Genetic carrier screening in donors: a challenging frontier

The article by Chang et al. (1) reported 3 pediatric cases of a rare, potentially lethal disease, adrenoleukodystrophy, at the time of testing a variant of unknown significance (VUS), that resulted from the same oocyte donor. The first child was diagnosed at the age of 4 years and died at the age of 5 years. After the families of the second and third children from the donor were each notified by their in vitro fertilization clinic, those 2 children were treated, and they survived. There is no indication whether the donor had children of her own during this time period.

These cases point toward current limitations in genetic screening of gamete donors, and the investigators raise numerous issues to improve the process. Although expanded genetic screening is increasingly becoming standard practice, carrier testing provided by different laboratories still differs in the number and types of mutations tested; results can be interpreted or communicated in different ways—to and by different individuals and entities—which may include donors, potential recipients, physicians, donor gamete programs, and banks. There is no standardized protocol or centralized mechanism for sharing reported results, any subsequent reclassifications, or other updates. Such limitations, separately or together, can result in lack of critically important genetic information for those directly affected, including other offspring from the same donor (through the use of previously stored eggs or embryos, subsequent donations, or the donor's own children).

In addition to complex genetic testing issues that are beyond the scope of this Reflection, these cases highlight a host of medical, legal, resource, and administrative issues in attempting to improve health outcomes in genetically related donors and offspring.

SHOULD THERE BE MANDATORY OR RECOMMENDED STANDARDIZED PANEL FOR GENETIC CARRIER TESTING OF PROSPECTIVE GAMETE DONORS?

Although aligning carrier testing of gamete donors and intended parents is appropriate, standardizing genetic tests among private companies would be challenging, although competition and proliferation of larger companies that offer expanded testing may lead to a similar result. Some companies now offer testing for >500 genes. The American College of Medical Genetics and Genomics's (ACMG's) 2021 guidelines recommend a standardized panel for any carrier screening and a list of 113 conditions, including the *ABCD1* gene (at the time of carrier screening a VUS) associated with the diagnosis of adrenoleukodystrophy in the 3 cases reported by Chang et al. (1).

Standardized professional or mandatory guidelines have been widely recommended for setting legal standards and consistency in health care generally and specifically for genetic testing. Both the ACMG and the American Society for Reproductive Medicine have issued professional guidelines for genetic carrier testing; however, commercial laboratories are not necessarily equipped to or consistently follow them (only 1 commercial laboratory tests for all 113 ACMG-listed conditions) (2, 3). If and when whole-genome sequencing should become widely and affordably available, it might address some of these issues while leaving and amplifying others, including how to curate relevant genetic information.

Unlike diagnostic screening, carrier screening neither looks for nor reports what may be hundreds of VUSs without the ability to assign a clinical value to them. From a practical and legal liability perspective, reporting these would require substantial educational tools; informed consent protocols for donors and recipients compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA); and other challenges for genetic laboratories, banks, and/or medical professionals to receive, interpret, and communicate the results while providing little clinically significant data.

SHOULD THERE BE A STANDARDIZED TIME PERIOD FOR POTENTIAL RECLASSIFICATIONS OF VUSs?

Without initial reporting of VUSs, any subsequent reclassification of an underlying mutation would not necessarily provide diagnostic information to a donor or any offspring. Currently, reclassifications occur on evidence-based timelines, and standardizing time frames for reclassifications may not be a realistic or best practice. If standardized carrier testing does not detect or report VUSs, reclassifications may be of limited utility for the health of donor-conceived offspring.

SHOULD THERE BE A CENTRALIZED SYSTEM OR REGISTRY FOR GENETIC INFORMATION RELATED TO DONOR-CONCEIVED OFFSPRING?

What may be achievable, as also suggested by the investigators, is development of a centralized mechanism or registry of donor gamete surveillance for receipt and updated dissemination of genetic information. No such voluntary or mandatory mechanism currently exists in the United States to gather and communicate existing, updated, or newly discovered donor-related genetic information between and among banks, recruiting programs, medical clinics, recipients, donors, and offspring. Despite the ASRM's guidelines that have long recommended the maintenance of "permanent records" of donors' screening, testing, and optimal retrieval cycles (3) and the 2013 Society for Assisted Reproductive Technology-created "Donor Egg Registry Task Force," which made specific recommendations to establish a donor registry (both the authors of this reflection were members of that task force), no centralized mechanism has ever been established, and recommendations by that task force and others to do so over the past 2 decades have failed. In late 2022, the ASRM announced the formation of a new task force, the "ASRM Task Force on the Needs and Interests of Donor Conceived People and their Families"; it is hoped that part of its mission will be to address genetic and medical history as well as identity-related issues.

The issue may be both more compelling and more complex for egg donors than for sperm donors given X-linked genetic conditions, the historical nature of egg donation, and recognized health care duties owed by physicians to their egg donor patients. With the majority of donor sperm frozen and distributed by a relatively few, large sperm banks, informal notifications, at least by those banks to clinics, patients, and donors, may be largely effective. Some egg donors are still recruited by individual medical programs or smaller stand-alone recruiting programs. Genetic screening can occur at the point predictions, with the medical program performing the donor's medical screening and cycle, introducing both a health law duty of care as well as more variability in testing, data collection, and retention. For frozen egg banks owned by, or affiliated with, these medical programs or providers, health law duties of care may apply. Despite the ASRM's recommended limits of 6 egg donations per egg donor and 25 families per sperm donor (per 800,000 population), no reporting system is in place to either document or communicate multiple donations at different sites or results from such donations (3).

There are undoubtedly major challenges to creating a centralized mechanism or independent registry to collect and make genetic donor-related information available and accessible to all those affected. The practical legal considerations include how to protect the privacy interests of those involved. Given HIPAA protections, both donors and recipients would need to specifically consent and agree to provide, receive, and share genetic information that is revealed by predonation testing, any follow-up reports, or later diagnosis of donors' or recipients' offspring. Access to counseling by qualified genetic counselors to assess and ensure quality reporting will be an important element. A system in which interested parties could independently enter and access entered information directly may address some liability concerns, including potential failures by professionals or administrators to adequately or accurately request, receive, or disseminate information, as has been raised in the wake of recently proposed (NY) and enacted (CO) state laws. Automated decision-support tools being developed in the field of genetics may ultimately be clinically useful. The substantial costs and resources to maintain any such mechanism or registry need to be addressed.

CONCLUSIONS

Genetic and genomic testing and screening have added novel elements to both medical practice and health laws. Responsibility and liability issues are unsettled and evolving. One legal analysis has identified 11 areas of potential legal liability surrounding genetic testing (not specific to gamete donation), including claimed failures to: test, accurately read and/or communicate test results, recontact for updates, or warn family members (which in a donor-conceived context may include genetically related individuals); overtesting; choice of specific panels or tests, inappropriate use or reliance on a test; and incorrect variant calls; among others (4).

Gamete donor carrier testing raises additional novel legal issues. Can a prospective donor decline testing or refuse to receive results for herself or her children? Because there is no right to be a gamete donor, can donation be conditioned on agreeing to various tests, disclosures, and even receipt and sharing of future updates? How would such duties be enforced? With some gamete banks being independent and others affiliated with medical programs, what legal standards and duties will apply to them? All of these questions might also impact both the availability and affordability of gamete donation.

As this case study indicates, today's VUS may be tomorrow's known pathogenic variant; yet current carrier testing for gamete donors may neither practically screen for nor report it. On the other hand, educating donors and recipients to encourage reporting any updated information and constructing a mechanism to effectively collect and safely disseminate it are available challenges waiting to be met. At a minimum, a centralized mechanism or registry could go a long way to protect those at risk of conditions that have been diagnosed in genetically related individuals. Beyond the complex genetic issues, the myriad of informed consent, technical, privacy, legal, resource, and financial challenges is real. However, the cost of not attempting to meet them can be fatal.

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