

Prenatal Genetic Testing: An overview of history, advancements, and impacts on health care

Jessica Neumann

Indiana State University

Abstract

The purpose of this research is to study prenatal genetic testing and the advancements that have been made since the human genome project has made the testing process simpler and less invasive. Prenatal genetic testing is a screen or a test that is performed in order to determine if an embryo or fetus has a certain disease or condition before its birth. A variety of different prenatal tests and screens have been studied to evaluate what genetic conditions are screened for and when. The scope of this paper focuses on the historical overview, advancements, patients, tests, and impacts related to prenatal genetic testing. Some questions are presented in the beginning of this paper in order to fully describe and understand prenatal genetic testing and the benefits and issues relating to it. Conclusion: Prenatal genetic testing and screening is available for many diseases, but the typical test screens for only a select number of diseases and conditions.

Keywords: Prenatal genetic testing, Prenatal genetic screening, genetic advancements

History of Prenatal Genetic Testing

Looking at the history, in brief, genes and genetics were terms that were not known 150 years ago. Many discoveries in the last century have contributed to the study of genomes as they are known today. In 1865, Gregor Mendel introduced the fundamental laws of inheritance that was essential to understanding that some characteristics and traits are passed down from parent to child through genes. In 1910, Thomas Hunt Morgan improved these rules by performing experiments that showed that certain phenotypes located on chromosomes were responsible for the appearance of the organism. Soon after in 1911, the first genetic map was attained through the mapping of the genes of a fruit fly. It was not until 1953 that the next major discovery was made regarding DNA by Watson and Crick. They discovered that DNA was double-stranded, helical, complementary, and antiparallel, which led to further discovery of the genetic code in the DNA in 1966. These discoveries of chromosomes and DNA paved the way for rapid discoveries of genetics and technologies in the past 50 years. In 1956 it was discovered that the normal human chromosome number was 46 and that there were ways to culture, stain, and view these chromosomes to differentiate them. With this they were able to discover what genes cause Trisomy 21, Turner Syndrome, and Klinefelter Syndrome. After 1966, genetic methods and procedures were performed on postnatal samples, and also in prenatal samples (Durmaz).

Although much has been discovered and there have been numerous amounts of advancements in the area of prenatal genetic screening in the past 50 years, there is still much research to be done in order to keep building the accuracy. This is important to allow patients and insurance companies to see the screening as a positive test, rather than an experimental test. With the health care system in the United States changing, it is ultimately important to look at how these scans will be used more accurately and how patients will feel about them. Some of

the questions that will be discussed in this paper include: What are the advancements that have been made in prenatal genetic screening/testing? What patients are getting these tests performed? What diseases and disorders do these prenatal scans recognize? How are these tests changing healthcare? The literature regarding these topics will be highly beneficial to understanding the influences and impacts that these screens have.

Prenatal genetic testing began in the 1960's in order to screen for chromosomal mutations in the fetus. The original test for determining these chromosomal mutations was called amniocentesis, which uses amniotic fluid from the amniotic sac to view the fetal genetic make-up. The first documented use of amniocentesis to determine the genetics of a fetus was reported by Fuchs and Riis in 1956. With the use of amniotic fluid, they were able to determine the sex of the fetus based on whether or not the Barr body was present in the chromosomes of the cells. In 1966 many similar results were published from scientists that had successfully used amniotic cells to view full human karyotypes. Two short years later in 1968, Harold Nadler used full chromosome analysis to report the first prenatal genetic disease with the use of amniocentesis, Trisomy 21 (Durmaz). Since this discovery, amniocentesis has been a common form of prenatal screening for chromosomal mutations, neural tube defects, X-linked conditions, and errors in metabolism during the 16-20th weeks of pregnancy.

In 1968 a scientist by the name of Mohr in Scandinavia introduced the idea of using a sample of chorionic villi to diagnose genetic disparities prenatally. Mohr used a trans-cervical biopsy of the chorion to obtain a sample of cells. In his experiments there was a high rate of infection and bleeding. After many attempts, the first successful procedure was performed in 1974 in China for the purpose of sex pre-selection. With this procedure they used a 3 mm cannula and a small tube to create a syringe like suction. They had 99 correct attempts, 6

incorrect attempts, and 4 prenatal losses. It was not until 1985 that the United States approved the use of early prenatal screening by chorionic villus sampling (CVS) with the first procedure done in San Francisco. In 1986, the Golbus group from San Francisco released data that in their first 1000 cases of chorionic villi sampling, 1.7% of samples were not adequate, and 3.8% of the procedures caused fetal losses (Woo).

The process of performing amniocentesis and chorionic villus sampling have both evolved over the years. They have found the best way to perform the procedures and the best time to perform them. The designated standard of care for amniocentesis is for the procedure to be performed in between 15-20 weeks. Amniocentesis is an invasive procedure which “your health care provider inserts a long, thin needle through your belly and into your womb. A small amount of fluid (about 4 teaspoons) is removed from the sac surrounding the baby” (Amniocentesis). The needle is inserted with the help of an ultrasound to direct the provider and verify its placement. It has been used most commonly to test for Down’s syndrome, spina bifida, anencephaly, and many other genetic diseases. Chorionic villus sampling is performed in between 10-12 weeks. Chorionic villus sampling can be performed through a transcervical procedure where a tube is inserted through the vagina and cervix into the placenta or a transabdominal procedure where a needle is inserted into the abdomen, uterus and then the placenta (Chorionic Villus Sampling). In both of these procedures, an ultrasound is used to guide the needle/tube to collect the chorionic villi tissue. Similarly to the amniocentesis procedure, chorionic villus sampling examines the presence of many genetic diseases, most commonly: Tay-Sachs, Down’s syndrome, and hemoglobinopathies.

Human Genome Project

As further research and investigation has been performed, more advanced screening and testing options have become available in the past ten years. Beginning in 1993, the Human Genome Project (HGP) began with hopes to map out and understand the complete human genome. This collaborative research project included more than 18 countries and took about ten years. They identified over 20,500 human genes that we can now identify the location of each of these genes. "HGP researchers have deciphered the human genome in three major ways: determining the order, or "sequence," of all the bases in our genome's DNA; making maps that show the locations of genes for major sections of all our chromosomes; and producing what are called linkage maps, complex versions of the type originated in early *Drosophila* research, through which inherited traits (such as those for genetic disease) can be tracked over generations" (An Overview of the Human Genome Project). In 2003, the final draft of the full sequence was published with hopes that this would be used as a manual to help prevent, detect, and cure disease.

Advancements

Due to the increase of knowledge that has been released about the human genome, many prenatal screens and tests have expanded what they are able to test for as well as how they are able to do it. Recently a new advancement became available where women were able to find out the genetic risks for their child earlier, and more simply. This new test is called cell-free fetal DNA testing which allows offices to simply draw blood from the patient rather than performing an invasive procedure such as amniocentesis or chorionic villus sampling. This blood draw can be performed as early as ten weeks of pregnancy, which is also weeks earlier than the more invasive procedures. When the blood is drawn, it is sent to a lab where they examine the blood

specifically for the cell-free fetal DNA. “Cell-free DNA are short DNA fragments from chromosomes found in circulation. In pregnancy, cell-free DNA from the fetus and the mother are both present in maternal blood” (Sparks). Each fragment of cell-free DNA is approximately 150-180 base pairs long. The cell-free DNA of the fetus is released into the mother’s blood stream when the placental cytotrophoblastic cells are shed into the mother’s circulation. This occurs during the first few weeks of pregnancy. At about ten weeks of pregnancy, approximately 10% of the maternal cell-free DNA is composed up of placental fragments. The fetuses cell-free DNA is mixed in with the mothers so in order to analyze these fragments, it must first be divided.

Once the cell-free fetal DNA is analyzed, the provider will become aware of the results. This process takes anywhere from 7-10 days and may vary company by company. Depending on the company that analyses the lab, and the physician’s office, the patient may receive a call only if the results are abnormal. If the results are normal, the results will be discussed at the patient’s next O.B. visit.

The benefits to this new type of testing are that it is: simple, accurate, and accessible. To have this test performed, a single blood test is drawn at ten weeks or after of pregnancy and this blood draw can be done at the patient’s physician’s office. The test is highly accurate and there is a low false positive rate, especially with trisomies. For example, the detection of Trisomy 21 in a prenatal test called “The Harmony Prenatal Test” has an accuracy rate of greater than 99% (Expecting Parents). The only time that these cell-free fetal DNA tests are not accurate is when the mother has gone through some sort of transplant procedure. An example of this is a bone marrow transplant, if the mother had a bone marrow transplant from a male at any point in her life, the cell-free DNA may show results of Y chromosomes, which would suggest a male baby.

This result can be inaccurate if the baby was actually a girl. This can also lead to inaccurate results of determining sex chromosomal abnormalities. More than 1,700 patient centers have access to this type of testing and have genetic counselors available for the decision making process and questions that may occur, before, during, and after the test is performed. There are many different tests that patients have available to them, each of which is a little different. They may vary by what diseases each one is testing for as well as what specific lab the blood sample will be sent to (Examples: Labcorp, Quest Diagnostics). The different labs that the blood sample can be sent to may make a difference when it comes to the patient's insurance. Some companies have partnerships with certain labs and require all of their patient's tests to be sent to one of their lab branches.

Patients Recommended for Genetic Testing

When it comes to prenatal genetic screening and testing, the majority of those women who receive testing such as cell-free fetal DNA testing, amniocentesis, or chorionic villus sampling are at high risk with their pregnancy. The risk factor of a pregnant women is determined by a variety of different conditions such as: advanced maternal age (35 years old or older), personal or family history of chromosomal abnormalities/mutations, fetal ultrasound abnormalities that suggest aneuploidy, or a positive serum screening test (Expecting Parents). "Women who will deliver at or after 35 years of age should be routinely offered either procedure, as the risk for a chromosomally abnormal fetus increased each year" (Mishell 344). At the age of 30, a woman has a 1 out of 952 chance of having a child born with Down's syndrome. As shown in Table 1, the age increased to 35, the risk increased to a 1 out of 385 chance of having a child with Down's syndrome. This risk continues to increase as maternal age progresses (Mishell 345). Knowing this is not only important when pregnant, but also prior to

pregnancy. When discussing maternal age and family history with a patient prior to pregnancy, “the family can make reproductive decisions ahead of time” (Burrow 218).

Table 1: Chromosomal abnormalities with advancing maternal age (Mishell 344)

Maternal Age	Risk of Down’s syndrome	Risk of chromosomal abnormalities
20	1:1667	1:526
25	1:1250	1:479
30	1:952	1:384
35	1:385	1:204
37	1:227	1:130
40	1:106	1:65
42	1:64	1:40
45	1:39	1:20
48	1:14	1:10

The serum screening test is typically performed through a blood draw between the 16th-20th weeks of pregnancy. This screen measures the amount of alpha fetoprotein in the mother’s serum from her blood to determine if further testing will be needed. Alpha fetoprotein is a protein that is produced by the liver of a fetus and released into the bloodstream of the fetus and the mother. The “normal” amount of alpha fetoprotein that should be present in the blood of the mother varies by the gestational age of the fetus. As the fetus grows older, the levels of alpha fetoprotein in the mother’s blood should increase. If the amount of alpha fetoprotein is higher or lower than average it can be an indicator of a chromosome mutation or abnormality. Initially

this test was used to strictly screen for fetuses with neural tube defects, but as research has advanced, it also identifies fetuses with other genetic diseases (Mishell). If the alpha fetoprotein is high, it is a possible indicator of an abdominal wall defect, or neural tube defects such as spina bifida or anencephaly. If the alpha fetoprotein is low, it is a possible indicator of diseases such as Down's syndrome (Sillence). Both high and low results are considered to be positive serum screen tests. When this test comes back positive, it is recommended that the patient gets further tests performed, such as a genetic screen. Before a genetic test is scheduled, an ultrasound is performed to verify the gestational date accuracy. If the date were to be wrong, the alpha fetoprotein screen will be recalculated with the updated gestational age (Alpha-Fetoprotein (AFP) in Blood).

In a study performed among a group of patients by BMC Medicine is a breakdown of patients that received prenatal, non-invasive genetic screening/testing. Approximately 50% of the patients that were receiving this screening received it due to advanced maternal age of 35 or greater while pregnant. The next highest category of 22% is of patients who had a positive serum screening test for Aneuploidy, 19% of patients had this prenatal testing because of ultrasound abnormalities, 4% of patients requested it themselves, 2% had family history of an aneuploidy, 2% had a previous child with aneuploidy, and 1% of the patients were screened for other various reasons (Neufeld-Kaiser).

Genetic Detections

There are a variety of different tests and scans available depending on the specific information you want to attain. The majority of cell-free fetal DNA tests detect increased amounts, trisomies, of 21, 18, 13, X and Y chromosomal material. A trisomy is when one

chromosome has three copies, instead of two. Trisomy 21 is commonly known as Down's syndrome which is associated with intellectual disabilities and can also have impacts on digestive disease and congenital heart defects. Trisomy 21 is the most common trisomy in newborns and is estimated that approximately 1 out of every 700 newborns are impacted by this disease (Down's syndrome). Trisomy 18 is also called Edwards Syndrome and is often associated with miscarriages, congenital heart disease, and many other medical conditions. Trisomy 18 is present in 1 out of every 5,000 newborns. Trisomy 13 is also called Patau Syndrome and very similarly to Trisomy 18, is associated with a high rate of miscarriages, congenital heart defects and other health conditions (Trisomy 18). Trisomy 13 is approximated to be present in 1 out of every 16,000 newborns (Trisomy 13).

When looking at the X and Y chromosomal material, these scans are able to detect the sex of the fetus as early as ten weeks, which is the earliest detection of sex in medicine. Dr. Diana Bianchi, an expert on prenatal diagnosis at Tufts University School of Medicine states that "many women are very excited by the idea that as part of their blood testing, they could find out pretty definitively if the baby is a boy or a girl" (Greenfield-Boyce). When looking at aneuploidies of the X and Y chromosomes, labs are able to detect specific diseases such as: Turner syndrome, Klinefelter syndrome, Triple X syndrome, and XYY syndrome. Turner syndrome (X) occurs in approximately 1 in every 2,000 – 5,000 newborn females and is also called gonadal dysgenesis. It is characterized by stunted growth, with the average height being 55 inches, a webbed neck, and a low posterior hairline. Klinefelter syndrome (XXY) occurs in 1 out of every 500 – 1,000 newborn males and is the most common sex chromosomal abnormality. It is characterized by fibrosis and hyalinization of the seminiferous tubules, increase in urinary gonadotropins, and impairment of Leydig cells. Triple X syndrome (XXX) occurs in 1 out of

1,000 newborn females and is characterized by tall and slender females that are often considered “super-females.” XYY syndrome (XYY) occurs in 1 of every 2,000 male births and is similar to Triple X syndrome, but it occurs in males rather than females (O’neil). These individuals frequently have larger builds and are considered “super-males” (Miller)

A test called “The Harmony Prenatal Test” is one of the most common tests performed that scans for the trisomies and sex chromosomal abnormalities stated above. Another common test that screens for these diseases is called “MaterniT21 Plus”. These tests look for the same thing, but are performed by different lab companies. With these tests, the health care provider can request more genetic material to be scanned for other issues, but the standard of care is simply trisomies and sex chromosomal abnormalities. There are also other prenatal genetic exams that screen for more than just these trisomies and sex chromosome abnormalities. A test called “Panorama Prenatal Test” screens for the trisomies and the sex chromosome abnormalities, as well as specific deletions in fetal genes, also known as Microdeletion syndromes. A microdeletion that the “Panorama Prenatal Test” screens for is 22q11.2 deletion syndrome which is more common in newborns than cystic fibrosis. 22q11.2 deletion syndrome can cause congenital cardiac defects, hypocalcemia, immune deficiency, palatal abnormalities, feeding difficulties and other medical problems. Panorama also screens for microdeletions that cause Prader-Willi syndrome, Angelman syndrome, Cri-du-chat syndrome, and 1p36 Deletion syndrome. Panorama does not screen for all microdeletions, just ones that are located on certain loci of the genes. Approximately 1 in every 1,000 newborns will have one of these microdeletions and the maternal age has no impact on these diseases (Panorama Test).

Impacts on Current Healthcare

Genetic testing in general has impacted the way that health care providers are able to treat as well as prepare their patients. They are able to determine the best individualized care for each of their patients. Knowing details about family history and about the human genome allow health care providers and genetic counselors to determine the care specifically for that genetic disease. When it comes to a positive result from prenatal genetic testing, these benefits not only will help the child, but will also help the parents prepare for their specific child's needs. The mother, provider and genetic counselor will be able to monitor the fetus for more specific health concerns and come up with the best treatment options. If the results come back negative for genetic mutations, the mother will not have to worry about finding time for extra doctor's visits and other tests.

Many health insurance companies will cover prenatal genetic testing for mothers, especially when the physician recommends it for a specific reason. An article from *Journal of Law, Medicine, & Ethics*, states that "private health care insurers such as United Health Group, WellPoint, Blue Cross/Blue Shield, Primary Health, and Aetna cover NIPT for pregnant women with personal or family histories of genetic conditions, prior affected pregnancies, of advanced maternal age, or who screen positive (serum or ultra-sound) for moderate to high risk of fetal abnormality." This all varies on the patient's insurance plan as well as the insurance company, but some patients may opt out of using insurance when paying for these tests. According to nih.gov, "some people may choose not to use their insurance to pay for testing because the results of a genetic test can affect a person's health insurance coverage. Instead, they may opt to pay out-of-pocket for the test" (Genetic Testing). Depending on the patient's plan, they may

encourage more invasive procedures such as amniocentesis or chorionic villus sampling because some companies still view cell-free fetal DNA as an experimental test.

Prenatal genetic testing has increased the amount of knowledge that parents and physicians have about the baby and fetus, but has also caused many ethical issues. Two of the ethical issues that are commonly brought up with prenatal genetic screening are the privacy of a person's genes, appropriate terminology, and abortions. Privacy can be a huge factor when a patient is deciding whether or not to have a genetic test performed on their child. The question arises of, "what are they doing with this information after I find out if there are genetic mutation?" According to the Advisory Committee on Genetic Testing to the Secretary of Health and Human Services, they concluded that "the current oversight of genetic tests [is] insufficient to ensure their safety, accuracy, and clinical validity," (Rebouché) but the Committee's recommendations have yet to become implemented. This causes some patients to be uneasy about genetic procedures in general.

In current times, the ways that medical professionals word and explain diagnoses is tremendously important. While communicating with a patient about their unborn child, the last thing the medical provider wants to do is to offend the patient. As times change, so does the socially acceptable vocabulary. For example, 20 years ago, certain terms such as "mental retardation" may have been a socially correct statement to say to a patient while explain a certain disease their child has been diagnosed. Currently, the more appropriate term to explain parts of a certain disease would be "metal disability." When mothers are having prenatal genetic tests performed, it is common for them to ask questions about the possible outcomes before the test, and ask about details after the test results come back. When dealing with sensitive subjects such diseases that may cause mental and physical impairments, it is important for medical providers to

know what language to use and how to approach the situation. This not only shows respect for the patient as well as the unborn child.

When it comes to abortions, it has been seen as a problem that patients are finding out the sex and the genetic mutations of the baby earlier, and it is causing some women to terminate their pregnancies soon after prenatal testing. Certain religions do not want female children, and other families do not believe that they want a child with a disability and instead of putting the child up for adoption they choose the termination route. “States have passed laws that ban abortion if the termination is for reason of the fetus’s sex, race, or diagnosis of fetal abnormality. In the latter, laws in Virginia and Nebraska allow genetic counselors to refuse to communicate any information, including testing results or options after testing, if the counseling, in the words of the Virginia law, “conflicts with the counselor’s deeply-held moral or religious beliefs” (Rebouché). Since these genetic tests can be performed as early as ten weeks of pregnancy, this becomes a deeper issue with abortions and if they should be legal in general or not.

Conclusion

Prenatal genetic testing is a common practice across the world, and has changed drastically in the last 20 years. Advancements using cell-free fetal DNA have increased the number of women having these tests performed due to early detections made and the non-invasive procedure used. High risk patients are the ones that typically go through prenatal genetic testing, those with advanced maternal age (35 years old or older), personal or family history of chromosomal abnormalities, fetal ultrasound abnormalities that suggest aneuploidy, or a positive serum screening test. Recent results have shown an increase of patients requesting these tests to be performed, even when their pregnancy is not at high risk for genetic defects.

These patients are often just wanting to check to make sure everything is alright with their pregnancy as well as find out the sex of their baby as early as ten weeks in, rather than 20 weeks. These tests typically screen for trisomy 21, 18, and 13, as well as sex chromosome abnormalities. Some tests, such as the “Panorama Prenatal Test,” screens for other genetic defects such as microdeletions. There are many testing options that are available for families and mothers to choose from depending on their specific situations and recommendations.

Until these advancements were made, “the physician was limited to the use of pedigree analysis and estimation of the risk using statistical methods in most mendelian conditions. Diagnosis was often based on phenotype, as it could be defined by physical examination, imagine tools such as radiography and ultrasound linkage to protein markers and the measurement of analysis in body fluids such as blood and urine” (Burrow 218). These tests are allowing better care for not only the mothers, but also for the fetuses. This is due to a combination of the preparation of the family, the specific specialized care provided by the health care provider, and the information provided by the genetic counselor.

More women are also willing to have prenatal genetic testing performed because of the non-invasive procedures that have been developed. In a NPR interview, a patient states: “I wasn't interested in going as far as getting an amniocentesis because of the risk associated with that, and so when I heard about this test, that was part of the reason that I was most interested in it” (Greenfield-Boyce). In the same interview, Dr. Mary Norton, an expert on maternal-fetal medicine and genetics in San Francisco says that “those of us in the field who do diagnostic procedures like CVS and amnio have seen a drastic decrease in the number of those procedures that are being performed, places are reporting doing fewer than half the number of procedures that were being done previously” (Greenfield-Boyce).

Although these tests are becoming more popular and wide spread, there are many ethical influences that have many people questioning if everyone should be allowed to have these tests performed on them. Some of these views are religious, and others are far from it. Different laws are being passed to try and restrict the decisions that people are choosing to make after prenatal genetic tests. It is unknown what further advancements will be made in the future, but with the amount that has changed in the past 20 years, it is likely that many more tests, along with restrictions, will be implemented into health care.

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