Management considerations for clinically relevant findings on expanded carrier screening in a sperm donor applicant population

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Objective: To describe the clinical experience of managing expanded carrier screening (ECS) results in sperm donor applicants at a sperm bank in the United States, including considerations around suitability determination and appropriate education of prospective donors and recipients.
Design: A retrospective review of donor genetic screening records from July 2017 to December 2021.
Setting: A U.S.-based sperm bank.
Patients: Donor applicants at a sperm bank.
Intervention: Not applicable.
Main Outcome Measures: To examine the rate of potentially significant health risks on the basis of ECS results to inform donor management and donor/recipient counseling considerations.
Results: Nearly 2% of donor applicants were identified as having potentially significant health risks on the basis of their ECS results, and most individuals had no clinical manifestations related to these findings.
Conclusion: There are unique challenges related to ECS in third-party reproduction for gamete providers, recipients, and their healthcare providers. A collaborative, multidisciplinary approach is necessary to help mitigate risks to donor offspring and maximize patient experience. Informed consent and access to a trained genetics professional are paramount when facilitating ECS on donor applicants and disseminating results to recipients. (Fertil Steril Rep® 2023;4:384–9. ©2023 by American Society for Reproductive Medicine.)
Key Words: Expanded carrier screening, sperm donor, gamete donor, genetic screening

Genetic carrier screening has evolved drastically because it was first introduced into the clinical space several decades ago. In clinical practice, there has been a significant shift to a pan-ethnic, or expanded carrier screening (ECS) model for prenatal and preconception carrier screening compared with the traditional ethnicity-based screening model (1). Consequently, the American College of Obstetricians and Gynecologists and the American College of Medical Genetics have published guidance surrounding ECS practices (2–4). These guidelines include criteria regarding which conditions should and should not be included on an ECS panel on the basis of their carrier frequency, severity, age of onset, gene, and disease association.

Carrier screening is also an important component in third-party reproduction. Changes in carrier screening practices of gamete donor recipients have resulted in a significant shift to ECS panels on prospective gamete donors (5). The American Society of Reproductive Medicine (ASRM) Practice Committee published updated guidance in January 2021 that outlines the recommended carrier screening approach for donors (6). These guidelines state that all gamete donors should be screened for carrier status for cystic fibrosis, spinal muscular atrophy, and hemoglobin disorders, and fragile X syndrome screening should be considered for oocyte donors. Importantly, the guidelines also state that performing ECS on prospective gamete donors may be appropriate and outline the limitations around ethnicity-based carrier screening. Programs that recruit and screen sperm and oocyte donors must be cognizant of ASRM's recommended carrier screening practices to ensure their donors are appropriately tested.

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Expanded carrier screening panels often include hundreds of genetic disorders, and as such, many individuals will screen positive as carriers for one or more disorders on any given panel (7). Indeed, prior studies have illustrated the high frequency of donors who are identified as carriers of one or more recessive disorders on an ECS panel (8). Furthermore, limited data indicate gamete donor recipients may be willing to use a donor who is a carrier for a condition with a mild presentation (9). Thus, excluding all prospective gamete donors who are identified as carriers for recessive conditions is not feasible or appropriate given the availability of reliable reciprocal screening for the reproductive partner. The ASRM guidelines state that although donors who are carriers of recessive disorders need not be excluded, there may be exceptions for those identified as being at-risk for health issues on the basis of their results (6). This guidance was explicitly outlined on the basis of the growing number of conditions on ECS panels in which carrier status may result in health risks for that individual. For example, homozygosity or compound heterozygosity in the *ATM* gene is associated with an autosomal recessive condition called ataxia telangiectasia, whereas carrier status for a single mutation in this gene is associated with a moderately increased risk for breast cancer (10). However, there is no additional direction with regards to which specific conditions, variants, or carrier statuses could impact an applicant's suitability in a donor program.

Anecdotal evidence suggests variability among gamete donor programs with respect to how ECS results are managed, and programs may opt to exclude donors with potentially clinically significant findings. This study aimed to describe the clinical experience of managing ECS results in sperm donor applicants at a public sperm bank in the United States, including considerations around suitability determination and appropriate education of prospective donors and recipients.

MATERIALS AND METHODS

A retrospective review of donor genetic screening records at a single sperm bank from July 2017 to December 2021 was performed. Expanded carrier screening was performed on sperm donor applicants as part of the routine donor qualification process through an outside reference laboratory after participants provided written consent for genetic testing. The genes included on the ECS panel were analyzed using multiple methodologies, including exon sequencing, copy number variation analysis, and multiplex ligation-dependent probe amplification. Specific methodologies varied on the basis of laboratory offerings at the time in which the potential donor (PD) entered the donor program. Potential donors were tested for between 261 and 283 autosomal recessive (AR) and X-linked conditions. The number of conditions tested varied on the basis of the timeframe in which the PD entered the program. Relevant data were extracted and categorized using carrier screening results.

Genetic counselors at the sperm bank evaluated the health risks to the donors as well as reproductive risks associated with being a carrier of a pathogenic or likely pathogenic mutation in each gene using published data, reference laboratory interpretations, and professional health management guidelines.

Potential donors were identified as having potentially significant health risks on the basis of their ECS results in the following scenarios:

- A PD was heterozygous or hemizygous for a variant, which may confer health risks to carriers on the basis of currently available data.
- A PD was heterozygous or hemizygous for a variant that may confer health risks to carriers on the basis of currently available data, specifically in the context of a significant personal or family medical history.
- A PD was homozygous or compound heterozygous for variants associated with an AR condition, which may confer health risks on the basis of currently available data.

This study was deemed exempt from approval by the Advarra Institutional Review Board because the data were analyzed using deidentified participants.

RESULTS

A total of 966 PDs had ECS during the donor qualification process between July 2017 and December 2021. Potential donors reported varying ethnic backgrounds. Investigating ethnicity distribution was outside the scope of this research; however, on the basis of a separate analysis, most donor applicants during this time identified as White and Caucasian (11). Of these applicants, 19 (1.97%) PDs were identified as having potentially significant health risks on the basis of their ECS results.

Of those 19, 11 PDs were found to be either heterozygous or hemizygous for conditions that may convey significant health risks to carriers, on the basis of laboratory interpretation and internal review. Nine of the 11 PDs were positive for a variant in a gene typically associated with an AR condition (Table 1) (10–13), and two of the 11 PDs carried variants in genes associated with X-linked conditions (Table 2) (14, 15).

Although both X-linked carriers were male, neither PD reported exhibiting symptoms of the condition. The only individuals known to have any health effects associated with these genetic findings were the two men found to have mutations in the low-density lipoprotein (LDL) receptor gene. They also had elevated LDL on their lipid panels.

Eight additional PDs were found to be either compound heterozygous or homozygous for variants in a gene associated with an AR condition (Table 3) (16–22). This included two donors who carried two copies of the D444H variant for biotinidase deficiency. These eight applicants with two mutations for AR disorders reportedly did not have any symptoms related to their genotype.

DISCUSSION

In addition to providing relevant reproductive risk information regarding donor carrier status for many recessive disorders, ECS results revealed clinically significant information related to personal health management for approximately 1 in 51 donor applicants out of nearly 1,000 individuals screened. In addition to stating the benefits of a pan-ethnic

TABLE 1

Clinically significant heterozygosity for autosomal recessive (AR) conditions.

Number of positive donor applicants	Gene	Associated AR disease	Associated potential health risks (heterozygotes)
3	*ATM*	Ataxia telangiectasia	Moderately increased risk for breast cancer (10)
1	*NBN*	Nijmegen breakage syndrome	Possible increased risk for certain types of cancer, particularly in the presence of a specific founder mutation. Conflicting evidence exists (10)
2	*FH*	Fumarase deficiency	Increased risk of developing hereditary leiomyomatosis and renal cell cancer (12)
2	*LDLR*	Familial hypercholesterolemia	Increased risk for coronary artery disease and myocardial infarction (13)
1	*TNXB*	Ehlers-Danlos syndrome	Increased risk for joint hypermobility, recurring joint dislocations, and chronic joint pain (14)

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carrier screening approach as opposed to ethnicity-based screening, the most recent ASRM gamete donor screening guidelines emphasize the importance of pretest counseling and informed consent (6).

The results of this study reinforce the need for donor applicants to be properly educated on the potential personal health risks that may be identified on an ECS panel (5). Apart from the two PDs carrying LDL receptor gene variants and presenting with elevated LDL cholesterol, none of the men were identified to have any obvious health risks associated with their ECS result. Many of the conditions associated with the clinically significant genes on carrier screening panels have later ages of onset, reduced penetrance, and variable disease severity (24), and thus the percentage of people who remain apparently asymptomatic will vary on the basis of the individual result. However, the lack of symptoms at the time of the result does not exclude the possibility of developing clinical manifestations in the future; thus, it is recommended that the PDs inform their personal healthcare providers about their test results to facilitate appropriate care as needed.

Guidance from ASRM states that "donors who are carriers for recessive conditions that confer significant health risks to carriers (e.g., ataxia telangiectasia and Nijmegen breakage syndrome) should be considered on a case-by-case basis" (6). This guidance preserves flexibility for gamete programs to retain donors that may otherwise be suitable for their program and allows more autonomy for recipients who may seek donors with specific traits and thus benefit from a larger donor pool. However, allowing donors with such variants to participate in a donor program necessitates that recipients are properly informed of the associated health risks and understand the potential implications for their offspring. This requires collaboration between donor programs and reproductive medicine providers to ensure the information is properly disseminated and that recipients have the opportunity for genetic counseling and informed consent before using that donor's gametes. Previous research suggests the benefits of implementing a patient education tool to avoid co carrier matches between donors and recipients (25); similar educational protocols around the risks associated with genetic screening results could be considered.

The ASRM guidelines also address potential donors identified with two mutations for recessive conditions who are apparently asymptomatic, stating that these individuals "should be considered on a case-by-case basis, with consideration of the specific condition, possible symptoms, impact on fertility treatments, and reproductive risk." There is varying clinical severity among the many conditions on an ECS panel. For example, in this study, two PDs were identified to carry two copies of the *BTD* gene variant known as D444H (Table 3). The *BTD* gene is associated with biotinidase deficiency, a relatively common condition that is often undetected but may be treated with biotin supplements when needed. Notably, the D444H variant is associated with a low risk of clinical manifestations (26). Ultimately, for donors identified with two mutations for a recessive condition, genetic counseling for recipients is appropriate to ensure they

TABLE 2

Clinically significant hemizygosity for X-linked conditions.

Number of positive donor applicants	Gene	Associated AR disease	Associated potential health risks (hemizygotes)
1	*DMD*	Duchenne muscular dystrophy	Delayed motor development and progressive muscle weakness, cardiomyopathy, and cognitive impairment (15)
1	*F9*	Factor IX deficiency	Prolonged or excessive bleeding after injury or trauma, joint bleeds, and deep muscle hematomas (16)

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TABLE 3

Clinically significant compound heterozygosity or homozygosity for autosomal recessive (AR) conditions.

Number of positive donor applicants	Gene	Associated AR disease	Associated potential health risks (compound heterozygotes/ homozygotes)
2	*BTD*	Biotinidase deficiency	When untreated, neurological abnormalities, vision problems, hearing loss, and cutaneous abnormalities (17)
1	*CAPN3*	Limb-girdle muscular dystrophy 2a	Weakness and atrophy of the proximal limb-girdle muscles, joint contractures (18)
1	*NEB*	Nemaline myopathy	Progressive weakness of the proximal muscles, particularly those in the face and neck (19)
1	*CYP21A2*	Congenital adrenal hyperplasia (because of 21-hydroxylase deficiency)	Excessive adrenal androgen biosynthesis results in virilization and salt-wasting (classic form); hyperandrogenism results in possible hirsutism, menstrual cycle changes, and infertility (nonclassic form) (20)
1	*SLC25A13*	Citrin deficiency	Neonatal intrahepatic cholestasis (newborns), failure to thrive and dyslipidemia (older children), hyperammonemia with neuropsychiatric symptoms (adults) (21)
1	*HBA1/2*	Alpha thalassemia	Generalized edema, severe anemia, neonatal death (Hb Bart syndrome); spleen and liver enlargement, jaundice, and bone changes (HbH disease) (22)
1	*USH2A*	Usher syndrome type 2a	Congenital, bilateral sensorineural hearing loss, and progressive, bilateral retinal degeneration (23)

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understand that all offspring will inherit a mutation for that condition when the donor's variants are on opposite chromosomes. Assuming the recipient has been screened negative for the condition, there would not be an increased risk to the health of the offspring, just as when the recipient used a donor who is a heterozygous carrier for that disease.

There are multiple considerations involved in the management of a donor applicant's ECS results:

- Many genetic testing laboratories have a robust variant curation process that considers published literature, population, and disease databases, and in silico predictive programs (27). Gamete donor providers should collaborate closely with their reference laboratory to understand what information may be provided on a genetic test result regarding the significance of a genetic variant identified via ECS, as well as the limitations of testing and reporting by the specific laboratory.
- It is unrealistic for an individual to maintain a thorough knowledge of each condition included on an ECS panel; however, professionals involved in a donor program need to be knowledgeable of genes associated with potential health risks to appropriately assess a donor's suitability for the program on the basis of his results and determine how those results should be handled. Additionally, it is important to be aware of genotype-phenotype correlations to properly educate donors and/or recipients about the specific variants as well as their relevance to the clinical presentation (4). A commonly encountered example of well-established genotype-phenotype correlations is 21-hydroxylase-deficient congenital adrenal hyperplasia caused by pathogenic variants in the *CYP21A2* gene. Specific variants are associated with a severe (classic) presentation of this condition, whereas other variants are associated with a mild (nonclassic) presentation (19). Additionally, not all genetic variants in high-risk genes may be associated with the heterozygote disease risk (e.g., variants in the *FH* gene that cause hereditary leiomyomatosis and renal cell cancer) (28).
- A donor's personal and family medical history may also contribute to the variant interpretation process, and other genetic factors may contribute to gene expression and risk for disease (27). Interpretation of ECS results within this context requires the collaboration of trained genetics professionals to gather a thorough 3-generation family history and examining physicians to document physical findings consistent with the clinical presentation of the variant or disease in question. Other health evaluations may also contribute to understanding the significance of an identified variant for the prospective donor. This is evidenced by the fact that the two donor applicants carried mutations for familial hypercholesterolemia and presented with elevated LDL cholesterol levels.

Although outside the scope of this research, a more detailed examination of best practices for appropriate dissemination of ECS results by gamete donor programs is warranted. This would ultimately help guide clinics and healthcare providers to effectively manage carrier screening for donor recipients.

Limitations of this study include donor recruitment being limited to a few major metropolitan areas in the U.S. where sperm donor collection sites are currently located; thus, donor applicants included in the data set may not represent all ethnic groups or socioeconomic backgrounds. Additionally, this study described results from a single reference laboratory and does not illustrate the variation in ECS panels across genetic testing laboratories.

Although this study described ECS results associated with potential health risks in a donor applicant population, the

results are also applicable to the general reproductive population and illustrate the necessity of pretest and posttest counseling and informed consent. Indeed, a recent retrospective study of over 73,000 carrier screens suggested that nearly 1% of individuals undergoing carrier screening will have a finding that may require clinical evaluation or surveillance (24). Not only can ECS help elucidate reproductive risks, but it may also provide insight into potential future health risks and health management opportunities for that individual. Once these variants are identified, reproductive options such as prenatal diagnosis or preimplantation genetic testing may be also available. Genomics and personalized medicine are a growing focus of patient care, and lessons learned from ECS can inform future best practices in genetic testing.

CONCLUSIONS

The number of genes on commercially available ECS panels continues to increase. That, coupled with the growing amount of genomic information available today, suggests that ECS will continue to present complex scenarios in interpreting and managing potential health risks. There are unique challenges related to ECS in third-party reproduction for gamete providers, recipients, and their healthcare providers. A collaborative, multidisciplinary approach is necessary to help mitigate risks to donor offspring and maximize patient experience.

Because ECS has become a routine approach to carrier screening for prospective gamete donors, donor programs should be aware of the potential implications of the test results for the health of donor applicants. Donor applicants should undergo informed consent before testing and be provided with educational resources as well as access to a trained genetics professional. Results disclosure and posttest counseling may be appropriate as needed. Donor applicants should also be given the opportunity to consent to or decline testing, given such considerations. Because genetic tests are performed increasingly on whole genome or whole exome platforms, additional counseling considerations, including incidental findings, misattributed parentage, and other potential risks, may become increasingly relevant to this process (29).

In addition, it is recommended that donor programs develop protocols and processes for the review and management of donors' results. They should also ensure that donors' results are disclosed to potential recipients. This allows recipients, in consultation with their personal healthcare providers, to seek genetic counseling and determine when a donor is suitable for their personal reproductive plans. Ultimately, when recipients can be properly informed, this may lead to donor programs taking a less exclusionary approach when determining donor suitability on the basis of ECS results. The evolution of such practices could result in a larger, more diverse donor applicant pool that allows prospective families to choose a donor most suitable for their reproductive needs.

Declaration of interests: L.I. is a full-time employee and stockholder at CooperSurgical Inc.; honoraria for faculty members at StartART 2021 and 2022; speaker at ARM/NPG 2023; scientific conference attendance (multiple) funded by CooperSurgical; Chair of the Genetic Counseling Professional Group (GCPG) of the American Society of Reproductive Medicine (2020–2021); and SART Liaison for the GCPG (2021–current). P.C. is a former employee of CooperSurgical Inc.; travel support; stock options from Cooper Surgical; and founder and owner of the telehealth genetic counseling company Tandem Genetics. The company has contracts with several laboratories and clinics to provide clinical support and/or genetic counseling for their patients. Calitar Consulting LLC was founded in March 2023, through which I have consulting contracts for laboratories, clinics, and others in the reproductive and genetic fields. Author Baldwin is a full-time employee of CooperSurgical Inc. J.L. is a full-time employee of California Cryobank, a subsidiary of CooperSurgical; previous Genetic Counseling Professional Group chair (2019–2020), unpaid position. J.P. reports Registration and travel expenses related to the 2022 ASRM Annual Conference were paid for by CooperSurgical Inc., the author's current employer. K.B. is a full-time employee of CooperSurgical Inc.

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