Louise Wilkins-Haug, MD, PhD
Associate Professor
Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School
Director, Center for Fetal Medicine and Prenatal Genetics
Brigham and Women's Hospital, Boston

New screening basics for the generalist

FAST TRACK

Among Ashkenazi Jews, DNA testing detects more than 95% of carriers of autosomal disorders

Thanks to advances in genetics, we know the mutations responsible for a growing number of inherited disorders, but making use of that information in a generalist practice is a challenge, given all the other tasks we must manage.

Overall, you must determine the extent to which you will provide and interpret genetic testing and when to refer patients to a specialist. This article aims to simplify that decision by reviewing guidelines and key studies in 3 areas:

- For genetic carrier screening for people of Ashkenazi Jewish heritage, add familial dysautonomia to the list of screened diseases.
- Screening for Down syndrome is now possible in the first trimester.
- Greater genetic risks may be present among children born as a result of assisted reproductive technology (ART), although it's unclear whether the cause is their parents' infertility or ART itself.

On the plus side, molecular DNA diagnostics are increasingly sophisticated, readily available, and cost-efficient. The downside: As the list of recommended studies grows, successful testing programs are harder to achieve because of the need to educate patients—and yourself—about each test.

Preconception testing may be especially advisable in women with infertility because it can identify carriers and detect conditions related to infertility or its treatment. With 1% of US births attributable to ART, the possibility of genetic effects continues to raise concern.

Add another disease to genetic carrier screening

ACOG Committee Opinion #298: Prenatal and preconception carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstet Gynecol. 2004;104:425–428.

Add familial dysautonomia to carrier screening when patients—or their partners—are of Ashkenazi Jewish heritage. That's the advice from an American College of Obstetricians and Gynecologists (ACOG) committee opinion. Also conduct previously recommended screening for Tay-Sachs disease, Canavan disease, and cystic fibrosis, and advise patients that testing is available for several other diseases as well (**TABLE 1**). For Tay-Sachs disease, screening also is urged for patients of French Canadian and Cajun descent.

ACOG emphasizes the importance of assessing these risks prior to pregnancy to allow time for the partner to be tested, if necessary.

Among the Ashkenazi Jewish population, DNA testing detects more than 95% of carriers of autosomal disorders by analyzing the small number of mutations responsible. Tay-Sachs was the first disease for which mutations were identified.

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TABLE 1

Autosomal diseases more common among people of Ashkenazi Jewish heritage

DISEASE	DESCRIPTION	ASHKENAZI HERITAGE		NON-ASHKENAZI HERITAGE	
		CARRIER FREQUENCY	CARRIER DETECTION	CARRIER FREQUENCY	CARRIER DETECTION
Tay-Sachs	Neurologic deterioration, death in early childhood, juvenile, and late-onset forms	1/30	98% by Hex A testing 94% by DNA	1/300	98% by Hex A testing 50% by DNA
Canavan	Neurologic deterioration, death during early childhood, some survivors into teens	1/40	98% by DNA	Undetermined	60% by DNA
Cystic fibrosis	Chronic pulmonary disease, pancreatic insufficiency, variable survivorship	1/29	97% by DNA	Varies by ethnicity	Varies by ethnicity
Familial dysautonomia	Impairment of sensory and autonomic nervous systems	1/32	99% by DNA	Unknown	Unknown
Fanconi anemia group C	Pancytopenia, developmental delay, and failure to thrive	1/89	99% by DNA	Unknown	Unknown
Niemann-Pick type A	Lysosomal storage disease with degenerative course similar to Tay-Sachs	1/90	95% by DNA	Unknown	Unique mutations, enzymatic levels poorly discriminate normal and carrier states
Mucolipidosis IV	Neurodegenerative disorder with marked developmental and growth retardation	1/127	95% by DNA	Unknown	Unknown
Bloom	Pre- and postnatal growth restriction, susceptibility to malignancies	1/100	95% by DNA	Unknown	Unknown
Gaucher's	Type 1: variable severity secondary to deposition in spleen, liver, and bones; presentation from chronic illness to asymptomatic	1/15	95% by DNA	Unknown	70% by >30 mutations

Modified from *ACOG Committee Opinion #298* and March of Dimes' *Genetic Screening Pocket Facts*; 2001

Familial dysautonomia is caused by a single mutation in the gene IKBKAP in more than 99% of affected patients. It has a carrier rate (1/32) similar to that of Tay-Sachs disease (1/30) and involves substantial morbidity of the autonomic and sensory nervous system, with symptoms such as abnormal sweating, pain/temperature insensitivity, and labile blood pressure. Treatment may relieve symptoms, but does not cure the disease.

Refer non-Ashkenazi partners of identified carriers. Although non-Ashkenazi partners are less likely to be carriers, the exact carrier frequency and detection rates for these people are unknown (except for Tay-Sachs disease and cystic fibrosis). In these situations, it may be wise to refer the patient and her partner for genetic counseling to clarify the sensitivity of DNA analysis and the advisability of possible alternative testing by enzyme analysis.

What a generalist should offer. Because the availability of genetic testing will continue to increase, ACOG recommends that generalists provide:

TABLE 2

Detecting Down syndrome: Which test is best?

MODALITY	SCREEN-POSITIVE RATE	DETECTION RATE
Maternal age >35 years	18%	30%
Triple screen (MSAFP, beta-hCG, estriol)	5%	65%
Quad screen (triple plus inhibin)	5%	75%
First-trimester (nuchal lucency, PAPP-A, free beta-hCG)	5%	80%
Integrated (first-trimester nuchal lucency and serum screen combined with second-trimester serum screen)	2.5%	90%

MSAFP = maternal serum alpha-fetoprotein, PAPP-A = pregnancy-associated plasma protein-A

FAST TRACK

ACOG recommends first-trimester ultrasound and maternal-serum screening for Down syndrome

- patient education on the disorders,
- referral sources for additional counseling and prenatal diagnostic testing,
- informed consent when obtaining samples for genetic testing, and
- assurance of confidentiality.

Encourage carriers to share test results with family members who may be at risk. As ACOG points out, there is no precedent for health-care providers contacting other family members with genetic testing information unless a patient-provider relationship already exists.

Screen for Down syndrome in the first trimester

ACOG Committee Opinion #296: First-trimester screening for fetal aneuploidy. Obstet Gynecol. 2004;104:215–217.

Screening for Down syndrome is now available in the first trimester; ACOG recommends using ultrasound and maternal serum screening, with 3 criteria:

- standardized, continuous quality assurance,
- ability to counsel patients about the testing options, and
- access to appropriate diagnostic testing.

Essential to the ACOG opinion was a collaborative study by Wapner et al[1] on a first-trimester screening program in numerous US centers. The results: a 79% detection of trisomy 21 at 11 to 14 weeks' gestation, with a screen-positive rate of 5%. This compares favorably with screening in the second trimester by a triple panel (maternal serum alpha-fetoprotein, beta-human chorionic gonadotropin, and estriol) or a quad panel (triple panel plus inhibin) (**TABLE 2**).

Integrated versus contingency screening. "Integrated" screening combines information from the first trimester (nuchal lucency and serum screen) with serum screening in the second trimester. This approach yields the lowest screen-positive rate (2.6%) and a high detection rate (90%), but has an important shortcoming: The results are not disclosed until the second trimester.

"Contingency" screening is emerging as an alternative: High first-trimester risks are relayed to the patient, while women with low screen values are excused from further testing. Patients with intermediate risk proceed to second-trimester serum screening.

Disadvantages of this approach include the need to coordinate the various steps and adequately inform the patient of them.

Added value of first-trimester nuchal lucency screening. Increased nuchal translucency alone is an important screen for structural abnormalities and adverse pregnancy outcomes. If a karyotypically normal fetus has an increased first-trimester nuchal lucency,

the possibility of a structural anomaly on second-trimester ultrasound increases 2- to 10-fold. Absolute risk rises with increasing nuchal lucency.

Since an average of 10% to 15% of the identified anomalies are cardiac defects, fetal echocardiogram and a comprehensive fetal survey are appropriate in the second trimester.

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Are children conceived with ART at increased risk?

Schieve LA, Rasmussen SA, Buck GM, et al. Are children born after assisted reproductive technology at increased risk of adverse health outcomes? Obstet Gynecol. 2004;103:1154–1163.

Children born as a result of ART may face a higher risk of inherited disorders and congenital malformations, but it is unclear whether the risks are due to their parents' infertility or to ART.

For this reason, it may be wise to refer ART patients for additional genetic counseling and fetal structural surveillance by ultrasound.

Schieve and colleagues attempted to clarify the risks by reviewing the theoretical and empiric literature. Two studies provide the bulk of evidence. In Western Australia, the background risk of birth defects doubled in infants conceived with ART: 9% risk in both intracytoplasmic sperm injection and IVF patients, compared with 4% with spontaneous conception.[1] This study is notable because ART programs are more highly regulated in Australia and similar methods were used to ascertain congenital anomalies in both groups.

A comparable study[2] in Sweden also noted an increased risk, but attributed it to the underlying cause of the parents' infertility rather than to ART itself. The reason: The increased risk disappeared when the authors adjusted for the period of "involuntary childlessness." However, they provided very little detail on how involuntary childlessness was defined and "whether and how strongly this measure is correlated with infertility severity in Sweden."[2]

Imprinting disorders among ART offspring. Schieve et al also explored imprinting disorders, since diseases such as Beckwith-Wiedemann syndrome are attributed to them. Imprinting is an epigenetic phenomenon in which the allele of only 1 parent is active at a particular gene locus. The inactive—or imprinted—allele is rendered nonfunctional, often through methylation. Gametogenesis and preimplantation are times of increased imprinting. Identified imprinted genes include those that control embryonic growth and differentiation.

Analyses of Beckwith-Wiedemann syndrome registries in the United States, France, and the UK[3–5] revealed a 3- to 6-fold increase in ART conception among infants with the syndrome. Case reports of other rare imprinted disorders such as Angelman syndrome and retinoblastoma are also beginning to appear.

Direct treatment effect not established. According to Schieve et al and others, evidence of an increased risk of defects following ART does not indicate whether a direct treatment effect is present. Future studies that address methodological flaws are sure to be time-consuming; they also will require large sample sizes and consistent ascertainment and ART treatment. ■

Dr. Wilkins-Haug reports no relevant financial relationships.

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FAST TRACK

Consider referring ART patients for genetic counseling and fetal structural surveillance by ultrasound