has a detection rate of approximately 90% for Down syndrome and trisomy 18 and approximately 80% for open neural tube defects (ONTDs), meaning 10% and 20% of these babies, respectively, will not be “picked up” on sequential screening. So, there are moms whose babies have these conditions who will have normal sequential screening. If you want definitive information on the conditions that are screened for in the sequential screen, you may want to consider having the amniocentesis following a normal sequential screen part 2.

HOW TO DECIDE

Sequential Screen - Should I have this test?

The following are some questions and thoughts to consider that may be helpful as you decide whether or not sequential screening is right for you...
• How would you feel if results indicated a higher risk for a genetic condition?
  ◦ Would you consider amniocentesis?
  ◦ Do you think this information would help you feel more prepared?
• If not, would you be ok waiting until the baby is born to know for sure if the condition is present if your sequential screen result returns high risk?
  ◦ For example, would you consider doing anything differently if you knew the baby had a genetic condition (e.g. prepare, consider placing baby for adoption, consider not continuing the pregnancy)?
• Does more information with the possibility of uncertainty make you anxious?
• Some women would prefer definitive answers and since sequential screening cannot provide that, they may choose to go straight to a more definitive test, such as amniocentesis.
• On the other hand, some women may feel comfortable with their chance of a genetic condition or are confident that, even if the baby did have a genetic condition, it wouldn’t alter their pregnancy plans. Or they may prefer not to face the decision of whether or not to have an amniocentesis if the sequential screen comes back high risk. In these cases some women may decide not to undergo any prenatal screening.

_Ultimately, the decision to have sequential screening or any other prenatal screening or diagnostic test is yours to make and should reflect your own personal beliefs, values, needs and personality._

What is Down syndrome? [READ MORE]

What is Trisomy 18? [READ MORE]

What are open neural tube defects (ONTDs)? [READ MORE]