

Beyond the “Jewish panel”: the importance of offering expanded carrier screening to the Ashkenazi Jewish population

Shelley Dolitsky, M.D., Anjali Mitra, M.D., Shama Khan, M.P.H., M.S., L.C.G.C., Elena Ashkinadze, M.S., L.C.G.C., and Mark V. Sauer, M.D., M.S.

Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey

Objective: To assess whether or not the current American College of Obstetricians and Gynecologists (ACOG) recommendations regarding carrier screening are sufficiently robust in detecting mutations in the Ashkenazi Jewish (AJ) population.

Design: Cross-sectional study.

Setting: Outreach program at university community center.

Patient(s): Self-identified Jewish students, 18–24 years of age, interested in genetic carrier testing.

Intervention(s): Expanded carrier screening (ECS) with the use of a commercially available targeted genotyping panel including >700 mutations in 180 genes.

Main Outcome Measure(s): Gene mutations found in this population were grouped into three categories based on ACOG’s 2017 committee opinion regarding carrier screening: category 1: the four commonly recommended genetic conditions known to be a risk for this population; category 2: 14 genetic disorders that should be considered for more comprehensive screening, including those of category 1; and category 3: the ECS panel, which includes category 2.

Result(s): A total of 81 students underwent screening and 36 (44.4%) were ascertained to be carriers of at least one mutation. A total of 45 mutations were identified, as 8 students were carriers for more than one condition. If testing were limited to category 1, 84% of the mutations would not have been identified, and if limited to category 2, 55% of mutations would have gone undetected.

Conclusion(s): Individuals of Ashkenazi Jewish descent are at significant risk for carrying a variety of single-gene mutations and therefore they should be offered panethnic ECS to increase the likelihood of detecting preventable disorders. (*Fertil Steril Rep*® 2020;1:294–8. ©2020 by American Society for Reproductive Medicine.)

Key Words: Expanded carrier screening, genetic diseases, Ashkenazi Jews

Discuss: You can discuss this article with its authors and other readers at <https://www.fertsterdialog.com/posts/xfre-d-20-00058>

Inherited single-gene disorders are a leading cause of infant morbidity and mortality in the United States, accounting for ~20% of annual infant deaths (1). Patients of Ashkenazi Jewish (AJ) heritage have an increased risk of being genetic carriers for certain diseases compared with the general population using conventional testing

platforms for screening, with an overall carrier rate ranging from 1 in 5 to 1 in 4 individuals (2, 3). Therefore, for many years the American College of Obstetricians and Gynecologists (ACOG) has recommended that patients of AJ ancestry be offered preconception carrier screening for four common inheritable conditions known to occur within

this population. These limited panels screen for Tay-Sachs disease, cystic fibrosis, familial dysautonomia, and Canavan disease (4). However, others have advocated for the use of a more comprehensive screening panel. As a result, ACOG recognized that screening for Bloom syndrome, familial hyperinsulinism, Fanconi anemia, Gaucher disease, glycogen storage disease type I, Joubert syndrome, maple syrup urine disease, mucopolysaccharidosis type IV, Niemann-Pick disease, and Usher syndrome should also be considered (4).

Given the higher genetic risks known to exist within the AJ population, independent carrier screening panels have been created, which are

Received April 6, 2020; revised July 12, 2020; accepted August 2, 2020.

S.D. has nothing to disclose. A.M. has nothing to disclose. S.K. has nothing to disclose. E.A. has nothing to disclose. M.V.S. has nothing to disclose.

Reprint requests: Shelley Dolitsky, M.D., Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, 125 Paterson Street, New Brunswick, NJ 08901 (E-mail: shelley.dolitsky@rutgers.edu).

Fertil Steril Rep® Vol. 1, No. 3, December 2020 2666-3341

© 2020 The Authors. Published by Elsevier Inc. on behalf of American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.xfre.2020.08.001>

commonly ordered in the prepregnancy period to test for a number of founder mutations. When mutations in the same gene (or for the same disease) are discovered in both partners, reproductive options such as preimplantation genetic testing of embryos (PGT-M) have been successful in decreasing the likelihood of conceiving a child affected by the genetic disorder.

Recently, the advent of panethnic expanded carrier screening (ECS), which is both readily accessible and relatively affordable, has further improved detection of carriers for an even broader array of conditions beyond the 14 mentioned by ACOG (3). Despite the availability of expanded panethnic carrier panels, many clinicians continue to order targeted testing, looking only for more common conditions known to occur within specific populations.

The objective of the present study was to assess whether the current ACOG screening recommendations for genetic testing are sufficiently robust in identifying single-gene mutational carrier status in an AJ population of college students interested in knowing their carrier status. We also sought to determine if commercially available panethnic screening tools might better serve their preconception testing and genetic counseling needs by increasing the detection rate of genetic disorders in this population.

PATIENTS AND METHODS

The study was reviewed and approved by the Institutional Review Board of Rutgers University. This was a cross-sectional study of undergraduate students (ages 18–24 years) enrolled at a single institution who voluntarily underwent genetic testing with the use of an ECS saliva test offered through an outreach program at Rutgers University Hillel in October 2015. All of the students were of self-reported Jewish descent. Saliva samples were tested at a single commercial laboratory (InheriGen, BioReference Laboratories). Test results were later disclosed to the students.

The genetic conditions tested in the ECS totaled 180 disorders (Supplemental Table 1, available online at www.fertstert.org). These mutations were then grouped into three categories based on ACOG's 2017 committee opinion regarding carrier screening (Table 1). Results from the individuals were then collated into three categories to determine the clinical utility of the various approaches in detecting carrier status. Descriptions of these diseases are provided in Table 2.

RESULTS

A total of 81 students were screened. The average age of the participants was 21 years old (± 2.5 years); 31 (38.3%) of the participants were male and 50 (61.7%) were female. In this sample, 36 (44.4%) were found to carry at least one autosomal recessive disease if the expanded carrier panel was used. Within the group of these 36 carriers, 28 individuals were found to be a carrier for only one mutation, 7 for two mutations, and 1 for three mutations, representing 45 total identified mutations (Table 3).

If this same group had undergone only a 4-mutation screen, 66.7% of the individuals in the group carrying mutations identified by means of the expanded panel would have

TABLE 1

Categories of disorders.

Category	Diseases
1	ACOG-recommended tests for Ashkenazi Jewish patients: Tay-Sachs disease Cystic fibrosis Familial dysautonomia Canavan syndrome
2	ACOG-recommended additional comprehensive panel: category 1 plus: Bloom syndrome Familial hyperinsulinism Fanconi anemia Gaucher disease Glycogen storage disease type I Joubert syndrome Maple syrup urine disease Mucopolidosis type IV Niemann-Pick disease Usher syndrome
3	Panethnic commercial panel of expanded carrier screening

Note: ACOG = American College of Obstetricians and Gynecologists.

Dolitsky. Expanded carrier screening of Jewish patients. *Fertil Steril Rep* 2020.

been missed, and 19.4% of them would have been missed using the 14-mutation panel. A significant number of positive test results were discovered only because the ECS panel was used.

DISCUSSION

It is well established that population-based genetic screening has been successful in substantially decreasing the burden of certain inherited disorders within specific at-risk populations. For example, the incidence of children born with Tay-Sachs disease decreased by more than 90% from the 1970s to 2000 owing to the development of screening tests for the disease (5). With the advent of ECS, clinicians now have the opportunity to further reduce the risk of transmitting autosomal recessive disorders within the AJ population.

Our study is consistent with others (6) demonstrating that offering ethnicity-based screening alone would fail to identify a percentage of carriers in the AJ population. If access to carrier screening for AJ patients was limited to only founder mutations (e.g., the comprehensive 14 disorders panel), 19.4% of carriers would not have been identified. Furthermore, if screening had been limited to only the four disorders specifically recommended by ACOG, only 33.3% of carriers would have been detected. This study is clinically significant, because many general obstetrician-gynecologists continue to follow ACOG's guidelines suggesting that ethnicity-based screening is adequate in characterizing the genetic disease carrier risk within the AJ population.

A multicenter study screened 23,000 individuals and found that the AJ population was the ethnic group most likely to be carriers for serious autosomal recessive disorders (7). The overall carrier rate in this population has been estimated to be from 1 in 5 to 1 in 4 surveyed; however, one group estimated

TABLE 2

Description and carrier frequencies of the category 3 diseases found in this population

Condition	Description	ECS frequency ^a	Carrier frequency in this study
Bernard-Soulier Syndrome	Low platelet count and abnormally large platelets (macrothrombocytopenia) (22)	Unknown, very rare	1 in 81
Carnitine palmitoyltransferase II (CPT II) deficiency	Three main types of CPT II deficiency: a lethal neonatal form, a severe infantile hepatocardiomyopathy form, and a myopathic form; involves primarily heart, liver, and kidneys (17)	1 in 500 AJ: 1 in 51	1 in 81
Congenital disorder of glycosylation type Ia	Developmental delay, hypotonia, failure to thrive, hypoglycemia (23)	1 in 71	1 in 81
Dihydropyrimidine dehydrogenase deficiency	Range of phenotypes from asymptomatic to seizures, developmental delay, impaired gross motor development (24)	1 in 51	1 in 81
Factor XI deficiency	Injury-related bleeding disorder (25)	1 in 500 AJ: 1 in 11	3 in 81
Familial Mediterranean fever	Recurrent fever and serositis (peritonitis, pleuritis, synovitis) (26)	AJ: <1 in 5	6 in 81
Medium-chain acyl-CoA dehydrogenase deficiency	Vomiting, poor oral intake, dehydration, lethargy, seizures, high mortality rate if undiagnosed during infancy (27)	White Europeans: 1 in 50	1 in 81
Nemaline myopathy	Facial weakness with eye muscles spared, generalized weakness (28)	AJ: <1 in 108	2 in 81
Smith-Lemli-Opitz syndrome	Multiple congenital anomalies and intellectual disability (29)	White Europeans: 1 in 70 to 1 in 30	4 in 81
Spinal muscular atrophy	Progressive weakness and paralysis of motor neurons (30)	1 in 50 to 1 in 25 (31) AJ population: 1 in 46 (31)	3 in 81
Stargardt disease	Progressive muscular dystrophy with visual involvement (32)	1 in 50	4 in 81
Wilson disease	Combination of hepatic, neurologic and psychiatric symptoms as a result of copper deposition in tissue (33)	White Europeans: 1 in 87 AJ: 1 in 100	1 in 81

^a As reported by the GenPath Inherigen Pan-Ethnic Expanded Carrier Screening (ECS) test used for this study (34).

Dolitsky. Expanded carrier screening of Jewish patients. *Fertil Steril Rep* 2020.

that the carrier frequency is much higher. Their study concluded that ~1 in 3.3 patients was a carrier of one disease and ~1 in 24 was a carrier for two diseases (6). This higher carrier frequency is largely a result of genetic drift, leading to a genetically homogeneous population with a high frequency of recessive alleles that are rare in the general population (8). For example, the carrier frequency of Tay-Sachs disease is ~1 in 30 in the AJ population versus 1 in 300 in the general population (8).

Due to the increased prevalence of inherited diseases within this group, patients and families are often more aware of their heightened risk of genetic diseases compared with the general population. Therefore, patients often seek out genetic testing preconceptually or at the time of infertility consultations (9). There are community-based screening programs (10) as well as an increasing number of direct-to-consumer commercial tests (11) that offer genetic testing, allowing individuals to complete their testing outside of the physician's office. These programs, however, often follow ACOG's recommendations and only include the limited "Jewish panel." Therefore, when AJ patients receive "negative" results, they are given a false sense of security and may be less likely to later pursue additional testing.

With this concern in mind, one population-based recommendation advocated for an expansion in ethnicity-based screening to include other diseases commonly found in the AJ population, such as familial Mediterranean fever and

nonclassic 21-hydroxylase deficiency (4). Although these diseases are not life threatening, the carrier rates are 1 in 6 (12) and 1 in 27, respectively (4). That recommendation, however, failed to include Smith-Lemli Opitz syndrome, which has 3.7% incidence in the AJ population (4) compared with 1.4% in the general population (13). Smith-Lemli Opitz syndrome is a disorder characterized by multiple congenital malformations, facial abnormalities, metabolic errors, and intellectual disability. It also causes pregnancy loss in up to 80% of affected fetuses (13). Four out of 81 (4.9%) of the students tested in this study were carriers for this disease. An additional four students (4.9%) were found to be carriers for Stargardt disease, which leads to vision loss (14).

Many other diseases that these students were noted to be carriers for are clinically significant: They can have a detrimental effect on quality of life, cause cognitive or physical impairment, and result in death of the child. Nemaline myopathy, which causes muscle weakness, can cause patients to be wheelchair bound or, in serious cases, die from respiratory failure (15). Congenital disorder of glycosylation type Ia causes strokes, seizures, blindness, and developmental delay; 20% of affected children die before 1 year of age (16). Babies affected by the most serious form of carnitine palmitoyltransferase II deficiency live for days to months; the least serious form leads to life-threatening kidney failure in childhood (17). As more and more genetic disorders are successfully characterized with the use of ECS, it seems judicious to

TABLE 3

Expanded carrier screening test results (n = 81)	
Disease	No. of patients that had positive screening result
Category 1	
Canavan syndrome	1
Cystic fibrosis	2
Familial dysautonomia	1
Tay-Sachs disease	3
Category 2	
Familial hyperinsulinism	2
Fanconi anemia C	1
Gaucher disease	3
Joubert syndrome	1
Maple syrup urine disease	2
Mucopolipidosis IV	1
Niemann-Pick disease	1
Usher syndrome type 3	1
Usher syndrome type 1F	1
Category 3	
Bernard-Soulier syndrome	1
Carnitine palmitoyltransferase II deficiency	1
Congenital disorder of glycosylation type Ia	1
Dihydropyrimidine dehydrogenase deficiency	1
Factor XI deficiency	3
Familial Mediterranean fever	6
Medium-chain acyl-CoA dehydrogenase deficiency	1
Nemaline myopathy	2
Smith-Lemli-Opitz syndrome	4
Spinal muscular atrophy	3
Stargardt disease	4
Wilson disease	1

Dolitsky. Expanded carrier screening of Jewish patients. Fertil Steril Rep 2020.

embrace the practice of broader surveillance to better define risk and detect carriers instead of using targeted testing strategies.

ECS has more recently come into favor because it provides information on many more genetic diseases that have varying ages of onset and phenotypes (18). It provides a huge repository of genetic information, although its clinical utility is still unclear and understudied. Much of the controversy about recommending ECS for the AJ population stems from the clinical relevance and the low carrier frequency of the diseases not specifically recommended for this population. For example, mucopolipidosis type IV can cause severe developmental delay and vision impairment, but the carrier frequency in the AJ population is 1 in 127 (8). Gaucher disease, which has the highest carrier frequency of all mutations, 1 in 15, is a condition that can be effectively treated with enzyme replacement therapy (8). However, one could argue that identifying carrier status provides critical information for reproductive counseling and family planning (4, 8). The technology is widely available and cost-effective for this population (19).

In 2015, ACOG, American College of Medical Genetics, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society of Maternal Fetal Medicine released a joint statement in which they encouraged providers to consider ECS for all women of reproductive age in the

preconception period (20). At the same time, they acknowledged that more research is needed to understand the clinical utility of ECS. They concluded that it is acceptable to use ECS, but not currently recommended (21). To our knowledge, this is the first study to sample a young at-risk population and highlight how many mutations would be missed when using the standard ethnicity-based genetic screening panels. Though preliminary, our data suggest that ethnicity-based screening is no longer the best method for screening an AJ population. This approach may also be applicable to other subpopulations that are often offered targeted ethnicity-based panels, such as the African, Mediterranean, and Asian populations. It could also be considered for the general population; the cited carrier rate for the AJ population is significantly lower than what was found in the present study (3), and future, broader studies might be beneficial to further assess ECS utility in the general population. The limitation of our study is primarily the sample size. In addition, this study was part of an outreach program that offered testing to young, single college students in an at-risk population; however, the recommended time for ECS would be immediately before conceiving.

Implementing ECS in the preconception period is instrumental in guiding reproductive decision making for couples planning to have children. It allows those discovered to carry recessive disorders the opportunity to pursue treatment options such as PGT-M, which is designed to avoid the transfer of an affected embryo. This approach would decrease the incidence of children born with these diseases, leading to decreased health care costs (18). The cost of ECS is similar to that of the targeted ethnicity-based panels and therefore, choosing a screening tool that excludes many mutations is difficult to justify from a fiscal analysis viewpoint (6, 18). With this in mind, the present study supports offering individuals of AJ descent panethnic ECS. Future studies are needed to address other subpopulations, such as the African, Mediterranean, and Asian populations, who may also benefit from panethnic ECS in place of targeted ethnicity-based panels.

REFERENCES

- Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. *Prenat Diagn* 2015;35:931-5.
- American College of Obstetricians and Gynecologists. Carrier screening for genetic conditions. ACOG committee opinion no. 691. *Obstet Gynecol* 2017;129:e41-55.
- Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med* 2008;10:54-6.
- Baskovich B, Hiraki S, Upadhyay K, Meyer P, Carmi S, Barzilai N, et al. Expanded genetic screening panel for the Ashkenazi Jewish population. *Genet Med* 2015;18:522-8.
- Kabac M. (2000). Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. *Eur J Pediatr* 2000;159(Suppl 3): S192-5.
- Scott SA, Edelman L, Liu L, Luo M, Desnick R, Kornreich R. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. *Hum Mutat* 2010;31:1240-50.
- Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson S, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med* 2013;15:178-86.
- Yao R, Goetzinger K. Genetic carrier screening in the twenty-first century. *Clin Lab Med* 2016;36:277-88.

9. Franasiak J, Olcha M, Bergh PA, Hong KH, Werner MD, Forma EJ, et al. Expanded carrier screening in an infertile population: how often is clinical decision making affected? *Genet Med* 2016;18:1097–101.
10. Jewish Genetic Screening Consortium. Resources for genetic screening. Available at: <https://www.jewishgeneticdiseases.org/resources-for-genetic-screening-2/>. Accessed March 30, 2020.
11. Henneman L, Borry P, Chokoshvili D, Cornel M, val El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. *Eur J Hum Genet* 2016;24:e1–12.
12. Mikula M, Buller A, Sun W, Strom CM. Prevalence of known mutations in the familial Mediterranean fever gene (*MEFV*) in various carrier screening populations. *Genet Med* 2008;10:349–52.
13. Lazarin GA, Haque IS, Evans EA, Goldberg JD. Smith-Lemli-Opitz syndrome carrier frequency and estimates of in utero mortality rates. *Prenat Diagn* 2017;37:350–5.
14. Tsang SH, Sharma T. Stargardt disease. *Adv Exp Med Biol* 2018;1085:139–51.
15. Yin X, Pu CQ, Wang Q, Liu JX, Mao YL. Clinical and pathological features of patients with nemaline myopathy. *Mol Med Rep* 2014;10:175–82.
16. Sparks S, Krasnewich D. PMM2-CDG (CDG-1a). GeneReviews. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK11110/>. Accessed May 27, 2020.
17. Genetics Home Reference. Carnitine palmitoyltransferase II deficiency. Available at: <https://ghr.nlm.nih.gov/condition/carnitine-palmitoyltransferase-ii-deficiency>. Accessed May 27, 2020.
18. Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. *Genet Med* 2019;21:1948–57.
19. Kraft SA, Duenas D, Wilfond BS, Goddard KA. The evolving landscape of expanded carrier screening: challenges and opportunities. *Genet Med* 2019;21:790–7.
20. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol* 2015;125:653–62.
21. American College of Obstetricians and Gynecologists' Committee on Genetics, Romero S, Rink B, Biggio JR, Saller DN Jr. Committee opinion: carrier screening in the age of genomic medicine. No. 690, March 2017. Available at: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-in-the-age-of-genomic-medicine>. Accessed May 27, 2020.
22. Berndt MC, Andrews RK. Bernard-Soulier syndrome. *Haematologica* 2011;96:355–9.
23. Woods AG, Woods CW, Snow TM. Congenital disorders of glycosylation. *Adv Neonatal Care* 2012;12:90–5.
24. Flegler M, Willomitzer J, Meisma R, Alders M, Meijer J, Hennekam RC, et al. Dihydropyrimidine dehydrogenase deficiency: metabolic disease or biochemical phenotype? *JIMD Rep* 2017;37:49–54.
25. Duga S, Salomon O. Factor XI deficiency. *Semin Thromb Hemost* 2009;35:416–25.
26. Sarı İ, Birlik M, Kasifoğlu T. Familial Mediterranean fever: an updated review. *Eur J Rheumatol* 2014;1:21–33.
27. Arnold GL, Saavedra-Matiz CA, Galvin-Parton PA, Erbe R, Devincintis E, Kronn D, Mofidi S, et al. Lack of genotype-phenotype correlations and outcome in MCAD deficiency diagnosed by newborn screening in New York State. *Mol Genet Metab* 2010;99:263–8.
28. Sarnat HB. New insights into the pathogenesis of congenital myopathies. *J Child Neurol* 1994;9:193–201.
29. Nowaczyk MJ, Irons MB. Smith-Lemli-Opitz syndrome: phenotype, natural history, and epidemiology. *Am J Med Genet C Semin Med Genet* 2012;160c:250–62.
30. d'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. *Orphanet J Rare Dis* 2011;6:71.
31. Hendrickson BC, Donohoe C, Akmaev VR, et al. Differences in SMN1 allele frequencies among ethnic groups within North America. *J Med Genet* 2009;46:641–4.
32. Tsang SH, Sharma T. Stargardt disease. *Adv Exp Med Biol* 2018;1085:139–51.
33. Huster D. Wilson disease. *Internist* 2018;59:159–74.
34. GenPath. InheriGen Pan-Ethnic Carrier Screening. Available at: <https://www.genpathdiagnostics.com/patients/womens-health/carrier-screening/inherigen-pan-ethnic-carrier-screening/>. Accessed June 1, 2020.