Polygenic Embryo Screening: Four Clinical Considerations Warrant Further Attention

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Abstract: Recent advances in developing polygenic scores have made it possible to screen embryos for common, complex conditions and traits. Polygenic embryo screening (PES) is currently offered commercially, and though there has been much recent media and academic coverage, reproductive specialists' points of view have not yet been prominent in these discussions. We convened a roundtable of multidisciplinary experts, including reproductive specialists to discuss PES and its implications. In this Opinion, we describe four clinically relevant issues associated with the use of PES that have not yet been discussed in the literature and warrant consideration.

Key Words: polygenic risk scores, PRS, polygenic embryo screening, trait screening

Opinion

Recent advances in developing polygenic scores for complex conditions and traits have made it possible to test embryos for risk of common conditions, such as diabetes, cancers, and psychiatric disorders, among others, as well as for traits like height and IQ. Polygenic embryo screening (PES) is currently offered commercially, and its recent emergence has generated wide media coverage,[1–5] as well as a number of papers assessing its potential utility.[6–9] Several researchers, including ourselves (GLM, SP, SC, TL), have explored the ethically relevant aspects of this new technology, such as the limited applicability of PES for those of non-European ancestry; the additional cost burden of using *in vitro* fertilization (IVF) and PES; the potentially misleading manner in which polygenic risk information may be presented (i.e., relative vs. absolute risk reduction; see below); and the ability to screen for multiple conditions and traits at the same time, which may include problematic phenotypes such as stigmatized disorders, desirable traits, and conditions for which lifestyle adjustments could meaningfully reduce risk.[10–14] These aspects of PES raise salient ethical questions. Should there be oversight as to which conditions and traits are included in these tests and, if so, by whom? What degree of uncertainty in test results is acceptable? Will the use of PES primarily by those with means to do so and those for whom polygenic risk scores (PRS) are more accurate (typically those of European ancestry) further exacerbate existing inequalities? How do we as a society decide what it means to be born

healthy? Could PES lead to further discrimination against those with stigmatized conditions? While we do not directly address these ethical issues in this piece, we want to emphasize the importance of continuing discussions on these topics.

Surprisingly, reproductive endocrinologists and infertility specialists (REIs), who would potentially be those offering and managing PES in the clinical setting, have largely not yet been involved in these discussions. Consequently, we held a roundtable to bring together REIs, ethicists, social scientists, lawyers, geneticists, and genetic counselors to discuss PES. Perceptions of PES varied considerably amongst roundtable participants. In fact, at least one roundtable participant felt that PES is not currently ethically or morally acceptable, and some questioned whether discussion of clinical challenges of PES was premature given concerns about its current utility and ethical permissibility. However, as PES is already commercially available, clinical considerations may add substantively to ongoing discussions about PES.

The following does not represent a consensus opinion, but rather identifies four clinically relevant, non-mutually exclusive issues our multidisciplinary group identified that have not yet been discussed in the literature and warrant consideration: 1) the expansion of who seeks assisted reproductive technology (ART) services and the downstream consequences of that expansion for clinical practice as well as society; 2) REIs offering or acceding to patient requests for PES despite their skepticism of whether there is sufficient evidence to support its clinical use; 3) predicted disagreements between REIs and intended parents about how to use PES, which could lead to friction in the clinician-patient relationship; and 4) offering PES may necessitate changes in REIs' practices.

The first clinically relevant consideration our roundtable identified is that PES may lead to a significant change in who seeks ART services. Currently, IVF is typically used by infertile individuals or couples, those who wish to prevent risk of monogenic disease (via preimplantation genetic testing; PGT-M), and those who need to use IVF to have a child for another reason (e.g., same-sex couples, those who have used fertility preservation techniques, etc.). The use of PGT has been increasing in both the US and Europe, though it still accounts for a minority of all IVF procedures.[15–17] Given the recent emergence of PES, there is now the potential for individuals or couples who would not otherwise have used IVF to seek it out in order to utilize PES. Our roundtable explored a number of motivations for PES that could lead to potential new ART patients.

Some intended parents may be persuaded by the commercial marketing and discourse that frames the choice to use PES as an informed and responsible approach to reproduction.[2,18–20] Others' interest, however, may be driven by recent evidence supporting potential large relative risk reductions that could be achieved by PES across multiple diseases.[7] Like those using PGT-M to prevent risk of monogenic conditions, PES would allow those with a history of polygenic conditions to screen and transfer embryos with lower risk for those conditions (e.g., Crohn's disease, type 1 diabetes, schizophrenia).[14] These parents may see PES as a valuable opportunity to give their future child the best possible chances of avoiding some health conditions, even while recognizing the potential limitations and the fact that absolute risk reductions are modest at best.[10,14]

If the availability of PES does lead to new users of IVF, there may be downstream consequences for both clinical practice and society. For example, widespread adoption of PES could significantly increase the number of viable embryos created and ultimately not transferred for implantation. Though the issue of non-transferred embryos is not new in reproductive medicine, it could become more complicated when there are significantly more unused embryos, and information about those embryos' risk of polygenic conditions is available. Could these embryos be viewed as inferior in some way? Could the children subsequently born from them face stigmatization or discrimination (e.g., by insurance companies) related to their identified higher risk of polygenic conditions? On the other hand, might PES create a market for leftover embryos considered to have desirable polygenic scores?[21]

Increased use of IVF would also put patients at additional risk and add burden to clinics. IVF is not entirely risk-free,[22–24] and thus, those opting for IVF to use PES would open themselves up to these additional risks. Decisions about whether to use IVF solely to use PES should weigh the risks of IVF to the mother and child, including risks of prematurity, multiple births, birth defects, cardiac defects, and pregnancy complications, against the potential benefits of PES. Roundtable participants agreed that REIs may find themselves facing these difficult decisions as they counsel intended parents about their choices unless additional professional policies or practice guidelines can help them anticipate and manage these challenges. In addition, a PES IVF cycle generally requires pretest genetic counseling, intracytoplasmic sperm injection, embryo biopsy, sample shipping, embryo freezing, posttest counseling, and frozen embryo transfer, and thus, additional needs for

staffing, training, equipment, space, and time in the clinic. Moreover, some intended parents may choose to undergo multiple cycles to get their desired embryo(s), adding further burden.

The second clinically relevant consideration is that REIs may offer or accede to patient requests for PES before they believe there is robust evidence to support routine clinical use. Our roundtable identified several reasons why REIs may choose to offer PES. First, as some of the companies marketing PES commercially use a patient-initiated, clinician-ordered model for their products, patient demand may lead some clinics to begin offering PES; even REIs who may have otherwise not chosen to offer PES may feel competitive pressure to do so, as PES becomes more widely known. Second, some REIs may choose to offer PES now despite their skepticism of its current utility because they feel it will eventually become common practice. Third, some REIs may feel that even small reductions in risk of polygenic conditions may be worth the effort and risk, and thus view offering PES as part of their responsibility to help their patients have the "healthiest" baby they can. Fourth, as observed elsewhere in the uptake of newborn genomic sequencing,[25] the technological imperative—the drive to use novel technologies merely because they are new and viewed as improvements over previously available techniques—can be a powerful driver of technology adoption.[26,27] Finally, if PES does become more commonly offered and used, it is possible that even the most skeptical of REIs may feel obligated to make PES available to their patients to avoid potential future liability for not offering this additional risk screening. These varied motivations predicted by our roundtable contributors portend a future in which there is great variation in where and how PES is offered, especially in the absence of formal guidelines or consensus recommendations.

The third clinically relevant consideration is that REIs and intended parents may disagree about how to use PES, which could lead to friction in the clinician-patient relationship. PES is expected to be effective for conditions with highly powered genome-wide association studies (GWAS). Yet, these conditions may not be the same for which parents may wish to screen their embryos. For example, many parents may be interested in screening their embryos for risk for autism, but PRS for autism have demonstrated limited power (in terms of variance accounted for) to date,[28] and do not take into account rare genetic variants, which play an important role in autism susceptibility.[29] Indeed, the available GWAS data may not even align with what parents may think of as being "healthy," and what counts as a healthy baby may vary between parents, as well as across

cultures. PES may lead to disagreements between REIs and parents as to which embryo is “healthiest” based on all the available information. For instance, REIs may wish to prioritize embryos for transfer based on morphology, while parents may be more concerned about risks of certain polygenic conditions. Parents may conceptualize risk differently than REIs, driven by their perceptions of polygenic conditions and other salient context (e.g., family history).[30] Parents may also want to select for traits, such as height or IQ, a strategy with which many REIs may disagree. Furthermore, some clinicians may determine that the risks of using IVF solely to use PES outweigh the benefit of PES, which may prompt them to refuse to provide these services to fertile intended parents due to the clinician’s professional obligation to provide a balanced evidence-based approach that minimizes overall harm to the patient.

The fourth clinically relevant consideration is that offering PES may necessitate changes in REIs’ practices. Though the companies offering PES typically also offer some counseling, patients will likely expect their REIs to help them understand and make decisions about the results of PES. This could lead to changes in how REIs counsel their patients. Counseling patients on PES results should carefully balance known risks and costs of IVF with potential benefit to potential offspring, which will take considerable clinical time, a precious resource given rapidly expanding demand for these services. Our roundtable was particularly concerned about how PES results could be adequately communicated to patients. As others have noted, it is important that PES results emphasize absolute risk reduction vs. relative risk reduction[10] to help parents put this information into context. For example, we (SC, TL, OZ) previously estimated that the relative risk reduction to be achieved by using PES for schizophrenia is nearly 50%.[14] However, this translates to absolute risk reduction of, at most, 0.5 percentage points. Though some groups of clinicians, such as genetic counselors, specialize in the communication of complex genetic risk related information, there are well documented concerns about the inadequacy of the size of this workforce; these concerns would only be exacerbated by the potential increase in demand that could be associated with widespread use of PES.[31] Given this and the societal reality of low numeracy,[32] REIs may face challenges explaining PES results effectively and efficiently.

The four clinical considerations we have raised may additionally challenge the current balance between professional medical judgement and patient preferences. Reproductive medicine has typically, within reason, prioritized patient preferences out of respect for reproductive autonomy. The advent of PES, especially in the

absence of professional guidelines and robust evidence to support its routine clinical use, may cause some REIs to rethink that balance. Given that reproductive autonomy is a core value in reproductive medicine, as well as within our larger social context, any change to this balance may be particularly fraught.

These issues, alongside other important ethical concerns raised by us and others elsewhere,[10,11] highlight the critical need to bring more people together to discuss PES and its potential implications. Indeed, this piece may have only uncovered a subset of the challenges PES may generate. Our roundtable of a group of multidisciplinary experts is a valuable first step in this goal. Because PES goes to the core of how we, as a society, define health and disease even before birth, we need ongoing discourse across disciplines and social roles. This discourse should include a wide range of REIs, as well as additional voices such as other clinicians, intended parents, patient advocates, bioethicists, geneticists, genetic counselors, policy makers, and industry representatives.

Data Availability

There are no new data reported in this manuscript.

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Authors' Roles

SP, SC, GLM, and TL led the conception, development, and oversight of the work and agree to be accountable for all aspects of the work. GA, JA, DB, AH, EJ, KK, EK, RBL, MM, IVdV, and OZ made substantial contributions to the conception of the work, revised the work critically for intellectual content, gave final approval for the work, and agree to be accountable for all aspects of the work.

Conflict of Interest

SC reports consulting fees from MyHeritage, a direct-to-consumer DNA testing company, which also offers polygenic risk scores. The company does not work on preimplantation genetic testing and was not involved in the development of this manuscript in any way. The remaining authors declare no conflicts of interest.

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