DOI: 10.1097/JPN.0000000000000374

CE **Continuing Education**

J Perinat Neonat Nurs • Volume 33 Number 1, 12–25 •

Beyond the Brochure

Innovations in Clinical Counseling Practices for Prenatal Genetic Testing Options

Dana Knutzen, MS, LGC; Katie Stoll, MS, LGC

ABSTRACT

Remarkable advancements related to preconception and prenatal genetic screening have emerged in recent years. While technology and testing options are more numerous and complex; fundamental genetic counseling issues remain the same. It is essential that with any prenatal genetic testing, women have an opportunity to make informed and autonomous decisions that are consistent with their personal needs and values. Opportunities to discuss testing options, including potential benefits and limitations, are often limited in obstetric visits due to time constraints or lack of sufficient provider education. As genetic testing is not considered a routine component of antepartum care, review of information regarding testing options is imperative so women can decide which, if any, testing to pursue. Developing new strategies to address the growing complexity of prenatal testing while ensuring provider education is accurate is crucial in imparting evidence-based care. This article will arm providers with the knowledge needed to educate women about currently available prenatal genetic screening and diagnostic tests along with guidance on the essential elements and importance of genetic counseling.

Key Words: decision making, genetic counseling, genetic testing, informed consent

Author Affiliations: Department of Obstetrics and Gynecology, Baylor College of Medicine (Ms Knutzen); and Genetic Support Foundation (Ms Stoll).

Disclosure: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Each author has indicated that he or she has met the journal's requirements for Authorship.

Corresponding Author: Dana Knutzen, MS, LGC, Department of Obstetrics and Gynecology, Baylor College of Medicine, The Children's Hospital of San Antonio, 315 N San Saba, Ste 930, San Antonio, TX 78207 (dana.knutzen@bcm.edu).

Submitted for publication: July 29, 2018; accepted for publication: September 17, 2018.

While genetic testing has been available in prenatal care settings for nearly half a century, the number and complexity of prenatal options have grown dramatically in recent years.[1,2] Initially, procedures such as amniocentesis could allow for fetal diagnosis of trisomy 21 and other chromosomal conditions, while carrier screening was available for a handful of single gene disorders (eg, Tay-Sachs disease [TSD], sickle cell anemia, and cystic fibrosis). Today prenatal diagnosis is available for hundreds of genetic conditions with noninvasive prenatal screening methods for chromosomal disorders becoming more sensitive and specific.

Many women may have preconceived ideas about prenatal genetic testing, influenced by friends and family, the media or commercial laboratories.[3] Although genetic testing is generally available to pregnant women, unlike other prenatal laboratory tests, these are not ordered routinely. Discussions regarding prenatal genetic testing options are typically conducted by a physician, midwife, or nurse-practitioner; however, appointments may be short with multiple topics to discuss, leaving little time to review prenatal screening options and testing nuances.[4,5] This scenario, coupled with the expansion of available prenatal screening options, may result in inadequate counseling by healthcare providers.[6] Thus, women may agree to testing, simply based on the fact that screening was offered, without making an informed decision.

Pretest counseling is provided to women so that they have an opportunity to make informed decisions about what, if any, prenatal genetic testing to undergo after weighing potential benefits, drawbacks, and limitations of tests in the context of specific needs and values. Women may find prenatal testing information helpful in preparation for an infant with a genetic condition or special medical needs. Others may elect to undergo prenatal testing because pregnancy termination is being

considered for a genetic diagnosis. In addition, some women decline prenatal testing because results will not change pregnancy management if a genetic condition is identified, thus screening may evoke unwanted anxiety. The purpose of this article was to incorporate an overview of currently available prenatal genetic screening and diagnostic tests with guidance on critical elements of pre- and posttest genetic counseling.

OVERVIEW OF GENETIC TESTING

To help women navigate various prenatal genetic testing options within established appointment time limits, clinicians are obligated to understand differences among available tests as well as risks and benefits before counseling patients. Generally, prenatal genetic testing is divided into 2 categories: screening tests and diagnostic tests.[1,7] Diagnostic testing during pregnancy involves a procedure such as amniocentesis or chorionic villus sampling (CVS) to allow for direct testing on fetal or placental cells.[2] These tests provide definitive information about a diagnosis of a chromosomal or single gene condition in the fetus. In contrast, screening tests, such as maternal serum and prenatal cell free DNA testing, can only determine if there is a higher or lower chance of a chromosomal or genetic condition in the pregnancy but cannot provide a definitive diagnosis.[1,7] Imaging modalities, such as ultrasound and fetal magnetic resonance imaging (MRI), can provide diagnostic information regarding birth defects but, like screening tests, cannot diagnose an underlying genetic etiology.[1,7] Finally, carrier screening for recessive disorders can identify those couples at increased risk to have a child with a genetic condition; however, a diagnostic procedure and test are needed to identify those fetuses that are affected.[8] Both screening and diagnostic tests are typically available to pregnant women but the amount of information desired by women can vary significantly.

ANEUPLOIDY SCREENING

Given that diagnostic invasive procedures carry a risk of miscarriage, screening tests performed on maternal blood allow for a mechanism to identify women who have a higher probability of a pregnancy affected with aneuploidy (eg, conditions caused by the presence or absence of chromosomal material).[7] There are generally 2 types of screening for aneuploidy: maternal serum screening and cell free DNA screening (cfDNA screening). Each type of aneuploidy screen has multiple versions offered by a number of laboratories, with each modality demonstrating different strengths and weaknesses.[7]

Maternal serum screening

Maternal serum screening for fetal aneuploidy requires measurement of specific analytes detected in pregnancy. The data obtained from these analyte measurements are then used to calculate a posttest probability for aneuploidy based on specific analyte values, maternal age, and other factors.[7] For example, lower than average levels of maternal serum alpha-fetoprotein during the second trimester of pregnancy are associated with a higher probability of trisomy 21 (Down syndrome).[9] Through discovery of new analytes and an association to aneuploidy risk, maternal serum screening has gone through many updates (eg, triple, quad, first trimester, sequential and integrated screening) and now includes evaluation of multiple maternal analytes in the first and second trimesters to screen for trisomy 21, trisomy 18, and in some cases trisomy 13 and Smith-Lemli-Opitz syndrome.[1,7] Analyte screening also screens for conditions other than aneuploidy, including neural tube and abdominal wall defects, given the association of these conditions with elevated maternal serum alpha-fetoprotein.[1,7]

Prenatal cell free DNA

Also referred to as noninvasive prenatal screening or noninvasive prenatal testing, this clinical test involves measurement of cell-free fragments of DNA in maternal serum for trisomy 13, 18, 21, and sex chromosome variations.[7,10,11] During pregnancy, shedding placental cells, which usually have the same genetic make-up as the fetus, enter the maternal bloodstream.[7,10] These placental DNA fragments can be detected and measured from about 10 weeks' gestation through the remainder of the pregnancy.[7,10] Next-generation sequencing allows for amplification of cell-free DNA with analysis to determine if genetic material is over- or underrepresented relative to what would be expected, and thus can predict if there is a higher or lower chance for aneuploidy in the pregnancy.[10,11]

The relative amount of placental cfDNA to maternal cfDNA is known as the fetal fraction.[7,10] In some cases the fetal fraction is insufficient for the test to be performed resulting in a "no-call" result.[7] Fetal fraction is inversely correlated to maternal body mass index and obese women are more likely to have a "no-call" result.[12] In addition, no call results have been associated with a higher likelihood of fetal aneuploidy.[7,10] Thus, it is recommended that women with a no-call result be offered genetic counseling and consideration of diagnostic testing.[10,13]

The positive and negative predictive values for aneuploidy, most notably Down syndrome, are higher with cfDNA screening than seen with maternal serum

screening.[14,15] The chance that a positive result is a true positive and not a false positive and the likelihood a negative result is a true negative is based on factors including maternal age, other screening test results (eg, maternal serum), and family history.[5,7] The sensitivity or detection rate, often listed as 98%–99% for Down syndrome, does not correlate with a 98%–99% chance that the fetus is affected in the event of a positive result as noted in Box 1.

This vital clarification is often misunderstood by both patients and providers.[11] Thus, some women assume that a pregnancy is affected based on a positive screening result before receiving posttest counseling. An online calculator developed by the Perinatal Quality Foundation and the National Society of Genetic Counselors is available to assist clinicians in understanding cfDNA results and is available at https://www.perinatalquality.org/Vendors/NSGC/NIPT/.

Initially cfDNA was utilized only as a screening test for Down syndrome, but it quickly advanced to include other chromosomal conditions, such as trisomy 13 and 18. The ability to assess the X and Y chromosomes allows for determination of increased probability of sex chromosome variations such as Turner syndrome or Klinefelter syndrome, and also allows for the prediction of fetal sex.[15] Fetal sex determination as early as 10 weeks has proven to be a successful selling point for cfDNA testing; however, professional societies, such as the American College of Obstetricians and Gynecologists (ACOG), Society of Maternal-Fetal Medicine (SMFM), and the American College of Genetics and Genomics (ACMG), advise that cfDNA screening should not be utilized for this purpose alone.[10,13,15] Additionally, many laboratories promote the use of cfDNA for the detection of rare microdeletion and microduplication syndromes; however, given the low prevalence of these conditions and increased possibility of false-positive results, inclusion in general screening is not recommended.[5,7,10]

Current professional guidelines from ACOG and ACMG support screening for aneuploidy for all pregnant women in the context of pretest counseling and informed consent.[7,13] It is not advised for women to undergo both cfDNA and analyte screening concurrently during pregnancy, and which test is optimal for each woman may be determined on a number of factors including maternal age and relative risk for aneuploidy, gestational age, maternal body mass index, and insurance coverage.[7,10] In addition, cost and insurance coverage typically factors into which test is ultimately selected, with currently evolving reimbursement trends likely affecting future practice patterns.

CARRIER SCREENING

Carrier screening identifies healthy women and partners who have an increased chance to have offspring with genetic disorders.[16] Research estimates that each person is a carrier of 2.8 severe recessive disorders, with inherited disorders accounting for 20% of infant mortality.[17] With autosomal recessive inheritance, carriers are typically healthy individuals who "carry" a deleterious

Box 1. Terminology for understanding screening tests[a,b]

Term	Definition	Example
Sensitivity	Proportion of affected pregnancies that are correctly identified as having the condition (true positive)	Percentage of fetuses with trisomy 21 with a positive result
Specificity	Proportion of unaffected pregnancies that are correctly identified as NOT having the condition (true negatives)	Percentage of fetuses that do not have trisomy 21 with a negative result
Positive predictive value (PPV)	Ratio of true positives to combined true and false positives	The percentage of all positive results that are *true* positives (fetuses actually have trisomy 21)
Negative predictive value (NPV)	Ratio of true negatives to combined true and false negatives	The percentage of all negative results that are *true* negatives (fetuses do not have trisomy 21)

[a]Explanation: A positive screening test for trisomy 21 includes true-positive results (fetus has trisomy 21) and false-positive results (the fetus does not have trisomy 21). The PPV allows you to determine the likelihood that a positive result is a true positive (the fetus actually has trisomy 21). The PPV is dependent on the prevalence of the disorder in a population. The prevalence of trisomy 21 (and other aneuploidy conditions) increases with maternal age. The PPV of a screening test for trisomy 21 is therefore higher with increasing maternal age, as the prevalence of trisomy 21 also increases.
Example: A cfDNA screening test for trisomy 21 in women who are 40 years of age has a PPV of approximately 90% while the PPV in 20-year-old women is approximately 50%. This means that in 40-year-old women, approximately 9 out of 10 cases with a positive screen for trisomy 21 can be expected to be a true positive, while 20-year-old woman would have a 50-50 chance that a positive result is either a true-positive or false-positive result. (Based on trisomy 21 prevalence at 16 weeks' gestational age with a screening test that has 99% sensitivity and 99.9% specificity for trisomy 21).
[b]From Lutgendorf and Stoll.[11]

mutation in a single copy of a gene. If both members of a couple carry a mutation in the same gene for the same recessive disorder, there is a 1 in 4 or 25% chance that their child is affected with each pregnancy as noted in Figure 1.[18,19]

If one member is found to be a carrier and the partner is unavailable or unknown, refinement of recurrence risk and option of prenatal diagnosis options are limited, as identification of a single variant will not differentiate between a fetus that is an unaffected carrier and one that may be affected.

Today's carrier screening options span ethnic groups and geographical boundaries.[20] Improved technology, along with an increasing inability to categorize individuals into a single ethnic group, has propelled offering screening for multiple disorders at one time.[16] Although ACOG and ACMG have carrier screening guidelines for specific disorders, most laboratory panels are set by commercial entities.[16,21] While panels with more options may appeal to a diverse society, disorders with less well-defined phenotypes and imprecise residual risks make counseling difficult[12] and do not replace current practice guidelines.[21]

Carrier screening can be divided into 3 primary categories: pan-ethnic (universal), ethnic–based, and expanded carrier screening panels.[20,21] Two professional organizations recommend pan-ethnic screening for cystic fibrosis and spinal muscular atrophy.[8,16,22,23] Screening for disorders based on an individual's ethnic background include disorders observed more frequently in the Ashkenazi Jewish population as well as hemoglobinopathies.[24,25] Expanded carrier screening panels typically screen for more than 100 disorders, as well as other recessive and X-linked conditions.[16,20] In addition, professional guidelines for screening for fragile X syndrome currently exist on the basis of the analysis of personal or family history.[26] Current professional guidelines are outlined in Box 2.

Pan-ethnic carrier screening: Cystic fibrosis

Cystic fibrosis is the most common life-limiting recessive disorder in Caucasians though recent treatment advances have extended average life expectancy, with median survival now predicted to exceed 50 years of age.[27] This type of carrier screening is offered, regardless of age, race, or ethnicity.[23] Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Although more than 2000 pathogenic variants have been identified, current screening recommendations include a core panel of 23 of the most common variants.[19]

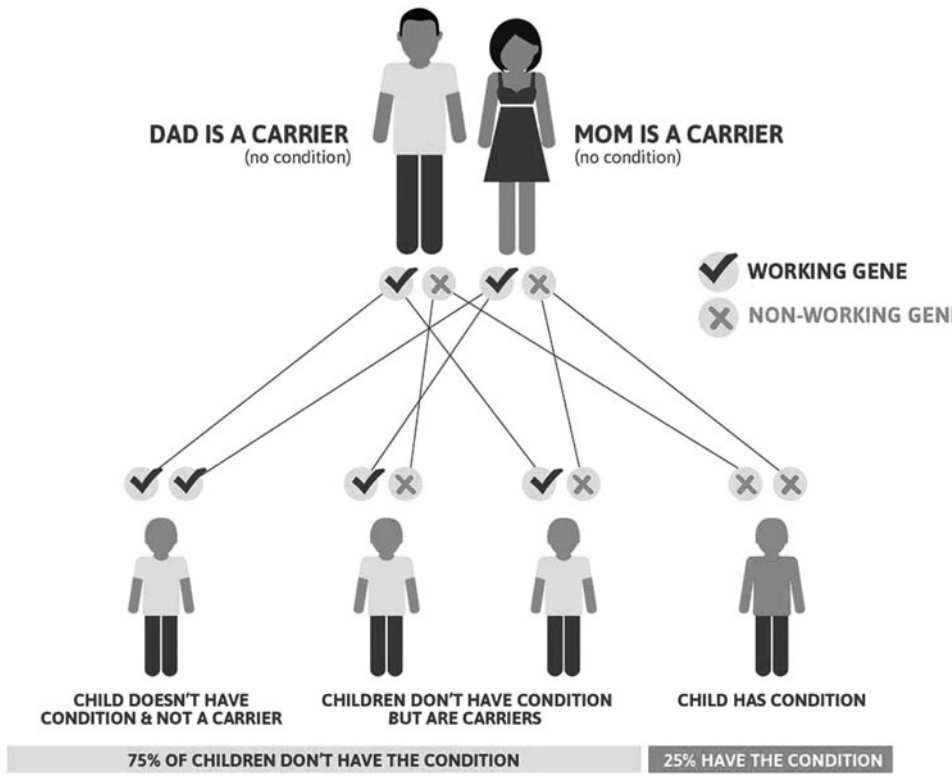

Figure 1. Autosomal recessive inheritance. Used with permission from Genetic Support Foundation[18] (www.geneticsupportfoundation.org).

Box 2. Carrier screening guidelines based on Current ACOG/ACMG recommendations[a]

Disorder	ACOG/ACMG recommendation	What to order
Cystic fibrosis (CF)	Pan-ethnic screening	Include 23 core mutation panel
Spinal muscular atrophy (SMA)	Pan-ethnic screening	Dosage analysis of *SMN1* gene
Individuals of Ashkenazi Jewish ancestry	Ethnicity-based	Initially offer: Tay-Sachs disease, Canavan disease, familial dysautonomia, Cystic fibrosis Screening considered: Niemann-Pick (type A), Bloom syndrome, Fanconi anemia (group C), Mucolipidosis IV, Gaucher disease, familial hyperinsulinism, glycogen storage disease type 1, Joubert syndrome, maple syrup urine disease, Usher syndrome
Individuals of French Canadian or Cajun descent	Ethnicity-based	Tay-Sachs disease
Hemoglobinopathies	Ethnicity-based	Complete blood cell count for all pregnant women Hemoglobin electrophoresis if African, SE Asian, or Mediterranean descent
Fragile X syndrome	Personal/family history	Personal history of premature ovarian insufficiency (POI) Family history of intellectual disability or autism

[a]From references 5, 8, 16, 19, 23, 29, 30.

Pan-ethnic carrier screening: Spinal muscular atrophy

Women are offered preconception or prenatal carrier screening for spinal muscular atrophy.[8,22] This disorder is the most common genetic cause of mortality in children younger than 2 years and affects approximately 1 in 10 000 live births.[22,28] Characterized by degeneration of spinal motor neuron cells, progressive muscle weakness and atrophy eventually evolve.[22] Other common complications include poor weight gain with growth and respiratory failure, scoliosis, and joint contractures. Onset ranges from prenatal to young adulthood, with increasing severity in earlier-onset forms of the disease as noted in Table 1.[8,19,22,29] Treatment includes gene therapy to limit disease progression and surgical intervention to improve nutrition and respiratory function.[19,29]

Spinal muscle atrophy is caused by mutations in the *SMN1* gene with approximately 95% of patients having inherited homozygous deletions of exon 7 in both copies of the *SMN1* gene.[29] In addition, a pseudogene residing near *SMN1*, known as *SMN2*, can alter the clinical severity of this disorder when present in multiple copies.[22] Statistics demonstrate that an estimated 1 in 40 to 60 people are unaffected carriers of SMA.[29] Carrier testing can be complicated by multiple

Table 1. Types of spinal muscular atrophy[a]

Type	Age of onset	Description
0 (congenital SMA)	Prenatal	Decreased fetal movements, severe hypotonia and weakness at birth, life expectancy ~6 mo
I (Werdnig-Hoffman disease)	<6 mo	Severe weakness and hypotonia, motor delays, problems feeding, failure to thrive, respiratory issues, life expectancy ~24 mo
II (Dubowitz disease)	6-18 mo	Low muscle tone but make developmental progress, scoliosis, progressive respiratory muscle weakness, life expectancy teens—3rd/4th decade
III (Kugelberg-Welander disease)	>18 mo	Initial ability to walk but lose this over time, legs more affected than arms, life expectancy is same as general population
IV	Adulthood	Onset of muscle weakness 2nd—3rd decade, life expectancy is the same as general population

[a]From American College of Obstetricians and Gynecologists,[8] King JR, Klugman,[19] Prior and Finanger,[29] and Sykes.[27]

factors including de novo (new) mutations not inherited from a parent and mutations not detected by carrier screening.[29] Given these nuances, carrier status is confirmed only when both parents are shown to carry a single pathogenic variant in one of two copies of the *SMN1* gene.[29]

Ethnic-based screening: Hemoglobinopathies

Hemoglobinopathies are a group of disorders that are characterized by abnormal hemoglobin. When there is an abnormality in the alpha globin genes (*HBA1* and *HBA2*) or beta globin gene (*HBB*), hemoglobin is not produced effectively resulting in anemia and other health problems. The hemoglobinopathies include structural hemoglobin variants as well as the thalassemias.[24] Testing for hemoglobinopathies is considered in certain ethnic groups and in pregnancy with the presence of anemia and normal iron studies.[24] A testing flow chart is provided in Figure 2.

Sickle cell disease (SCD) is characterized by abnormally shaped red blood cells resulting in obstructed blood flow and decreased oxygenation throughout the organ systems. More than 100 000 people in the United States are affected with SCD with most individuals being of black or African-American descent.[30] Treatment for SCD includes managing symptoms to relieve pain and prevent infections.

Sickle cell disease is caused by a specific mutation in the *HBB* gene resulting in a variant known as hemoglobin S.[19,30] Approximately 1 in 10 African Americans are known to be carriers of hemoglobin S and thus said to have sickle cell trait.[8] Hemoglobin S is also seen more frequently in individuals of Greek, Italian (particularly Sicillian), Turks, Arabs, Southern Iranians, and Asian Indians.[8] Sickle cell disease may also result from coinheritance of hemoglobin S along with a second *HBB* variant such as hemoglobin C, D, or E or beta thalassemia.

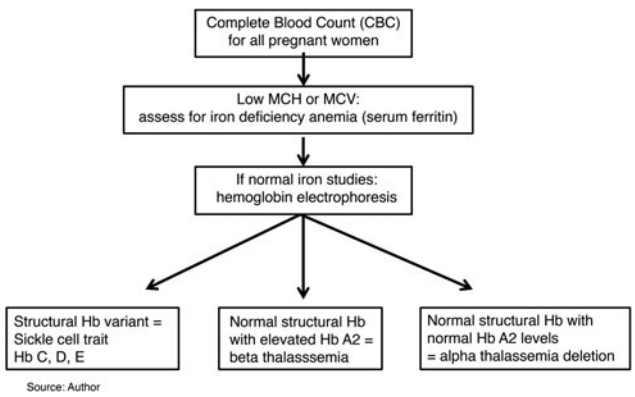

Figure 2. Screening for hemoglobinopathies. Abbreviations: Hb = hemoglobin; MCH = mean corpus hemoglobin; MCV = mean corpus volume. From American College of Obstetricians and Gynecologists,[24] Prior and Finanger,[29] and Sykes.[27]

Beta thalassemia is caused by multiple pathogenic variants in the *HBB* gene, which in turn indicates the amount of beta chain (hemoglobin A) produced from each gene.[19] Persons with beta thalassemia major have alterations in both copies of the *HBB* gene and present within the first 2 years of life with severe anemia and extramedullary erythropoiesis, poor growth, and jaundice.[19] Death typically occurs by the age of 10 years unless treated with periodic blood transfusions or bone marrow transplantation.[19] While individuals with beta thalassemia intermedia also have 2 mutations in the *HBB* gene, these variants are typically less severe, allowing some production of beta chains and thus variable amounts of hemoglobin A.[19] Beta thalassemia minor or trait refers to individuals with a single mutation in the *HBB* gene, resulting in a mild asymptomatic anemia. Beta thalassemia occurs more frequently in individuals of Greek (Mediterranean), Middle Eastern, Asian, Hispanic, and West Indian descent.[19]

Two genes are responsible for alpha thalassemia, alpha globin genes *HBA1* and *HBA2*. Each individual has 2 copies of a *HBA1* gene and 2 copies of a *HBA2* gene, one each on separate strands of chromosome 16, for a total of 4 alpha globin genes.[19] How an individual is affected by alpha thalassemia depends on how many of the alpha globin genes are deleted as noted in Figure 3.[19]

Occasionally, a point mutation rather than a deletion may be the underlying genetic factor in alpha thalassemia and, when coupled with alpha thalassemia trait, may result in more significant disease.[24]

Conditions more common in individuals of Ashkenazi Jewish ancestry

People of Ashkenazi Jewish descent are primarily of Eastern European origin and make up the majority of Jewish individuals in the United States.[31] Carrier frequencies for certain recessive disorders, like TSD are increased in this population, secondary to a founder effect, in which a mutation occurred in a single individual within a small community that then underwent significant population expansion. The single mutation is then inherited by multiple members, thus increasing the carrier frequency and disorder incidence.[25,32] Current guidelines indicate that carrier screening is offered to persons where one or both members are of Ashkenazi Jewish descent.[8] If only one member is Jewish and testing confirms their carrier status, partner testing is offered.[8]

Tay-Sachs disease is a severe, progressive neurodegenerative lysosomal storage disease resulting in buildup of GM2 gangliosides in the central nervous system

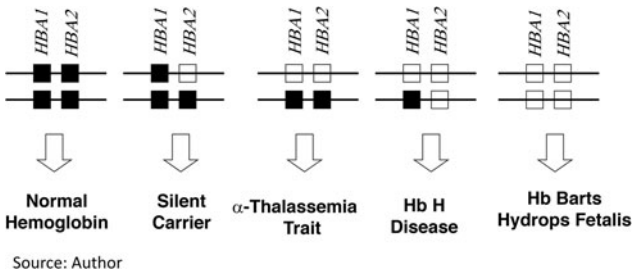

Figure 3. Possible outcomes for alpha thalassemia. Normal hemoglobin: Individuals with 4 working copies of the alpha globin genes (no deletions); have normal hemoglobin levels and are not affected nor carriers for alpha thalassemia. Silent carriers: individuals with 3 working copies and one deletion; typically have no health problems and normal hemoglobin levels. Alpha thalassemia trait: 2 working copies and 2 deletions; typically have no health concerns but can demonstrate mild anemia. Individuals of Southeast Asian descent typically have both deletions on the same chromosome (cis; as shown) and thus are at risk to have a child with hemoglobin Bart's disease, individuals of African descent have a deletion on each chromosome (trans; not shown). Hemoglobin (Hb) H disease: one working copy and 3 deletions; typically develop mild to severe health concerns such as moderate-severe anemia, hepatosplenomegaly, mild jaundice, chronic fatigue, and bone changes and may require frequent blood transfusions. Hemoglobin Bart's disease (Hb Barts): deletions in all 4 alpha globin genes; typically have fetal onset of edema, pleural and pericardial effusions resulting in hydrops fetalis and severe anemia typically resulting in death in the newborn period. From American College of Obstetricians and Gynecologists[8,24] King and Klugman.[19]

(CNS) causing early childhood death.[8] Through community education and screening programs, the incidence of TSD in the Jewish population has declined dramatically with most affected children now being born to non-Jewish parents.[25,31] Carrier screening for other disorders in the Ashkenazi Jewish population is also recommended.[8] A brief description of each is provided in Table 2.[8,20,33–40]

Fragile X syndrome and FMR1-related disorders

Fragile X syndrome is the most common inherited form of intellectual disability, occurring in approximately 1 in 3600 males and 1 in 4000–6000 females.[8] The disease spectrum has expanded to include learning disabilities, attention-deficit/hyperactivity disorder, and autism in both genders. Although not known to be associated with structural birth defects, a characteristic pattern of features in affected males has been described.[40]

Fragile X syndrome is caused by an altered *FMR1* gene located on the X-chromosome and follows an X-linked pattern of inheritance as noted in Figure 4.[41]

The most common alteration involves expansion of a trinucleotide repeat with an associated effect on methylation. In the presence of a family history of intellectual disability, carrier frequency is approximately 1 in 86, while the risk is lower, 1 in 257, for females with no known risk factors.[8]

Current guidelines advise against routine carrier screening for fragile X syndrome unless requested by a woman.[8] Women considering pregnancy or already pregnant with a family history of fragile X-related disorders, intellectual disability, or autism are offered fragile X carrier screening.[8] Additionally, women with unexplained premature ovarian insufficiency or an elevated follicle stimulating hormone before 40 years or males and females over age 50 years with fragile X-associated tremor/ataxia syndrome (FXTAS; intention tremor and ataxia, difficulties with memory and cognitive decline, atrophy and Parkinson-like features)[40] are also offered screening to identify those who may be premutation carriers for *FMR1*-related disorders.

Expanded carrier screening panels

Expanded carrier screening panels, which can vary in size, include an ability to screen for multiple disorders simultaneously, regardless of personal or family history or ethnic background.[21] While appealing to patients and healthcare providers, expanded carrier screening panels have several limitations as outlined in Table 3.

When a larger number of disorders are included on the panel, there is a greater chance of identification of a carrier of one or more disorders.[42] The chance that both individuals are carriers for the same disorder is greatest with consanguinity or within the same ethnic group.[5] When carrier status is identified for the same disorder, prenatal diagnosis through CVS or amniocentesis is typically offered.

DIAGNOSTIC TESTING

Diagnostic tests provide definitive information, a yes-or-no answer, about diagnosis of a chromosomal or single gene condition in the fetus. Diagnostic testing includes chorionic villi sampling (CVS) or amniocentesis.[43] Each procedure allows for assessment of the number of chromosomes present in a fetus, also known as a karyotype.[43] Initially, diagnostic testing was only offered to women who were believed to have a higher chance of a genetic or chromosomal condition, with most procedures performed for advancing maternal age. Current professional recommendations state that all women may be offered assessment for fetal aneuploidy through screening or diagnostic testing regardless of age.[7,43]

Amniocentesis

Amniocentesis for prenatal genetic testing is usually performed between 15 and 20 weeks' gestation.[1,2] Amniotic fluid contains fetal cells (amniocytes), which

Table 2. **Carrier screening for disorders seen more frequently in Ashkenazi Jewish population**[a]

Disorders	Description	Carrier frequency	Genetic analysis for Ashkenazi Jewish individuals
Cystic fibrosis	Chronic respiratory infections, pancreatic insufficiency, infertility in males secondary to CAVD.	1/24	Gene: *CFTR*; 23 core mutation panel (5 mutations detect 97% of carriers)
Canavan disease	Degenerative neurologic disorder with onset in infancy with macrocephaly, hypotonia, developmental delays (DD)/intellectual disabilities (ID); life expectancy is childhood or adolescence	1/41	Gene*: ASPA*; 2 mutations detect 97.4% of carriers
Familial dysautonomia	Disorder of the sensory and autonomic nervous system resulting in abnormal suck, feeding difficulties, episodic vomiting, temperature insensitivity, abnormal sweating	1/32	Gene: *IKBKAP*; 2 mutations including IVS20(+6T->C) which accounts for 99%
Tay-Sachs disease	Severe, progressive neurodegenerative lysosomal storage disease resulting in build-up of GM2 gangliosides in the central nervous system causing death in early childhood	1/30	Gene: *HEXA*; 3 mutations detect 92%–99% of carriers. Enzymatic analysis of hexosaminidase A demonstrates low activity in carriers.[b]
Fanconi anemia (Group C)	May exhibit short stature, skeletal anomalies (upper/lower extremities), pigmentary differences, bone marrow failure with increased risk of malignancy and solid tumors[c]	1/89	Gene: *FANCC*; one mutation (IVS4+4A>T) detects >99% of carriers
Niemann-Pick type A	Cherry red spot in eye, failure to thrive, hepatosplenomegaly, neurologic deterioration, life expectancy is early childhood	1/90	Gene: *SMPD1*; 3 mutations detect ~90% of carriers
Bloom syndrome	Short stature, skin rash during sun exposure, increased risk for cancer, learning disabilities (LD)	1/107	Gene: *BLM*; 1 mutation (2281del6ins7) >99% of carriers
Mucolipidosis type IV	Severe developmental delays with progressive visual impairment	1/127	Gene: *MCOLN1;* 2 mutations account for 95% of carriers
Gaucher disease	Various types with hepatosplenomegaly, anemia, thrombocytopenia, bone disease with types 2 and 3 also demonstrating CNS findings.	1/15	Gene: *GBA;* 4 mutations account for ~90% of carriers
Familial hyperinsulinism	Increased levels of insulin resulting in hypoglycemia, can present with seizures, hypotonia. Unless treated, results in brain damage	1/68	Gene: *ABCC8*; 2 mutations account for 97% of carriers
Glycogen storage disease type 1	Organ malfunction secondary to build-up of glycogen in cells. Age of onset typically 3–4 months.	1/70	Genes: *G6PC* and *SLC37A4*; one mutation in *G6PC* accounts for the majority of carriers
Joubert syndrome	Hypotonia, ataxia, abnormal breathing, ID/DD and presence of "molar tooth sign" on MRI	1/92 – 1/100	Multiple genes associated with JS but one mutation (p.Arg73Leu) in *TMEM216* gene observed more frequently in AJ descent.

(*continues*)

Table 2. **Carrier screening for disorders seen more frequently in Ashkenazi Jewish population[a] (*Continued*)**

Disorders	Description	Carrier frequency	Genetic analysis for Ashkenazi Jewish individuals
Maple syrup urine disease	Urine smells "sweet" in infants, poor feeding, lethargy and DD. Life expectancy=lethal without treatment	1/97	Genes: *BCKDHA, BCKDHB, DBT;* 3 mutations in the *BCKDHB* gene account for the majority of carriers
Usher syndrome	Type I: congenital profound hearing loss, vestibular difficulties and retinitis pigmentosa (RP); Type III: postlingual hearing loss, variable vestibular difficulties, late-onset RP	1/78 – 1/120	Genes: *PCDH15* (type 1F), one mutation (R245X) detects 95% of carriers and *CLRN1* (type III), one mutation (N48K) detects 75% of carriers

[a]From references 8, 19, 31-39.
[b]Enzymatic analysis of hexosaminidase A is the preferred screening method for TSD in those of non-Jewish descent as this assay detects ~98% of carriers, regardless of ethnic background.[8] Enzymatic testing performed in serum, with the exception of pregnant women/those taking oral contraceptives, where analysis is best in leukocytes to minimize the occurrence of false-positive results.
[c]Some individuals do not show any physical symptoms.

are primarily sloughed from fetal skin and the urinary tract and used for genetic testing. Biochemical studies on amniotic fluid can also be performed to evaluate markers such as alpha fetoprotein and acetylcholinesterase to diagnose open neural tube defects.[1] Risk of miscarriage associated with amniocentesis is reported as 0.11% or approximately 1 in 900.[44]

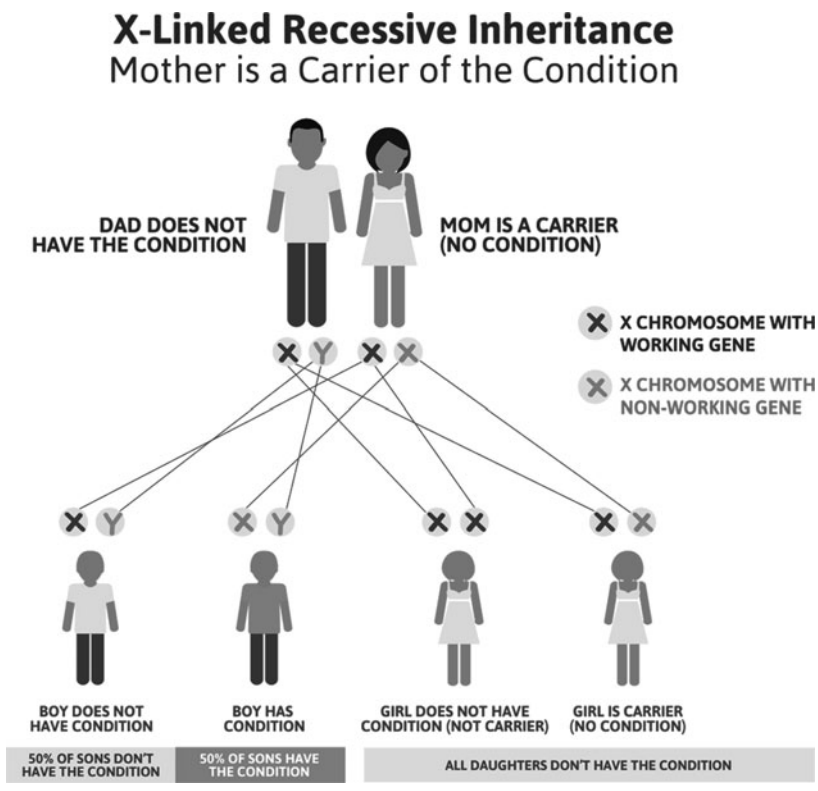

Figure 4. X-linked recessive inheritance. Used with permission from Genetic Support Foundation[41] (www.geneticsupportfoundation.org).

Table 3. **Limitations of expanded carrier screening panels**[a]

Not comprehensive	ECS panels do not screen for all genetic disorders
Vary by laboratory	ECS panels vary by laboratory and typically incorporate a variety of genetic analyses when screening for disorders. This analysis includes assessing for common mutations, thus missing mutations that may be specific to certain ethnic groups or those with a positive family history. A "negative" result is therefore of little significance if testing was not tailored to the patient's ethnicity or family history.
Degrees of severity	ECS panels include disorders with various degrees of severity; from lethal disorders in childhood to those with treatable conditions. Some disorders may demonstrate high phenotypic variability even when the same underlying mutation is present, making counseling regarding potential outcome difficult to estimate.
Residual risk	A negative carrier screen reduces, but does not eliminate, the chance that an individual is a carrier for a disorder. A residual carrier risk will remain in the setting of a negative result.
Diagnostic	ECS panels may identify 2 pathogenic variants for a disorder, thus diagnosing an individual rather than determining their carrier status.
Rare disorders	ECS panels include rare disorders where the carrier frequency is unknown. When one member of a couple is found to be a carrier of a rare disorder, it may be difficult to calculate accurate recurrence risks given the inability of knowing the carrier frequency in the general population.

[a]From references 5, 16, 20, 21.

Chorionic villus sampling

Chorionic villus sampling (CVS) is commonly performed between 10 and 13 weeks' gestation and involves aspirating placental villi transcervically or transabdominally.[1,2] The genetic make-up of the chorionic villi is usually congruent with the fetus; therefore, aneuploidy or other genetic mutations identified by CVS can be diagnostic of chromosomal or genetic conditions.[1] In rare situations, incongruence of a chromosomal abnormality between the placenta and the fetus can occur due to non-disjunction early in embryonic development leading to placental mosaicism.[45,46] Miscarriage rate is currently estimated to be 1 in 455 or 0.22%.[44]

While CVS is considered a diagnostic test, caution must be given when used as a follow-up test to high-risk cfDNA results as both rely on placental cell analysis.[5] Confined placental mosaicism, the possibility that abnormal cells may only reside in a placenta and not in the fetus, is a phenomenon that may suggest that a fetus with an abnormal cfDNA and CVS result is truly affected, when actually the abnormal cells are only present in placenta.[2,5]

Chromosome microarray analysis

Karyotype analysis was the gold standard for diagnostic aneuploidy testing for decades, but is now often forgone for the newer technology of chromosome microarray analysis. Chromosomal microarray allows detection of chromosomal deletions and duplications that are too small to be seen by traditional karyotype analysis.[47] Deletions and duplications are known as "copy number variants" and can cause varying degrees of health concerns and severity, including birth defects and intellectual disabilities.[47] Previous studies estimate that approximately 6% of fetuses with structural abnormalities are found to carry copy number variants of clinical significance, versus 1%–2% of fetuses with normal ultrasound evaluations.[48]

A leading professional organization recommends that microarray testing be offered in place of fetal karyotyping when a structural anomaly is detected on ultrasound.[47] For indications such as advanced maternal age or an abnormal first trimester screen, either CMA testing or karyotyping can be offered.[47] Additional studies such as whole exome sequencing (WES) and genetic testing for single gene disorders on amniocytes are also possible when there are unique concerns based on ultrasound findings or family history.[43]

FETAL IMAGING

Imaging modalities, such as ultrasound and fetal magnetic resonance imaging (MRI), may aid in screening and diagnosis of fetal, placental, and maternal abnormalities including birth defects. Like screening tests, however, imaging cannot detect an underlying genetic etiology but can provide information that may alter medical management or birth route. While deemed safe during pregnancy, the use of these devices is "expected to answer a relevant clinical question or otherwise provide medical benefit to the patient."[49(e210)]

Ultrasound

Ultrasonography is a readily available fetal imaging method used throughout pregnancy. During the first trimester, a fluid-filled area at the back of a fetal neck is measured and referred to as nuchal translucency. Elevated values raise concern for a fetal aneuploidy (eg, trisomy 21) or a major structural anomaly (eg, cardiac defect).[50]

Second-trimester ultrasound has become a routine assessment for fetal anatomy. Typically performed between 18 and 22 weeks' gestation, ultrasound focuses on detecting structural fetal anomalies, soft markers for aneuploidy, placental location, and fetal size.[50] Soft markers such as a thickened nuchal fold or an absent nasal bone in the presence of an increased risk on maternal serum or cfDNA screen can further raise concern for an underlying aneuploidy. Identification of soft markers or a major structural anomaly typically prompts referral for maternal-fetal medicine and genetic counseling to allow for further discussion of prenatal diagnosis options and, in some cases, such as with open neural tube defects, fetal surgical intervention.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of a fetus can provide additional details of a suspected or ill-defined structural fetal anomaly after the first trimester. Although initially too slow to capture a moving fetus, new MRI scanners offer single-shot images that allow for optimal imaging without using fetal sedation.[51] Benefits include higher quality of imaging not reliant on operator experience and enhanced imaging of soft tissue that can be performed without using ionizing radiation.[47] Limitations include availability, gestational age, and that fetal anatomy and pathology can differ than that of a newborn.[51]

Fetal MRI may be most beneficial when assessing specific structural anomalies. Abnormalities of the CNS, including ventriculomegaly, may be the most common reason for imaging but clarification of the extent of fetal masses, such as teratomas, can also be helpful.[52] For congenital anomalies requiring surgery, such as open neural tube defects or congenital diaphragmatic hernia, MRI may assist with candidacy for fetal surgery and estimating likelihood of survival.

DISCUSSION

Prior to 2007, healthcare providers had limited prenatal genetic testing options to review with a defined set of women considered to be at increased risk.[6,53] Information could be reviewed during obstetric visits with formal genetic counseling requested in the setting of abnormal test results. With the recommendation to offer prenatal genetic screening options to all women regardless of age or other risk factors and the explosion of available genetic tests, healthcare providers may find themselves limited in their understanding of testing options and what information they can provide during an obstetric visit.[2,6] This coupled with an estimated 2500 clinical genetic counselors currently in practice in the United States covering all specialty areas; it is impractical to refer all pregnant women for genetic counseling.[54] Thus healthcare providers, other than genetic counselors, must have the information and skill set necessary to help guide patients through navigating the myriad of testing options.

The American College of Obstetricians and Gynecologists recommends that pretest counseling occur at the initial obstetric visit and be a "process of shared decision making" including a discussion of the woman's risks for genetic disorders and the differences between screening and diagnostic tests.[2(e112)] Informing women that there is no genetic test that can guarantee the birth of a healthy baby is imperative along with documentation in the medical record of her decision to pursue or decline testing. Discussion of risks for aneuploidy or carrier status may need to be presented in numerical (e.g. fractions, percentages) or with pictorial images to meet various learning styles.

Effective counseling begins with healthcare providers having a clear understanding of available prenatal genetic testing options as well as the benefits and limitations of the tests being offered.[55] Information discussed is centered around a woman's needs, level of apprehension regarding abnormal or inconclusive results, test limitations, and partner involvement for carrier screening.[56] Providing possible scenarios may help patients understand how their decisions to pursue or decline testing can affect pregnancy. For example, an apprehensive patient who would refuse diagnostic testing regardless of screening results may wish to decline prenatal screening tests to minimize the emotional impact of an abnormal result. Alternatively, a woman who voices concerns for aneuploidy or a known familial diagnosis may elect to pursue diagnostic testing directly. When time is dedicated to providing pretest counseling, women are more inclined to make autonomous decisions and have decreased anxiety when receiving abnormal results.[57–59]

As testing should not be considered routine and informed consent always obtained, alternative strategies to address the complexity of testing options in a short time period may need to be considered.[55] Group counseling has been employed by some clinics to address benefits and limitations of testing to multiple patients in one setting, thus removing discussions from the initial obstetric visit.[53,55,57,58,60] Flow charts, brochures, and

Table 4. **Genetic counseling resources**

Resource	Description	URL
Video series produced by Genetic Support Foundation and the Washington State Department of Health regarding prenatal genetic testing to support patient education and pretest genetic counseling.	A series of 7 educational videos for patients, each approximately 3–4 min in length on the topics such as cfDNA screening, analyte screening, ultrasound, and amniocentesis. Available in Spanish and English.	https://geneticsupportfoundation.org/videos
Cell Free DNA Screening Infographic produced by the American College of Obstetricians and Gynecologists	A printable 2-page infographic describing cfDNA screening for patients, with explanation of predictive value.	https://www.acog.org/Patients/FAQs/Cell-free-DNA-Prenatal-Screening-Test-Infographic
Provider talking points regarding positive cfDNA screening results produced by the National Society of Genetic Counselors	A resource for providers with details on how to interpret and communicate with patients about a positive cfDNA screen.	https://www.nsgc.org/page/abnormal-non-invasive-prenatal-testing-results
NIPT/Cell Free DNA Screening Predictive Value Calculator: Developed by the Perinatal Quality Foundation and the National Society of Genetic Counselors.	An online calculator to assess the positive and predictive value for conditions included on cfDNA screening panels.	https://www.perinatalquality.org/Vendors/NSGC/NIPT/

videos developed by professional organizations (not commercial laboratories with competing interests) can also provide supplemental, unbiased information to patients regarding prenatal screening options.[53,55,61] Accessing electronic or web-based tools prior to the initial obstetric visit can provide an overview of available testing options, allowing time during the visit for patient-centered counseling.[53,55] Examples of various resources to assist providers with counseling are included in Table 4.

Healthcare providers delivering abnormal screening test results require awareness that this information may evoke anxiety and confusion in women about what the result may actually mean.[42,62] In situations in which a woman is unaware that testing was performed or for those with limited health education or a previous child with aneuploidy, extended posttest counseling with visual aids may help clarify confusion and concerns.[62] It is crucial that any abnormal results are interpreted in the context of the patient, the pregnancy and her family history and referral for genetic counseling should be considered.

CONCLUSION

Prenatal genetic testing options are numerous and complex. It is essential that healthcare providers allow time for review of various options, including discussion of benefits and limitations, so women have an opportunity to make informed independent decisions. Knowledge regarding what tests are available, current professional recommendations, and a general understanding of the nuances of testing are imperative to providing accurate information to women and their families.

References

1. Wilson KL, Czerwinski JL, Hoskovec JM, et al. NSGC Practice Guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. *J Genet Counsel*. 2013;22:4–15. doi:10.1007/s10897-012-9545-3.
2. American College of Obstetricians and Gynecologists. Committee on Genetics Society for Maternal Fetal Medicine. Committee Opinion No 682: microarrays and next generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. *Obstet Gynecol*. 2016;128:e262–268.
3. Lewis C, Hill M, Chitty LS. A qualitative study looking at informed choice in the context of non-invasive prenatal testing for aneuploidy. *Prenat Diagn*. 2016;36:875–881. doi:10.1002/pd.4879.
4. Johnston J, Farrell R, Parens E. Supporting women's autonomy in prenatal testing. *N Engl J Med*. 2017;377(6):505–507. doi:10.1056/NEJMp1703425.
5. Fonda Allen J, Stoll K, Bernhardt BA. Pre- and posttest genetic counseling for chromosomal and mendelian disorders. *Semin Perinatol*. 2016;40(1):44–55. doi:10.1053/j.semperi.2015.11.007.

6. Minkoff H, Berkowitz R. The case of universal prenatal genetic counseling. *Obstet Gynecol*. 2014;123(6):1335–1338.
7. American College of Obstetricians and Gynecologists. Practice Bulletin 163: screening for fetal aneuploidy. *Obstet Gynecol*. 2016;127(5):e123–e137. doi:10.1097/AOG.0000000000001406.
8. American College of Obstetricians and Gynecologists. Committee Opinion No. 691: carrier screening for genetic conditions. *Obstet Gynecol*. 2017;129:e41–e55.
9. Chasen ST. Maternal serum analyte screening for fetal aneuploidy. *Clin Obstet Gynecol*. 2014;57(1):182–188. doi:10.1097/GRF.0000000000000017.
10. American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine. Committee Opinion 640: Cell-Free DNA screening for fetal aneuploidy. *Obstet Gynecol*. 2015;126(3):e31–e37.
11. Lutgendorf MA, Stoll KA. Why 99% may not be as good as you think it is: limitations of screening for rare diseases. *J Matern Fetal Neonatal Med*. 2016;29(7):1187–1189. doi:10.3109/14767058.2015.1039977.
12. Livergood MC, LeChien KA, Trudell AS. Obesity and cell-free DNA "no calls": is there an optimal gestational age at time of sampling? *Am J Obstet Gynecol*. 2017;216(4):413.e1–413.e9. doi:10.1016/j.ajog.2017.01.011.
13. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2016;18(10):1056–1065. doi:10/1038/gim.2016.97.
14. Norton ME, Jacobsson B, Swamy GK, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med*. 2015;372(17):1589–1597. doi:10.1056/NEJMoa1407349.
15. Benn P, Borrell A, Chiu R, et al. Position statement from the chromosome abnormality screening committee on behalf of the board of the International Society for Prenatal Diagnosis. *Prenat Diagn*. 2015;35(8):725–734. doi:10.1002/pd.4606.
16. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider. *Obstet Gynecol*. 2015;125(3):653–662.
17. Bell CJ, Dinwiddie DL, Miller NA, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. *Sci Transl Med*. 2011;3(65):65ra4. doi:10.1126/scitranslmed.3001756.
18. Autosomal recessive inheritance. Genetic Support Foundation Web site. https://www.geneticsupport.org/genetics-101/inheritance-patterns/autosomal-recessive/. Updated April 7, 2017.
19. King JR, Klugman S. Ethnicity-based carrier screening. *Obstet Gynecol Clin N Am*. 2018;45:83–101. https://doi.org/10.1016/j.ogc.2017.10.010.
20. Rose NC, Wick M. Carrier screening for single gene disorders. *Semin Fetal Neonatal Med*. 2017:1–7. http://dx.doi.org/10.1016/j.siny.2017.06.001
21. American College of Obstetricians and Gynecologists. Committee Opinion No. 690: carrier screening in the age of genomic medicine. *Obstet Gynecol*. 2017;129:e35–e40.
22. Prior TW. Carrier screening for spinal muscular atrophy. *Genet Med*. 2008;10(11):840–842.
23. American College of Obstetricians and Gynecologists. Committee Opinion No 486: update on carrier screening for cystic fibrosis. *Obstet Gynecol*. 2011;117(4):1028–1031.
24. American College of Obstetricians and Gynecologists. Practice Bulletin No. 78: hemoglobinopathies in pregnancy. *Obstet Gynecol*. 2007;109(1):229–237.
25. Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med*. 2008;10(1):54–56. doi:10.1097/GIM.0b013e31815f247c.
26. American College of Obstetricians and Gynecologists. Committee Opinion No. 469: carrier screening for fragile X syndrome. *Obstet Gynecol*. 2010;116(4):1008–1010.
27. Sykes J, Stanojevic S, Goss CH, et al. A standardized approach to estimating survival statistics for population-based cystic fibrosis registry cohorts. *J Clin Epidemiol*. 2016;70:206–213. doi:10.1016/j.jclinepi.2015.08.026.
28. Hendrickson BC, Donohoe C, Akmaev VR, et al. Differences in *SMN1* allele frequencies among ethnic groups in within North America. *J Med Genet*. 2009;46:641–644. doi:10.1136/jmg.2009.066969.
29. Prior TW, Finanger E. Spinal muscular atrophy. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington; 1993–2018. https://www.ncbi.nlm.nih.gov/books/NBK1352/. Updated December 22, 2016.
30. Bender MA. Sickle cell disease. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2018. https://www.ncbi.nlm.nih.gov/books/NBK1377/. Updated August 17, 2017.
31. Klugman S, Gross SJ. Ashkenazi Jewish screening in the twenty-first century. *Obstet Gynecol Clin N Am*. 2010;37:37–46. doi:10.1016/j.ogc.2010.01.001.
32. Schrijver I, Klum M, Gardner PI, et al. Comprehensive arrayed primer extension array for the detection of 59 sequence variants in 15 conditions prevalent among the (Ashkenazi) Jewish population. *J Mol Diagn*. 2007;9(2):228–236.
33. Bali DS, Chen YT, Austin S, et al. Glycogen storage disease type I. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1312/. Updated August 25, 2016.
34. Mehta PA, Tolar J. Fanconi anemia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1401/. Updated March 8, 2018.
35. Ong T, Marshall SG, Karczeski BA, et al. Cystic fibrosis and congenital absence of the vas deferens. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1250/. Updated February 2, 2017.
36. Parisi M, Glass I. Joubert syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1325/. Updated June 29, 2017.
37. Pastores GM, Hughes DA. Gaucher disease. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1269/. Updated June 21, 2018.
38. Schiffmann R, Grishchuk Y, Goldin E, Mucolipidosis IV. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1214/. Updated July 30, 2015.
39. Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1370/. Updated June 18, 2015.
40. Saul RA, Tarleton JC. FMR1-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018.

https://www.ncbi.nlm.nih.gov/books/NBK1384/. Updated April 26, 2012.
41. X-linked inheritance. Genetic Support Foundation Web site. https://www.geneticsupport.org/genetics-101/inheritance-patterns/x-linked/. Updated July 19, 2018.
42. Rothwell E, Johnson E, Mathiesen A, et al. Experiences among women with positive prenatal expanded carrier screening results. *J Genet Counsel*. 2017;26(4):690–696. doi:10.1007/s10897-016-0037-8.
43. American College of Obstetricians and Gynecologists. Practice Bulletin No. 162: prenatal diagnostic testing for genetic disorders. *Obstet Gynecol*. 2016;127(5):e108–e122.
44. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015;45:16–26.
45. Hahnemann JM, Vejerslev LO. Accuracy of cytogenetic findings on chorionic villus sampling (CVS)—diagnostic consequences of CVS mosaicism and non-mosaic discrepancy in centres contributing to EUCROMIC 1986-1992. *Prenat Diagn*. 1997;17(9):801–820.
46. Grati FR. Chromosomal mosaicism in human feto-placental development: implications for prenatal diagnosis [Review]. *J Clin Med*. 2014;3(3):809–837. doi:10.3390/jcm3030809.
47. American College of Obstetricians and Gynecologists. Committee on Genetics Society for Maternal Fetal Medicine: Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. *Obstet Gynecol*. 2013;122(6):1374–1377.
48. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med*. 2012;367:2175–2184
49. American College of Obstetricians and Gynecologists. Committee Opinion No. 723: guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol*. 2017;130(4):e210–e216.
50. Edwards L, Hui L. First and second trimester screening for fetal structural anomalies. *Semin Fetal Neonatal Med*. 2018;23:102–111.
51. Ertl-Wagner B, Lienemann A, Strauss A, Reiser M. Fetal magnetic resonance imaging: indications, technique, anatomical considerations and a review of fetal abnormalities. *Eur Radiol*. 2002;12:1931–1940.
52. Verburg B, Fink AM, Reidy K, Palma-Dias R. The contribution of MRI after fetal anomalies have been diagnosed by ultrasound: correlation with postnatal outcomes. *Fetal Diagn Ther*. 2015;38:186–194. doi:10.1159/000380821.
53. Stoll K, Kubendran S, Cohen S. The past, present and future of service delivery in genetic counseling: keeping up in the era of precision medicine. *Am J Med Genet*. 2018;1–14. doi:10.1002/ajmg.c.31602.
54. Hoskovec JM, Bennett RL, Carey ME, et al. Projecting the supply and demand for certified genetic counselors: a workforce study. *J Genet Counsel*. 2017;27(1):16–20. doi:10.1007/s10897-017-0158-8.
55. Metcalfe SA. Genetic counseling, patient education, and informed decision-making in the genomic era. *Semin Fetal Neonatal Med*. 2017:1–8. doi:10.1016/j.siny.2017.11.010.
56. Agatisa PK, Mercer MB, Coleridge M, Farrell RM. Genetic counselors' perspective about cell-free DNA: experiences, challenges, and expectations for obstetricians. *J Genet Couns*. 2018:1–12. https://doi.org/10.1007/s10897-018-0268-y.
57. Gammon BL, Otto L, Wick M, Borowski K, Allyese M. Implementing group prenatal counseling for expanded noninvasive screening options. *J Genet Couns*. 2017:1–8. https://doi.org/10.1007/s10897-017-0178-4.
58. Hunter AG, Cappelli M, Humphreys L, et al. A randomized trial comparing alternative approaches to prenatal diagnosis counseling in advancing maternal age patients. *Clin Genet*. 2005:67(4):303–313.
59. Cloutier M, Gallagher L, Goldsmith C, Akiki S, Barrowman N, Morrison S. Group genetic counseling: an alternate service delivery model in a high risk prenatal screening population. *Prenat Diagn*. 2017;37(11):1112–1119. doi:10.1002/pd.5149.
60. Knutzen DM, Stoll KA, McClellan MW, Deering SH, Foglia LM. Improving knowledge about prenatal screening options: can group education make a difference? *J Matern Fetal Neonatal Med*. 2013;26(18):1799–1803.
61. Kloza EM, Haddow PK, Halliday JV, O'brien BM, Lambert-messerlian GM, Palomaki GE. Evaluation of patient education materials: the example of circulating cell free DNA testing for aneuploidy. *J Genet Couns*. 2014;24(2):259–266. doi:10.1007/s10897-014-9758-8.
62. Van Schendel RV, Lieve Page-Christiaens GCM, Beulen L, et al. Women's experiences with non-invasive prenatal testing and emotional well-being and satisfaction after test-results. *J Genet Couns*. 2017;26:1348–1356. doi:10.1007/s10897-017-0118-3.

The CE test for this article is available online only. Log onto the journal website, www.jpnnjournal.com, or to www.NursingCenter.com/CE/JPNN to access the test. For more than 15 additional continuing education articles related to neonatal topics, go to NursingCenter.com\CE.

Instructions:

- Read the article. The test for this CE activity is to be taken online at www.NursingCenter.com/CE/JPNN.
- You will need to create (its free!) and login to your personal CE Planner account before taking online tests. Your planner will keep track of all your Lippincott Professional Development online CE activities for you.
- There is only one correct answer for each question.
- A passing score for this test is 12 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Professional Development: 1-800-787-8985.

Registration Deadline:
March 5, 2021

Provider Accreditation:

Lippincott Professional Development will award 1.5 contact hours for this continuing nursing education activity.

Lippincott Professional Development is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749. Lippincott Professional Development is also an approved provider of continuing nursing education by the District of Columbia Board of Nursing, #50-1223, Florida Board of Nursing, #50-1223, and Georgia Board of Nursing, CE Broker #50-1223.

Disclosure Statement:

The authors and planners have disclosed that they have no financial relationships related to this article.

Payment:

- The registration fee for this test is $17.95.