

Why do women with screen negative results occasionally have babies with Down syndrome or an Open Neural Tube Defect?

It is unusual for women to have a baby with either of these abnormalities, and it is even more unusual for a woman with a *screen negative* result, but it does sometimes happen. This is because the screening test cannot completely distinguish affected from unaffected pregnancies. However small the risk is, we cannot rule out the possibility of the baby having Down syndrome or an open neural tube defect.

What does a screen positive result for Down syndrome mean?

A *screen positive* result means that you are in a **high risk group** for having a baby with Down syndrome. If your result is in this group, you will be offered genetic counseling and the option of a diagnostic test such as CVS or amniocentesis.

The result is called *screen positive* if the risk of Down syndrome in your pregnancy is 1 in 200 or greater in the first trimester or 1 in 270 or greater in the second trimester. Most women with *screen positive* results do not have a pregnancy with Down syndrome. For example, of 20 women with *screen positive* results for Down syndrome, only one would actually have a pregnancy with Down syndrome.

What does a screen positive result for Open Neural Tube defects mean?

A *screen positive* result means that you are in a group with an increased risk of having a baby with an open neural tube defect. If your result is in this group, you will be offered genetic counseling, an ultrasound scan examination at 18 to 20 weeks of pregnancy, and the option of an amniocentesis. This is organized by your doctor or hospital.

What is Chorionic Villus Sampling (CVS)?

If your result is screen positive in the first trimester then CVS may be an option. CVS is a diagnostic procedure that extracts a small amount of placental material which is usually an excellent source of genetic material from the fetus. This test is performed either transcervically or transabdominally between 10 to 12 weeks of gestation, but only transabdominally after 12 weeks gestation. There is a small risk associated with CVS. Less than one percent of women may have a miscarriage as a result of the procedure. Results are usually available in five to seven days, and the detection rate is greater than 99 percent for chromosomal abnormalities, such as Down syndrome. Follow-up evaluation for open neural tube defects is necessary.

What is Amniocentesis?

Amniocentesis is usually performed between 15 and 20 weeks, and is a procedure in which the doctor obtains a sample of amniotic fluid that surrounds the developing fetus. The sample is then sent to the laboratory for testing. This fluid sample can be used to diagnose both chromosomal problems such as Down syndrome and Trisomy 18, as well as open neural tube defects such as spina bifida.

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Amniocentesis is an invasive procedure, which means that there is a small risk of miscarriage (less than 1 in 200) associated with it. Results of the test for Down syndrome and Trisomy 18 will take about 7-14 days. Results of the test for open spina bifida will take about 2-5 days.

No test can guarantee that your baby will be free of all birth defects, but if the result of the amniocentesis is negative, it will almost certainly rule out Down syndrome and/or other chromosome abnormalities.

What are the advantages of risk assessment?

The test may give you and your healthcare provider important information about your pregnancy and your developing baby. If your baby is found to have a serious birth defect, you can receive professional counseling about how your child's physical and mental development may be effected. The individual capabilities and potential of children with birth defects are considerations which you may wish to discuss with your genetic counselor or other healthcare provider. Other options, such as adoption and termination of pregnancy may be discussed with you by your healthcare provider. Further information and support are available through groups such as your local Down Syndrome Society and Spina Bifida Association.

Further information and support are available through groups and local organizations as listed below:

- March of Dimes** www.marchofdimes.com
- National Down Syndrome Society** www.ndss.org
- National Association for Down Syndrome** www.nads.org
- Smith-Lemli-Opitz Syndrome** www.smithlemliopitz.org
- Spina Bifida Association** www.sbaa.org
- Trisomy 18** www.trisomy.org



MODIFIED SEQUENTIAL INFORMED CONSENT

I have read and understand the information in this pamphlet regarding screening for the Modified Sequential Test.

- Yes, I want to have the Modified Sequential Test.
- No, I do not want to have the Modified Sequential Test.

Patient Name: _____

Patient Signature: _____

Date: _____

IMPORTANT: Retain Copy in Patient File



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MODIFIED SEQUENTIAL TEST



FIRST STAGE
Results Reported

Information for Patients

First and Second Trimester
Risk Assessment
for
Down Syndrome and
Open Neural Tube Defects

SECOND STAGE
Final Results Reported



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The MODIFIED SEQUENTIAL Test

Risk Assessment

What does the Modified Sequential test involve?

The Modified Sequential test is performed in two stages. The first stage is ideally performed at 12 weeks of pregnancy, but any time between 11 and 13 weeks of pregnancy is acceptable. The second stage is ideally performed at 16 to 18 weeks of pregnancy, but may be performed as early as 15 weeks and no later than 22 weeks.

The first stage involves:

- An Ultrasound scan examination to precisely determine the gestational age of the pregnancy through the crown rump length (CRL) of the baby.
- Taking a sample of your blood to measure the concentration of pregnancy associated plasma protein-A (PAPP-A) and total human chorionic gonadotropin (*total β-hCG*).
- A Nuchal Translucency (NT) measurement between 11 weeks 0 days and 13 weeks 6 days.

After the first stage evaluation two risk groups are identified.

- High risk: Patients at a risk of 1 in 200 or greater are offered genetic counseling and the option of an invasive diagnostic test such as CVS or amniocentesis. (See "What does a screen positive result for Down Syndrome Mean?")
- The remaining patients will benefit from proceeding to the second stage.

The second stage involves:

Taking a second blood sample to measure the concentration of four different markers:

- alpha-fetoprotein (AFP)
- unconjugated estriol (uE3)
- inhibin-A
- total human chorionic gonadotropin (*total β-hCG*)

The NT measurement and the levels of the five markers in your specimen are used, together with your age, to estimate your risk of having a Down syndrome pregnancy.

In pregnancies with Down syndrome, PAPP-A, AFP and uE3 levels tend to be decreased and nuchal translucency measurement, inhibin, and total β-hCG levels tend to be increased compared to unaffected pregnancies. The level of AFP in the second blood sample is also used to determine if there is an increased risk of open spina bifida, anencephaly or an abnormal opening of the baby's abdominal wall.

What is a risk?

A risk is the chance of an event occurring. For example, a risk of Down syndrome of 1 in 100 means that if 100 women have this test result, we would expect that 1 of these women would have a baby with Down syndrome and that 99 would not. This is the same as a 1% chance that the baby has Down syndrome and a 99% chance that the baby does not.

What is Down syndrome?

Down syndrome is caused by the presence of an extra chromosome number 21 in the cells of the developing baby. In an unscreened population about 1 in every 700 (1.4 per 1000) babies is born with Down syndrome. Usually it is not inherited and so a baby can be affected even if there is no history of Down syndrome in the family.

Down syndrome is the most common cause of severe mental disability and is often associated with physical problems such as heart defects or difficulty with sight and hearing. It is not possible to assess the degree of handicap before the baby is born. About 9 out of 10 babies with Down syndrome will survive their first year and nearly half of these will reach 60 years of age.

What are Open Neural Tube Defects (ONTD)?

The two main kinds of open neural tube defects (ONTDs) are open spina bifida and anencephaly.

Babies with open spina bifida have an opening in the spine that can result in damage to the nerves controlling the lower part of the body. This causes weakness and paralysis of the legs, and sometimes bowel and bladder problems. Babies with these problems are also more likely to have a collection of fluid on the brain, called hydrocephalus, which can be treated surgically but may lead to mental disability.

Babies with anencephaly have a large part of the skull missing and the brain is not properly formed. They always die before or very soon after they are born. In about 1 in every 5 babies with spina bifida the spinal opening is covered with skin or thick tissue. This is called closed spina bifida and will not be detected by the blood test. This condition is usually less severe than open spina bifida.

Can other abnormalities be identified?

Yes. The risk of two other disorders can be estimated. One is Trisomy 18, a rare and usually fatal disorder caused by the presence of an extra number 18 chromosome in the cells of the developing baby. The risk of Trisomy 18 can be estimated using PAPP-A, AFP, uE3 and total β-hCG, and is reported only when the risk is high. The second is called Smith-Lemli-Opitz syndrome (SLOS), a genetic disorder caused by an error in the synthesis of cholesterol. Smith-Lemli-Opitz syndrome is associated with many problems in the developing baby, most important are mental retardation and poor growth. The risk of Smith-Lemli-Opitz syndrome (SLOS) can also be estimated using AFP, uE3 and total βhCG and is reported only when the risk is high.

Why is your age taken into account?

Any woman can have a baby with Down syndrome but the chance of this happening increases as a woman gets older. We use age as one of the factors when working out your risk of pregnancy with Down syndrome. It means that an older woman is more likely to have a result in the higher risk group (*screen positive*) and be offered a diagnostic test.

Why will some patients have to wait until the second stage to have a risk estimate?

Patients with high risk results have been identified in the first stage. Risk assessment ends for them. The remainder of patients proceed to the second stage. At this point, adding additional markers helps distinguish affected from unaffected pregnancies more effectively and reduces the chances that a Down syndrome pregnancy is missed. It also reduces the chance that an invasive diagnostic test, such as amniocentesis will be indicated.

What happens if I am too late for the first stage of the Modified Sequential test?

We cannot report a screening result for the Modified Sequential test. You could have a screening test based on the second stage alone (the AFP+QUAD test).

What happens if I cannot attend for the second stage of the Modified Sequential test?

If you do not attend for the second stage of the Modified Sequential test, a screening result cannot be reported. We will try to contact your healthcare provider on two occasions after the recommended date for your second blood sample. If we do not receive your second blood sample a Down syndrome risk is given based on information from the first stage only.

If you know you will not be able to attend for the second blood test, please discuss this with your healthcare provider. You could have the screening based on the first blood test and the ultrasound examination alone (the Combined test) but this is less effective than the Modified Sequential test.

When will the results of the second stage be available?

The results of the test are usually ready within three working days of the second blood sample being taken. Results are sent to your doctor, midwife or healthcare provider. The result will be either *screen negative* or *screen positive*. *Screen positive* results are telephoned and faxed to your doctor, healthcare professional, or midwife. If you do not receive your results or have further questions please telephone LENETIX® at (516) 248-0036 to speak with a genetic counselor.

What does a screen negative result mean?

If the risk of Down syndrome, based on the Modified Sequential test, is lower than 1 in 270 and the AFP level is less than two and one half times the normal level for your stage in pregnancy, then the result is called *screen negative* and a diagnostic test would not be offered.

Although a *screen negative* means that you are not at high risk of having a baby with Down syndrome or an open neural tube defect, a *screen negative* result does not completely rule out the possibility of a pregnancy with either of these abnormalities.

