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The Case for Remedial Germline Editing—The Long-term View

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We conclude that so long as heritable genome editing interventions are consistent with the welfare of the future person and with social justice and solidarity, they do not contravene any categorical moral prohibition.


Heritable monogenic diseases—each the byproduct of a variation in a single gene that is present at birth—comprise more than 10,000 distinct human diseases and affect millions of people worldwide. Some of the more common monogenic diseases include cystic fibrosis, Tay-Sachs disease, and sickle cell anemia, although the majority of single-gene disorders are rare. Researchers have calculated the total global prevalence of all monogenic disorders at birth to be several percent. Although some monogenic disorders can be managed, particularly if detected early, many give rise to lifelong morbidity and can shorten life span. Reducing, if not eliminating, the global burden of genetic disease remains a distant goal at this time.

Two technologies under consideration to tackle this challenge are preimplantation genetic diagnosis (PGD) and remedial germline editing (RGE). Preimplantation genetic diagnosis is an established diagnostic technique, widely deployed today to identify a genetic defect in embryos created through in vitro fertilization, with the goal of transferring only embryos lacking the defect to the mother’s uterus. Remedial germline editing is a novel therapeutic paradigm that has has yet to be applied in the clinic to correct a heritable deleterious mutation in a fertilized egg. We predict that, in time, safe and efficacious RGE will eclipse PGD, the relative shortcomings of which are becoming increasingly apparent.

Although both approaches rely on in vitro fertilization, they have striking differences, and understanding such differences is important for policy makers and agencies that prioritize and fund research and approve clinical applications.

Limitations of Preimplantation Genetic Diagnosis

When 1 or both prospective parents have a known genetic abnormality that could cause a monogenic disorder in their offspring, PGD allows identification of unaffected embryos for uterine transfer. This means that the technique, by its nature, leads to only a subset of the embryos being eligible for transfer. Concurrent advanced maternal age also may contribute to a smaller complement of transferable embryos because of a decline in the quantity and quality of eggs that occurs with aging. As a result, PGD cycles are routinely associated with a limited complement of transferable embryos and low birth rates. This reality was recently driven home by a series of 2000 PGD cycles with a birth rate markedly reduced compared with the rate for couples who underwent in vitro fertilization for infertility alone (18% vs 38%). In addition, in a highly unusual set of cases, a considerably worse birth rate (2.6%) was noted for a total of 38 PGD cycles in 7 couples hoping to conceive a “savior sibling” to be an immunologically compatible stem cell donor to treat an older sibling with Fanconi anemia. Given the modest birth rate associated with PGD, couples at risk for heritable disorders must be prepared to undergo multiple cycles in the hope of securing a successful outcome.

With such a high level of uncertainty regarding success, along with the high costs, inevitable discomfort, and mental anguish associated with PGD, it is unsurprising that the idea of developing a safe and effective approach to RGE is compelling. Recent calls to ban RGE on the grounds that PGD provides an alternative fail to consider PGD’s significant shortfalls.

Genome Editing Challenges

It is the goal of RGE to correct gene mutations in embryos at the time of fertilization. Preclinical research to eliminate unintended genomic alterations in edited human embryos is ongoing, as are efforts to minimize embryonic mosaicism (a mix of edited and unedited cells in an embryo).
Several recent advances offer encouragement that such genome editing challenges will be overcome. Studies in human embryos aimed at mending a monogenic mutation that causes familial hypertrophic cardiomyopathy proved highly promising. Another recent advance is the development of a powerful and precise “prime editing” tool, which enables targeted genomic insertions and deletions without generating a double-strand DNA break (as occurs with the widely used CRISPR-Cas9 gene editing technique).

Assuming these and future innovations succeed in achieving precise genomic alterations, and clinical applications using the approach pass muster by the US Food and Drug Administration (FDA), the case for RGE is compelling. First, unlike PGD, RGE increases the number of embryos available for transfer because it is applied at the time of fertilization to all available embryos, mutant and intact alike. Remedial germline editing also can be used when PGD is not feasible in cases when all embryos are inevitably affected, such as when 1 parent has 2 copies of a dominant mutation or when both parents have 2 copies of a recessive mutation.

In addition, unlike PGD, RGE not only corrects a gene mutation in a fertilized egg, the corrected gene would be inherited by the next and future generations. Remedial germline editing is thus positioned to break long-standing chains of heritable monogenic disease. (And given the high stakes involved, any such intervention must not be permitted absent the FDA’s full concurrence). Unlike PGD, a safe and efficacious RGE avoids the ethical and sectarian concerns related to discarding embryos found to have heritable genetic defects. These attributes render RGE uniquely suited to the task of tackling the constellation of monogenic afflictions.

Two prominent international panels are grappling with this very issue. The final reports of the International Commission on the Clinical Use of Human Germline Genome Editing and the World Health Organization’s Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing are due later this year.

The panels would do well to recognize the potential substantial advantages of RGE over PGD, and that the 2 techniques are mutually exclusive. They cannot be sequentially applied to maximize the number of transferable embryos because RGE is applied at the time of fertilization and it is ill-suited to correct genetic defects identified by PGD in day 5 blastocysts. Given PGD’s unavoidable limitations, future efforts at curtailing heritable monogenic disorders would do well to prioritize safe and effective RGE.

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