The clinical content of preconception care: genetics and genomics

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The prevalence of paternal and maternal genetic conditions that affect pregnancy varies according to many factors that include parental age, medical history, and family history. Although some genetic conditions that affect pregnancy are identified easily early in life, other conditions are not and may require additional diagnostic testing. A complete 3-generation family medical history that includes ethnicity information about both sides of the family is arguably the single best genetic "test" that is applicable to preconception care. Assessment of genetic risk by an experienced professional has been shown to improve the detection rate of identifiable risk factors. Learning about possible genetic issues in the preconception period is ideal, because knowledge permits patients to make informed reproductive decisions. Options that are available to couples before conception include adoption, surrogacy, use of donor sperm, in vitro fertilization after preimplantation genetic diagnosis, and avoidance of pregnancy. Future technologic advances will increase the choices that are available to couples.

Key words: family history, genetics, preconception

Applications of genetics (the scientific study of heredity) and genomics (the study of an organism's complete genetic makeup) are expanding into virtually every sphere of healthcare; preconception care is no exception. However, the evidence-based application of genetics and genomics to preconception care is a work in progress for several reasons. First, less research attention has been given to genetic and genomic interventions in the preconception setting than to those in the prenatal period. Second, conducting prospective randomized trials in either the prenatal or preconception period is problematic ethically and legally. Finally, genetic technologies are emerging at a mind-numbing pace, and time will be required to develop evidence to support their utility.

Despite the rapid evolution of this field, individuals who provide medical care to any person who is considering pregnancy should be aware of recommendations for genetic care in the preconception and prenatal period.[1,2] Some recommendations apply to all individuals. Other recommendations are more important for patients with specific risk factors. In many cases, these recommendations draw heavily on consensus and expert opinion. Additionally, most prenatal care guidelines have been extrapolated to the preconception period. Logically, this makes sense; however, formal studies that demonstrate the validity of this extrapolation are lacking and likely will never be completed. One final caveat is that the diversity and rarity of many genetic disorders that affect pregnancy ensure that any document that contains recommendations, including this one, will be incomplete.

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All individuals

Obtaining a complete 3-generation family medical history that includes ethnicity information about both sides of the family is arguably the single best genetic "test" that is applicable to preconception care. Additionally, a discussion of obstetric and medical history and parental age at anticipated delivery are critical aspects of a preconception healthcare visit. Family history and other historic data provide an inexpensive and noninvasive assessment of conditions that might affect pregnancy. Learning about these risks in the preconception period is ideal. Improved knowledge about the heritability of a disorder can allow individuals to make informed reproductive decisions and can improve prenatal care during pregnancy. Options that are available to couples before conception include adoption, surrogacy, use of donor sperm, preimplantation genetic diagnosis after in vitro fertilization with transfer of unaffected embryos, and avoidance of pregnancy. Future technologic advances likely will broaden further the choices that will be available to couples.[3-7]

Providers of preconception care should also urge women to take a multivitamin, with at least 400 μg of folate, daily beginning at least 1 month before conception. Folate has been shown to reduce the incidence of neural tube defects and may also reduce the incidence of other malformations such as orofacial clefting, limb deficiencies, cardiac defects, urinary tract defects, and omphalocele. Women with a history of medical conditions such as epilepsy or diabetes mellitus or a previous gestation with a neural tube defect may require increased folate intake.[8-10]

Finally, in addition to the testing discussed in Table 1, all couples, regardless

TABLE 1
Recommended counseling/testing by race/ethnicity

Ethnicity (of at least 1 member of the couple)	Disorders with recommended counseling/testing	Type of test
White	Cystic fibrosis[a]	DNA testing of *CFTR* gene[11]
European	Cystic fibrosis[a]	DNA testing of *CFTR* gene[11]
Ashkenazi Jewish	Canavan disease, cystic fibrosis,[a] familial dysautonomia, Tay-Sachs disease, Gaucher's disease, Niemann-Pick disease *Type A*, Bloom syndrome, mucolipidosis IV, Fanconi anemia Group C	Canavan disease: DNA testing of *ASPA* gene[13,15,19]
		Cystic fibrosis: DNA testing of *CFTR* gene[11,13,15,19,20]
		Familial dysautonomia: DNA testing of *IKBKAP* gene[13,15,19]
		Tay-Sachs disease: enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[13,15,19]
		Gaucher's disease: DNA testing of *GBA* gene[13,15,19]
		Niemann-Pick disease *Type A*: DNA testing of *SMPD1* gene[13,15,19]
		Bloom syndrome: DNA testing of *BLM* gene[13,15,19]
		Mucolipidosis IV: DNA testing of *MCOLN1* gene[13,15,19]
		Fanconi anemia Group C: DNA testing of *FANCC* gene[13,15,19]
French-Canadian	Tay-Sachs disease	Enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[12,14,19]
Cajun	Tay-Sachs disease	Enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[12,14,19]
African	Sickle cell disease/trait, thalassemia	Complete blood count with red blood cell indices (RBC), iron indices, hemoglobin electrophoresis[16,17,18]
Mediterranean	Thalassemia	Complete blood count with red blood cell indices and iron indices; hemoglobin electrophoresis if anemia and normal iron indices[16,17,18]
Asian	Thalassemia	Complete blood count with red blood cell indices and iron indices; hemoglobin electrophoresis if anemia and normal iron indices; DNA testing of alpha-globin genes for alpha thalassemia if Southeast Asian with low mean corpuscular volume anemia but normal iron studies[16,17,18]

[a] Cystic fibrosis should be discussed with patients of all races/ethnicities.

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of ethnicity, should be made aware of the availability of cystic fibrosis–carrier screening.[11]

Recommendation. All women who are considering pregnancy should have a screening history in the preconception visit. Providers should ask about risks to pregnancy that are based on maternal age, maternal and paternal medical conditions, obstetric history, and family history. Ideally, a 3-generation family medical history should be obtained for both members of the couple with the goal of identifying known genetic disorders, congenital malformations, developmental delay/mental retardation, and ethnicity. If this screening history indicates the possibility of a genetic disease, specific counseling should be given that may include referral to a genetic counselor or clinical geneticist. *Strength of recommendation:* B; *quality of evidence:* III.

All women should take a multivitamin with at least 400 μg of folate daily, starting at least 1 month before conception. Women with specific risk factors may require higher daily dosages of folate. *Strength of recommendation:* A; *quality of evidence:* II-2.

All couples should be made aware of the availability of cystic fibrosis–carrier screening. *Strength of recommendation:* B; *quality of evidence:* III.

Couples with ethnicity-based genetic risk factors

Ancestry influences the probability of being a carrier of many disorders that affect pregnancy. Typically, carriers themselves will not show any signs of a genetic disorder, and there is often no known family history of the condition. The guidelines for testing by ethnicity include conditions for which there is evi-

TABLE 2
Details from personal or family history that should prompt further counseling

Chromosomal disorders (eg, Trisomy 21)
Clotting disorders
Deafness
Developmental delay/mental retardation (eg, Fragile X syndrome)
Early infant death
Heart defects
Other known genetic disorders (eg, phenylketonuria, Marfan syndrome)
Neural tube defects
Familial cancer syndromes (known or suspected)
Family history of other congenital malformations
Neural tube defects
Orofacial clefts
Recurrent miscarriages
Sickle cell disease or trait
Sudden infant death syndrome
Thalassemia
Thrombophilia

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dence that testing is effective or for which there is strong expert opinion that testing should be performed. However, this is not meant to imply that these conditions do not occur or should be ignored in populations of other ethnicities. Individuals of mixed ancestry or ethnicity should consider carrier testing that is recommended for any component ethnicity. A formal referral could be considered if practitioners are unsure which disorders should be tested. Table 1 contains a summary of counseling/testing by ethnicity.[11-20]

Carrier testing can have important psychologic consequences for an individual and should only occur after informed consent is obtained. Choosing the appropriate test and interpreting results of testing can be complex and may vary between different ethnic groups. For example, with the current recommended mutation panel, negative carrier testing for cystic fibrosis in an Ashkenazi Jewish couple would result in a different chance of having an affected child than negative testing in an African American couple. Depending on the provider's proficiency in genetics, carrier testing may necessitate referral to genetic services.[11,13,15,19,20]

Recommendation. Couples who are at risk for any ethnicity-based conditions should be offered preconception counseling about the risks of that condition to future pregnancies. Screening and/or testing should be offered based on the couple's preferences. This may require referral to a genetic counselor or clinical geneticist. *Strength of recommendation:* B; *quality of evidence:* II-3.

Couples with genetic risk factors that are based on specific family history

If at least 1 member of a couple has a family history of developmental delay, congenital anomalies, or other known or suspected genetic conditions, the couple should be referred to a qualified healthcare provider for appropriate counseling and potential testing.[2,4] If a disorder in the individual's family has been identified as having a genetic cause, it may be possible to test an individual to determine whether the couple is at risk for having an affected child. For example, a family history of known genetic conditions such as cystic fibrosis or Tay-Sachs disease should prompt the offer of testing for at least the person with affected relatives. If the person is found to have inherited a gene that could cause the disorder in their children, the partner could be tested to quantify the overall risk. In the case of an X-linked disorder such as hemophilia, sex selection should be discussed.[2,21-26] Table 2 gives information about examples of family history findings that should prompt further counseling/testing.

Recommendation. Individuals who are identified as having a family history of developmental delay, congenital anomalies, or other genetic disorders should be offered a referral to an appropriate specialist to better quantify the risk to a potential pregnancy. *Strength of recommendation:* B; *quality of evidence:* II-3.

Couples with genetic risk factors that are based on previous pregnancies

A history of recurrent pregnancy loss (classically defined as > 2 spontaneous abortions) should prompt testing of both parents for genetic conditions such as chromosomal anomalies and hereditary thrombophilia.[17,27,28] Testing for chromosomal anomalies can be performed by a test of peripheral blood for chromosome analysis (karyotyping).[2] If a chromosomal anomaly such as a balanced translocation is found, providers should discuss the use of in vitro fertilization with preimplantation genetic diagnosis to increase the chance of an unaffected pregnancy.[29-31]

Recommendation. If at least 1 member of a couple is found to have a chromosomal anomaly, in vitro fertilization with preimplantation genetic diagnosis should be discussed. *Strength of recommendation:* C; *quality of evidence:* III.

Individuals with risk factors caused by known genetic conditions

Individuals with known genetic conditions should be counseled regarding optimal control of their condition and the chances of having affected offspring; these individuals should be aware of how the presence of a genetic disorder could affect both their health and the health of the fetus. For example, women with sickle cell disease have an increased risk of preterm labor and premature rupture of membranes; women with Marfan syndrome have an increased risk of aortic dissection during pregnancy.[32,33]

In certain genetic disorders, there are specific recommendations for management in the preconception period. For example, women with sickle cell disease require increased amounts of folate; women with phenylketonuria should maintain low phenylalanine diets before conception, because infants who are born to women with phenylketonuria with phenylalanine levels of > 20 mg/dL are more likely to have microcephaly, developmental delay, growth restriction, and heart defects.[17,34,35]

Recommendation. Suspected genetic disorders may require further work-up

TABLE 3
Further resources

Resources	Comments
American College of Medical Genetics (www.acmg.net)	Includes links to the latest standards and guidelines for clinical genetics laboratories, with disease/phenotype-specific standards and guidelines
CDC National Office of Public Health Genomics (cdc.gov/genomics)	Resources on how human genomic discoveries can be used to improve health and prevent disease
Gene tests (genetests.org)	Reviews about specific conditions, laboratory and clinical directories, handouts for patients
Genetic Alliance (geneticalliance.org)	Information about specific disorders and advocacy, support, and discussion groups
Genetic and Rare Diseases Information Center (rarediseases.info.nih.gov/html/resources/info_cntr.html)	Information about specific disorders, explanations for patients, financial assistance information, and access to specialists
National Society of Genetic Counselors (nsgc.org)	Directory of genetic counselors, guidelines for counseling specific conditions
Online Mendelian Inheritance in Man (ncbi.nlm.nih.gov/sites/entrez?db=omim)	Searchable database of genes and genetic disorders that targets healthcare professionals
PubMed (ncbi.nlm.nih.gov/PubMed)	Medical literature database
US Surgeon General's Family History Initiative (hhs.gov/familyhistory)	Education about family health history through tools such as My Family Health Portrait

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before conception. Known or discovered genetic conditions should be managed optimally before and after conception. *Strength of recommendation:* B; *quality of evidence:* II-3.

Comment

No provider is expected to be aware of every genetic condition that possibly could affect a pregnancy; however, it is important that all providers be able to do 2 things. First, providers should be able to ask the right questions to determine who might be at risk. This includes the ability to take a 3-generation family history. Second, providers should know when to refer a patient and to whom a patient should be referred. There is a wide array of excellent educational resources regarding genetic disorders and family history that are available on the web. Table 3 contains a list of resources. Finally, providers should keep in mind that this is a very rapidly expanding field. Researchers are unraveling the genetic causes of many conditions for which screening and testing may soon become available.[36] ■

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