Gamete donors: to test, or how much to test? These are the questions

Because the demand for donor gametes continues to grow, molecular testing has migrated into the realm of gamete donation. This rapid evolution in genetic screening raises questions. How extensive should screening be? Should standards for donor genetic screening be consistent with the general population? Who is responsible for testing, and how should a recipient's expectations of a gamete donor's genotype be guided?

In this issue, Bayefsky et al. (1) provided valuable insight by highlighting the inconsistencies in testing paradigms and challenging the current approaches to donor gamete screening. They emphasized that, in the US, donor testing has blossomed in the wake of private gamete banks. Donors routinely undergo karyotyping as well as expanded carrier screening (ECS), and they contend that, at a time of increasing demand, such testing places an asymmetric burden on donors, ultimately shrinking the pool of available donors. The Food and Drug Administration (FDA) regulates gamete donor screening but offers no guidance on genetic screening. The American Society for Reproductive Medicine (ASRM) emphasizes that donors must not be known carriers or have a strong family history of autosomal or X-linked disorders (2). The ASRM recommends screening all nonidentified donors for cystic fibrosis, spinal muscular atrophy, and hemoglobinopathies, although ECS may be appropriate. The American College of Obstetricians and Gynecologists (ACOG) affirms that ethnic-specific, pan-ethnic, and ECS are acceptable strategies for prenatal carrier screening (3). This illustrates that in the US, no definitive standard specifically addressing gamete donor genetic screening exists.

Enhanced screening may confer some advantages, including a reduced genetic disease burden, which would reduce the cost of the disease, and greater recipient comfort with their donor selection. A study of ECS projected a reduction in disease burden and, in doing so, a potential treatment cost-effectiveness in comparison to minimal genetic screening (4). Amidst the already difficult process of fertility care, the weight of selecting a gamete donor can amplify patient apprehension. Understandably, recipients seek an abundance of information to facilitate choosing the "ideal" donor. The added insights provided by ECS may assist by potentially alleviating the decision-making strain.

Alongside the possible benefits are the greater direct and indirect costs of donor screening and the potentially negative ramifications for the donors. As Bayefsky et al. (1) report, there already exists an income-based disparity in fertility care access, and increasing donor screening costs would exacerbate this. Regardless of who bears the direct cost of screening (bank, clinic, or recipient), adding ECS will increase the indirect cost by shrinking the donor pool.

Current autosomal recessive screening paradigms target low-prevalence conditions, and the investigators argue that, for consistency, screening donors for autosomal dominant (AD) conditions should follow. The investigators note that such screening could clarify the risk of a potential donor given that the late onset or incomplete penetrance of some AD diseases can make donor status unknown at the time of gamete donation. They challenge the logic of testing to avoid an illness that confers a 25% probability of transmission, despite avoiding screening for illnesses that confer a 50% chance of transmission. The investigators acknowledge that this would further complicate the screening process, add cost, increase anxiety, and potentially impede a donor's ability to acquire life, health, or disability insurance, but at least it would be consistent with requiring screening for recessive illnesses. However, neither ACOG nor ASRM endorse routine AD screening.

Knowing one's recessive carrier status is unlikely to impact a donor's self-perception or insurance accessibility, yet introducing AD screening could. Current practice regarding AD testing includes genetic counseling to inform people of the potential consequences of testing positive. Ethical dilemmas surface when balancing a donor's right to refuse learning of their AD test results and a clinician's fiduciary responsibility to prevent potential harm. Although AD testing may be more consistent with current screening approaches, the logistical and ethical complexities would further burden gamete donors and likely dissuade some from completing the process, thus further limiting the donor gamete pool.

It is vital to consider whether the standard for genetic screening should be consistent between those seeking fertility care and the general population. The current standard, as established by ACOG, emphasizes prenatal screening. As ACOG and ASRM deem ECS acceptable, those seeking donor gametes should have equal access to these screening options. From an ethical standpoint, distinctive screening standards for donor recipients are hard to justify; therefore, until a clear reason for screening to be different between groups arises, the standards should remain consistent with the general populace. Nonetheless, the complexities inherent with donor gametes differ from those in the general population. The FDA regulations mandate freezing nonidentified donor sperm, and frozen egg banking is now common. As such, there is an asynchrony in timing between gamete donation and recipient utilization. This necessitates relying on the donor for screening and may be the reason for imposing ECS on donors, an unfortunate artifact of the need to provide recipients with the opportunity for ECS according to ACOG's guidance.

Bayefsky et al. (1) highlight that recipients may opt out of ECS although donors cannot, further underscoring the asymmetries in testing and the disproportionate burden on donors. This discrepancy, the investigators suggest, may arise from recipients' status as paying customers seeking a commodity, the value of which is based solely on the assurance of a healthy offspring. However, the basis of donor selection is likely more complicated. Considered factors may include physical traits, faith, cognitive, and intellectual features, as well as disease potential. As with most difficult decisions, emotion is a common contributor, and donors are unlikely to be viewed as interchangeable. Choices made by consumers

are individual, personal, and driven by a combination of motivations, perceptions, attitudes, and beliefs (5). It is inconsistent for recipients to disregard their own genotype when their donor choice was based solely on this factor. The fact that a donor is being considered in the first place, coupled with a recipient's choice to defer their own testing, may reflect that they are less genetically centric.

Thus, who should be responsible for guiding the shifting expectations concerning donor gamete screening? The authors suggest that market pressures allow both donor banks and recipients to set expectations. It seems less likely that donor banks would encourage increased screening because it would add to their costs and limit donors. This would undermine a bank's ability to provide services and would thus be self-defeating. Testing may stem from gamete recipients striving for the "perfect" donor. However, shrinking the pool of potential donors would limit selection and potentially eliminate characteristics that are more important to them. Hence, it is important to recognize that professional societies, fertility clinics, and providers may be steering this shift. A patient's clinician must provide counsel consistent with guidelines and, in doing so, present the options put forth by ACOG and ASRM. It is often the provider or clinic that assumes the responsibility for compliance with screening; thus, without ECS, they may perceive themselves exposed to the risk of a bad, albeit rare, genetic outcome. It has become common practice for infertility patients to undergo ECS, and this is likely at a higher rate than encountered within the general population. As such, this screening approach may have spilled over into the recipient-donor dyad. Some fertility clinics require patients to sign waivers when they decline ECS, again implying that the motivation for ECS may not arise from donor banks or recipients. Therefore, the asymmetry described by the investigators may stem from the centers providing treatment.

The investigators suggest remediation through government oversight. Although this could lead to a more balanced practice, it seems unlikely, at least within the US. The FDA has refrained from weighing in, and the fragmented nature of the republic makes it almost impossible to imagine a federal fiat at this time given recent rulings by the US Supreme Court. In the unlikely event that such oversight were to occur, it would originate at the state level, potentially adding further inconsistencies to the screening process.

With greater demands for donor gametes, it is important to navigate expectations and maintain a reasoned approach to genetic screening. Arguments for either increased genetic screening or maintaining a minimal baseline can be made. It is important to weigh these in accordance with the standards that are followed for the general population. Until we decide that ECS should be the universal standard, counseling regarding genetic screening should remain in line with the currently established standards. Although both recipients and donor banks may play a role in the changing perceptions and expectations of donor screening, fertility providers are key in guiding patients through the donor gamete decision-making process. At times of such resource scarcity, there is a need for better counseling of those requiring donors, a greater appreciation for those providing a valuable gift, and less reliance on tests to manage the hopes and expectations of those involved. Bayefsky et al. (1) have provided us with an important message to consider.

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