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OPINION

Ethical considerations of preconception and prenatal gene modification in the embryo and fetus

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ABSTRACT: The National Academies of Sciences and Medicine 2020 consensus statement advocates the reinstatement of research in preconception heritable human genome editing (HHGE), despite the ethical concerns that have been voiced about interventions in the germline, and outlines criteria for its eventual clinical application to address monogenic disorders. However, the statement does not give adequate consideration to alternative technologies. Importantly, it omits comparison to fetal gene therapy (FGT), which involves gene modification applied prenatally to the developing fetus and which is better researched and less ethically contentious. While both technologies are applicable to the same monogenic diseases causing significant prenatal or early childhood morbidity, the benefits and risks of HHGE are distinct from FGT though there are important overlaps. FGT has the current advantage of a wealth of robust preclinical data, while HHGE is nascent technology and its feasibility for specific diseases still requires scientific proof. The ethical concerns surrounding each are unique and deserving of further discussion, as there are compelling arguments supporting research and eventual clinical translation of both technologies. In this Opinion, we consider HHGE and FGT through technical and ethical lenses, applying common ethical principles to provide a sense of their feasibility and acceptability. Currently, FGT is in a more advanced position for clinical translation and may be less ethically contentious than HHGE, so it deserves to be considered as an alternative therapy in further discussions on HHGE implementation.

Key words: human heritable genome editing / fetal gene therapy / gene modification / ethical lens / ethical principles / National Academies of Sciences and Medicine 2020 consensus statement

Introduction

Gene modifying technologies (GMTs), encompassing gene addition and gene editing (GE) strategies, facilitate treatment in numerous monogenic disorders, ranging from perinatally-lethal diseases (e.g. α-thalassemia major (ATM), primary immunodeficiencies) to major debilitating conditions (spinal muscular atrophy (SMA), cystic fibrosis (CF)) affecting large populations globally (Piel, 2016; Ernst *et al.*, 2020; Guggino and Cebotaru, 2020). As most genetic diseases manifest during childhood, early prevention is required to reduce poor health outcomes (Scheuner *et al.*, 2004; O'Connell *et al.*, 2020). CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) is a GMT poised to make substantial impact in perinatal medicine by making prenatal correction of pathogenic mutations a technical possibility. With heritable human genome editing (HHGE), which applies CRISPR/Cas9 tools to the human embryo (or gametes), the intention is to ensure healthy, disease-free genetically-related offspring without the ability to transmit mutations to their progeny (Rossant, 2018). Additionally, HHGE may be the only option for couples at risk of Y-chromosome microdeletions, or autosomal genetic disorders where one or both parents are homozygous for dominant or recessive alleles.

The National Academies of Sciences and Medicine (NASEM) 2020 consensus statement ('the Report') advocates the reinstatement of

research in HHGE and suggests an *inevitability* of HHGE implementation as a potential future strategy within the confines of a narrow set of criteria for clinical application (The_Royal_Society *et al.*, 2020). The Report is likely to become an authoritative source of information for scientists and physicians involved in research policy development and eventual counseling of prospective parents on possible GMT options for hereditary diseases. However, it critically omits discussion of alternative technologies such as potential prenatal interventions to mitigate pathological effects of genetic diseases in existing or future children. Published following the birth of 'CRISPR babies' Lulu and Nana (Begley, 2018; Doxzen and Halpern, 2020), the Report states that, at this stage, only carrier parents of monogenic diseases caused by well-characterized mutations with high penetrance and serious morbidity should be considered for the research application of HHGE. The Report lists specific conditions in its Category A (CF, sickle cell disease, β-thalassemia major) and in a small subset of its Category B (e.g. Huntington's disease). Although the Report provides a robust comparison of HHGE and certain postnatal somatic GE strategies, it does not consider alternative perinatal therapies which have already been applied to Category A candidate diseases in research settings, the importance of which is acknowledged in the World Health Organization Position Paper on human genome editing (World_Health_Organization, 2021), which did not compare the two strategies.

In this Opinion, we discuss HHGE in relation to prenatal GMT viewed through ethical and technological lenses. For our purposes, HHGE refers to application of the CRISPR-Cas9 system to certain germline cells. Though it can be applied to spermatogonial stem cells, oocytes matured *in vitro* or gametes derived from induced pluripotent stem cells (Vassena *et al.*, 2016; Plaza Reyes and Lanner, 2017), we will confine our discussion to HHGE in the embryo.

Alternatives to HHGE for correcting genetic disease in early development

Monogenic disorders can be addressed at one of three stages (Fig. 1): preconceptionally, to produce disease-free offspring; prenatally, to mitigate intrauterine pathogenesis; postnatally, in early infancy before major morbidity or lethality manifests (Traeger-Synodinos, 2013; O'Connell *et al.*, 2020). Established clinical methods to address monogenic disease preconceptionally include carrier screening in at-risk populations, and personalized ART, such as preimplantation genetic testing for monogenic diseases (PGT-M) with embryo selection following IVF (Goodeve, 2008; Su *et al.*, 2011; Barrett *et al.*, 2017). Genomic interventions have become steadily ingrained in reproductive services, as expected pregnancy outcomes include disease-free offspring in addition to live births. PGT-M requires at least one IVF cycle, trophectoderm biopsy and genotyping to ensure that only mutation-free embryos are transferred (Ben-Nagi *et al.*, 2019). This is useful for at-risk carrier couples willing to undergo a lengthy medical process, and accepting the possibility that they may ultimately not have an embryo suitable for transfer. Prenatal strategies include invasive genetic diagnosis with selective pregnancy termination before the legal gestational limit. Postnatal interventions range from palliative (e.g. enzyme replacement therapy) to potentially curative (e.g. gene addition therapy) (Mukherjee and Thrasher, 2013; Mendell *et al.*, 2021; Sun and Roy, 2021).

Prenatal technologies employ GMTs to target the developing human before birth, when it is possible to correct gene mutations before pathogenesis commences. Prenatal fetal gene therapy (FGT), which like HHGE has yet to be translated clinically, provides a viable option for curing Category A candidate disorders (Nishida *et al.*, 2015; Dighe *et al.*, 2018; Shangaris *et al.*, 2019; Cortabarria *et al.*, 2020). FGT involves delivering transgenes encoding the correct version of aberrant disease-causing genes to somatic cells (Mattar *et al.*, 2012; Peranteau and Flake, 2020), potentially reducing disease burden, supported by robust years-long evidence of successful correction, safety and longitudinal surveillance in non-human mammalian recipients (Mattar *et al.*, 2012; O'Connell *et al.*, 2020). Proof-of-cure and safety have been demonstrated in high-fidelity animal models of blood disorders, neurometabolic diseases and SMA, especially when compared with postnatal therapies (Abi-Nader *et al.*, 2012; Mattar *et al.*, 2012; Roybal *et al.*, 2012). The International Fetal Transplantation and Immunology Society (iFeTIS) published consensus statements in support of fetal stem cell transplantation (SCT) and gene therapy, as the main advantage is the higher therapeutic efficacy compared with postnatal intervention (MacKenzie *et al.*, 2015; Almeida-Porada *et al.*, 2019). FGT can be considered for its unique benefits over postnatal somatic GMT, including reduced immune-toxicity and access to immune-privileged organs like the central nervous system (Mattar *et al.*, 2012; Massaro *et al.*, 2018; Almeida-Porada *et al.*, 2019; Peranteau and Flake, 2020). The distinct advantage of early intervention is recognized in clinical gene therapy trials of severe combined immunodeficiency syndrome (SCID) and SMA (Thrasher *et al.*, 2005; Waldrop *et al.*, 2020; Houghton and Booth, 2021; Sun and Roy, 2021), and illustrated in recent clinical trials of early-onset severe monogenic diseases actively recruiting very young children (Supplementary Table SI). We will limit our discussion to a comparison of HHGE and FGT, particularly focusing on the ethical controversies accompanying their application in clinical research. HHGE and FGT share scientific methods, and when the technology is available, either intervention may be applied to an appropriate disease candidate. HHGE and FGT permit intervention early in development before a disease manifests, primarily because of the advantageous temporal factors enhancing the likelihood of therapeutic success (Fig. 2). Those involved in clinical research will need to determine which intervention is more ethically acceptable. Likewise, policy-makers and research funders must decide which technology to support.

Principle of proportionality in HHGE and FGT

One of the most important questions to answer is if potential clinical benefits afforded by these technologies are commensurate with the effort and resources invested, particularly if healthcare is publicly funded. Invoking a proportionality principle, emphasizing appropriateness and non-excessiveness, may aid in assigning priority to one technology over the other. The proportionality principle assures patients and other stakeholders that no more harm is borne than necessary, and that benefits outweigh risks and burdens (Hermerén, 2012). Applying proportionate actions toward curing devastating genetic diseases means selecting the least-risky option that can achieve the intended

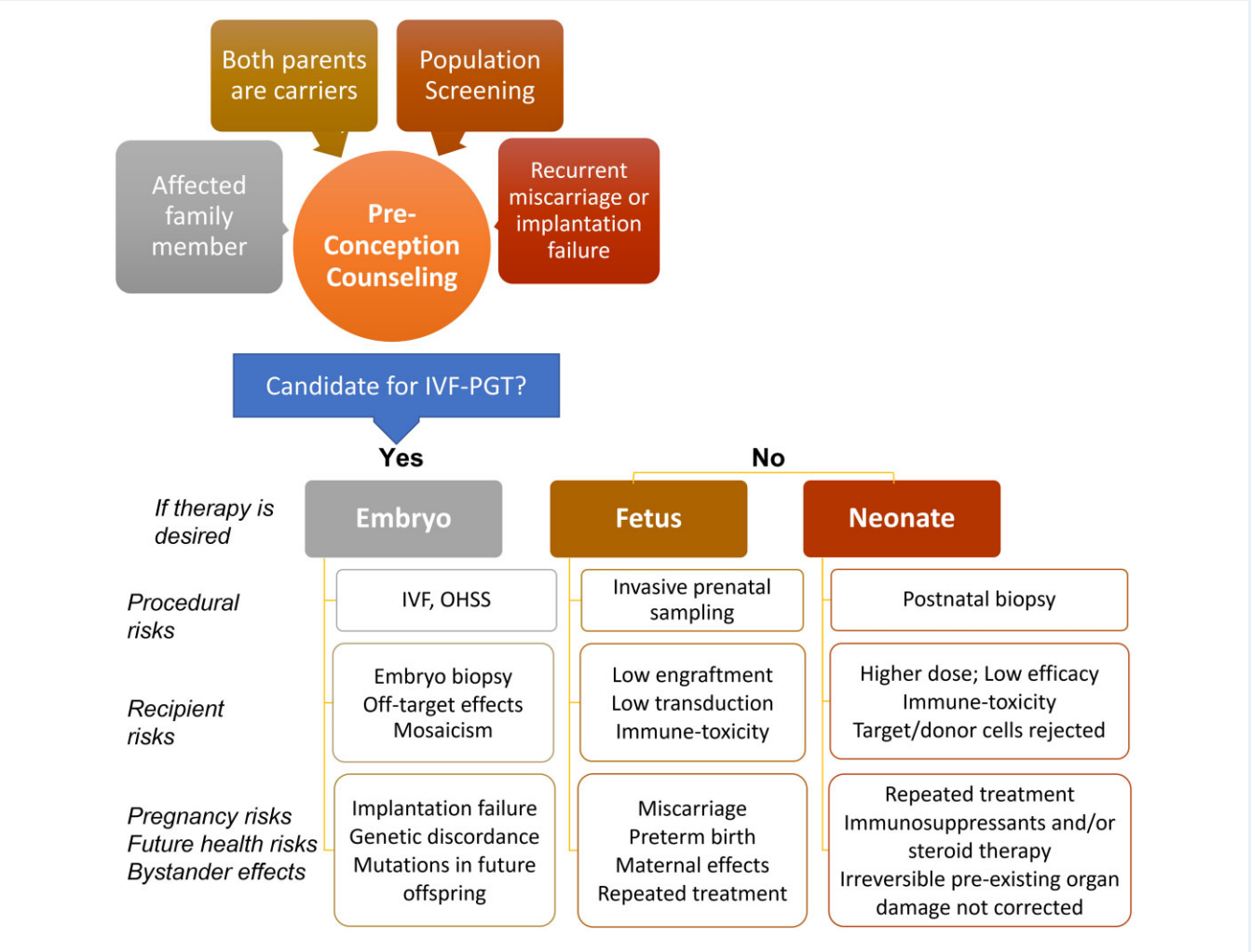

Figure 1. Proposed workflow to counsel a couple known to be at risk of having a baby with a genetic disease toward heritable human genome editing and/or perinatal gene therapy. Ideally, couples complete genetic screening prior to conception to assess carrier status, discuss risk of inheritance with the clinical geneticist, and determine the suitabilty and value of IVF, preimplantation genetic diagnosis and embryo gene editing. Prenatal diagnosis is presented as an alternative option followed by fetal or neonatal therapy. Risks of individual treatments are presented in the schema. OHSS, ovarian hyperstimulation syndrome; PGT, pre-implantation genetic testing.

therapeutic effects, while not excessively consuming finite resources. Such risks should be understood on societal and individual levels.

A key difference between HHGE and FGT is that only the former intentionally modifies the human germline. Even if there is no guarantee that future progeny's gametes will carry the corrected genetic sequences (Mehravar *et al.*, 2019), germline transmission following HHGE would be absent only if mosaicism, where some embryonic cells remain uncorrected, results in unedited germline cells. Germline transmission may affect an unknown number of future generations in ways not yet anticipated. Precisely because of this, some have called for a moratorium on editing the human germline, pending widespread societal consensus on the appropriateness of applying this technology to a particular condition (Baylis, 2017; Lander *et al.*, 2019). On one hand, concerns over detrimental effects may be directed at the risks to future generations. On the other, there is a present concern that if the human genome is the 'common heritage of humanity' (Primc, 2020), alterations to this heritage should be undertaken only if there is global agreement on the permissibility of such actions. Meanwhile, FGT carries a small probability of germline transmission, estimated at ~1 in 6250 in animal models (Kazazian, 1999; Almeida-Porada *et al.*, 2019), which may be further mitigated by vector engineering for specific-cell targeting and gene-editing. So, while both HHGE and FGT treat disease-causing mutations before birth, HHGE aims to permanently eliminate genetic mutations from the familial lineage thus relieving future generations' risk of the same hereditary condition (Ishii, 2017; Rossant, 2018; He *et al.*, 2020).

Proportionality analysis also requires individualized benefit-risk assessment directed at the mother-to-be and future child. It is worth noting that ~25% of PGT-M cycles neither produce unaffected embryos nor yield healthy completed pregnancies (Gutiérrez-Mateo *et al.*,

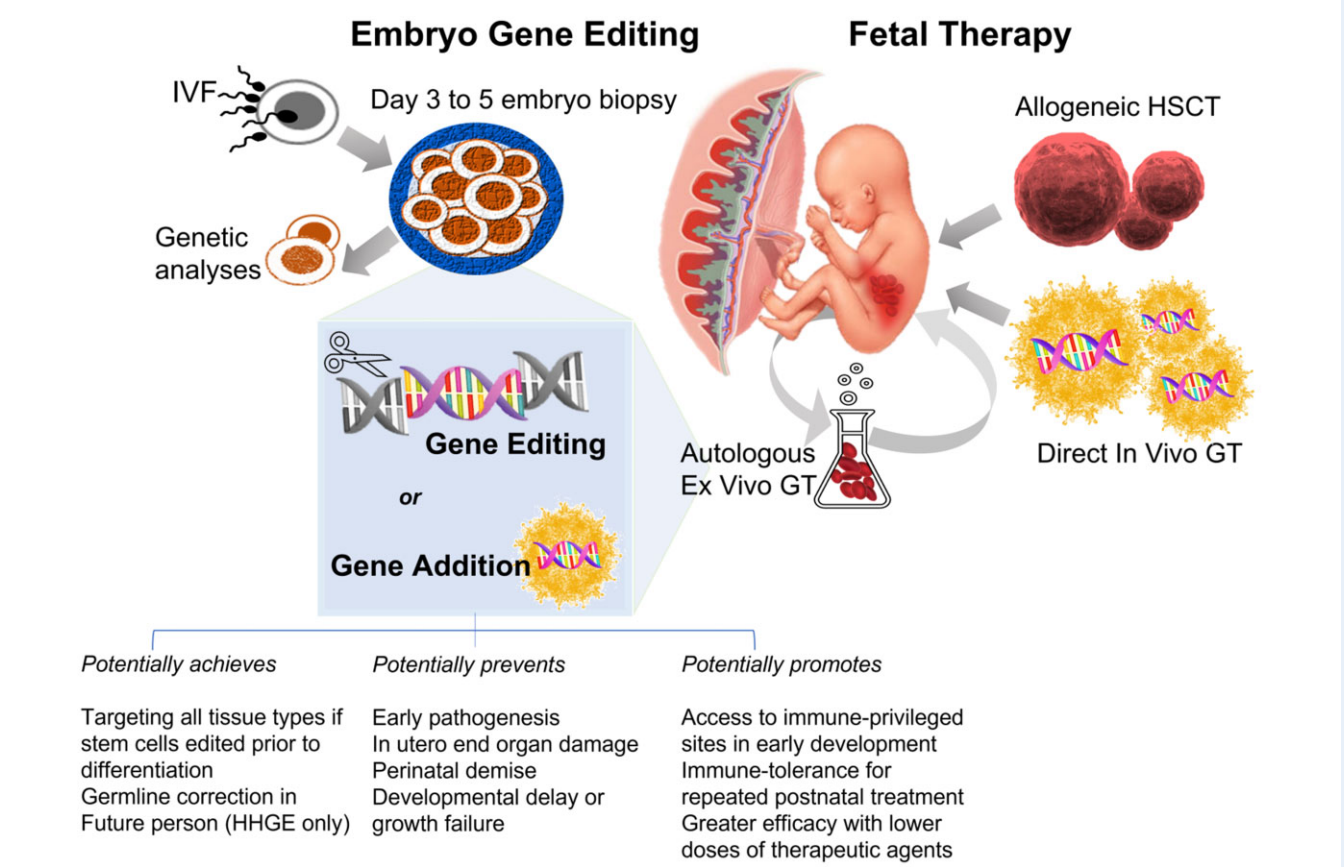

Figure 2. Strategies to achieve genetic modification in the embryo by *ex vivo* gene editing or gene addition therapy. The authors propose that embryo gene editing may be achieved *in vitro* following confirmation of the genetic mutation by embryo biopsy (currently performed on Day 3 to Day 5 embryos). Alternative strategies in the fetus include direct *in vivo* gene addition therapy via injection of viral vectors carrying the necessary transgenes, *ex vivo* gene editing or gene addition therapy of autologous HSC harvested from the fetus, or transplantation of allogenic hemopoetic stem cells from a non-affected donor. Embryo gene editing can potentially achieve germline correction in future generations, while pre- or post-conception gene editing or addition may achieve efficient correction of multiple tissue types (by correcting stem cells), resulting in reversal or arrest of early pathogenesis, acquisition of immune tolerance and avoidance of perinatal demise. GT, gene therapy; HHGE, heritable human genome editing; HSCT, hemopoetic stem cell transplantation.

2009). In fact, academic physicians have recently debated if GE should replace embryo selection following PGT (Wells *et al.*, 2019), particularly advantageous for situations in which the few implantable embryos produced by IVF *all* carry the disease mutation. HHGE may produce mutation-free embryos, saving time and cost particularly for women with reduced ovarian reserve who are less likely to produce good-quality embryos, the primary factor affecting cumulative live-birth rates (Niinimäki *et al.*, 2015; Zhao *et al.*, 2020). Certainly, a policy of PGT-M and HHGE may reduce embryo wastage and the need for multiple IVF cycles. As HHGE is dependent on IVF-PGT-M, several courses of follicular stimulation may be required to produce sufficient embryos, risking maternal morbidity from ovarian hyperstimulation and invasive procedures (Zhao *et al.*, 2020). Embryo damage from delivery of CRISPR-Cas9 editing tools can cause physical harm to the embryo and unpredictable molecular perturbations (Sato *et al.*, 2016; Le *et al.*, 2021), risks also carried by IVF-PGT. The impact of these multiple processes on the embryo's ability to implant and develop into a viable fetus is unknown (Ben-Nagi *et al.*, 2019; Aluko *et al.*, 2021).

A clear safety concern of HHGE is mosaicism resulting in unpredictable (perhaps uncorrected) phenotypes. Conversely, undesirable off-target mutations and insertions/deletions may be retained in the embryonic cells designated to become gametes, increasing the likelihood of germline transmission of new mutations to future progeny. Preclinical experiments in human and non-human mammalian embryos demonstrate a wide range of mosaicism, an outcome which can be reduced by applying a high concentration of editing agents as early as possible in the embryonic timeline (Mehravar *et al.*, 2019). This is challenging in clinical practice, given the necessary interval between embryo production by IVF, biopsy, molecular diagnosis and editing. Because of these undesirable molecular effects, implementation of HHGE should be accompanied by prenatal or postnatal genetic diagnosis. It is unclear what other biological impact HHGE will have on the embryo and

subsequent pregnancy, and if manipulation will increase pregnancy loss or complications. Numerous editing steps will cause physiological stress to the embryo and may affect embryo survival and implantation. About 18% of IVF cycles produce only one transferable embryo per cycle. Even among women under 25 years of age, 40% will produce only 1–2 blastocysts per cycle and 50% have three or fewer evaluable blastocysts (Franasiak *et al.*, 2014). Approximately 4.5% of IVF-PGT-M cycles performed for at-risk couples (heterozygous carrier parents with a 25% chance of producing a homozygous recessive embryo) will be candidates for HHGE (Gyngell *et al.*, 2017). This demonstrates the tightly restricted context in which HHGE may be applied (Viotti *et al.*, 2019).

Compared to postnatal gene therapy, advantages of FGT include: greater cellular transduction efficacy, higher potential for phenotypic correction; lower immunogenic toxicity; greater efficacy at penetrating physiological barriers, e.g. blood–brain barrier; and specific organ targeting (Peranteau and Flake, 2020). Most monogenic diseases do not require gene modification at the level of embryonic cells as cellular pathology is often limited to specific organs (Mattar *et al.*, 2012). FGT can achieve targeted delivery of GMT agents, potentially limiting off-target effects. These benefits are appreciated when treating diseases with severe early-onset manifestations, for example ATM, as therapeutic efficacy is significantly better in younger recipients without substantial end-organ damage (Waldrop *et al.*, 2020; Houghton and Booth, 2021). Though clinical GMT trials for β-thalassemia are restricted to children over 5 years of age (Supplementary Table SI), promising outcomes from SMA and SCID trials encourage physicians to consider extending these technologies to at-risk fetuses (Amjad *et al.*, 2020). The long history of invasive fetal therapy demonstrates the relatively low-risk nature of minimally-invasive fetal access for stem cell harvest or transplantation (Moise, 2014; Kreger *et al.*, 2016). FGT carries a 1–2% miscarriage risk per invasive fetal procedure, higher if the fetus is ill at the time of therapy (e.g. hydrops fetalis from ATM). Mosaicism, off-target mutations and low-frequency vector integration into the host genome can arise following FGT (Chan *et al.*, 2019), but in animal models the integration sites were random and avoided disruption of known genes.

Comparing high-expense HHGE and FGT, the calculated risks to maternal health may be appropriate for the potential payload of a disease-free disability-free future child, when the science has advanced to the point at which therapeutic effectiveness and safety have been optimized *in vivo*. A poor outcome would be an incompletely-corrected phenotype, perhaps due to sub-therapeutic transgene expression and incomplete reversal of tissue damage, resulting in a child with significant disability or at risk of off-target effects (e.g. tumorigenesis). In this scenario, the negative outcome is disproportionate to the high cost of treatment. As spontaneous pregnancy failure affects 10–30% of IVF-PGT-M cycles (Ben-Nagi *et al.*, 2019), a negative outcome is perceivable despite the resources invested into HHGE. Stakeholders, including policy-makers and funders, must use available evidence to decide if the known and unknown risks are proportionate to the gains to prospective parents, the future child, future generations, and society at large. Focusing on the main aim of curing disease should not distract from the reality of finite resources and the need for judicious allocation to benefit at-risk communities (Fins and Miller, 2020).

The maternal–fetal conflict

HHGE and FGT are experimental procedures directly benefiting the unborn child, and offer no direct clinical benefit to the prospective mother. HHGE does not place the mother at risk of bystander effects as all genetic manipulation is completed *in vitro* and imposes no surgical risks to the mother other than those associated with IVF. Maternal autonomy could still be affected by concerns about the outcome of the intervention and adverse effects on the child. As caregiver burdens remain unequally distributed and delegated to women, the choice of HHGE may be affected by such considerations. In comparison, FGT may result in adverse maternal bystander effects, some of which cannot be quantified such as the remote effects (tissue transduction, integration mutagenesis) of transplacental trafficking of gene therapy vectors, though maternal risks from invasive procedures used to deliver gene therapy agents are minimal (Almeida-Porada *et al.*, 2019; Sagar *et al.*, 2020). With the focus on the health of the unborn child, maternal risks and desires may be easily overlooked. Ethical regulations typically only require the mother to consent to any experimental fetal procedure, though other regulations require both parents to grant permission for participation in studies which offer the prospect of direct benefit solely to the fetus (Johns_Hopkins_Medicine, 2005). If only the mother's consent is required, treatment can proceed even in the presence of conflicting views between the mother and her partner. Conversely, maternal autonomy overrides fetal beneficence and the mother always retains the right to refuse treatment. This may not prevent situations in which a physician's desire to act in the best interest of the fetus may lead to conflicted situations in which the mother feels coerced into consenting to intervention, or experiences guilt for not 'sacrificing' herself for her baby, which carry ethical or legal ramifications particularly if the mother then withdraws consent for fetal intervention (Rodrigues *et al.*, 2013; Briscoe *et al.*, 2016).

While a preimplantation embryo does not meet the criteria of a 'patient', alterations to the embryo should still be consistent with the well-being of the future child (Nuffield Council on Bioethics, 2018). A physician–maternal conflict may arise if the embryo carries a persistent genetic mutation post-HHGE and the parents nevertheless request embryo transfer. Transfer of these embryos may violate the ethics of non-maleficence (to the future child) and duty of care (to the mother) to transfer disease-free embryos (Pennings *et al.*, 2007; Ethics_Committee_of_the_American_Society_for_Reproductive_Medicine, 2017). Certainly, the physician's obligations to this novel mother-HHGE-treated embryo dyad should be parsed in greater detail through wider ethical debate. One perspective may be that HHGE does not *save lives*, and rather is a 'selective reproductive technology', a means of producing healthy future persons who may not exist otherwise, which is also true of IVF-PGT and embryo selection (Rulli, 2019; Schaefer, 2020). This distinction calls into question which party benefits from the strategy chosen. Here, the prospective parent, rather than GE recipient, by fulfilling a deeply-held desire for healthy genetically-related offspring, is arguably the primary beneficiary of HHGE, yet the future person bears the burden of both desirable and undesirable gene effects. Whereas the moral *obligation* to develop a technology like FGT for the fetus *qua* patient is strong, whether there is a similarly strong moral *obligation* to develop HHGE remains an open debate.

A question of human enhancement

An important debate is the delineation of boundaries between *curing* human disease and human *enhancement*. This is a realistic scenario, given the genetic basis of desirable physical features, and arguments for selecting the best features (Porter, 2017), which can possibly be justified from the population health perspective (Piel, 2016; Schaefer, 2020). HHGE and FGT may be appropriated not just for disease-causing mutations, but to also produce non-disease-related traits matching the future parents' preferences (Segers *et al.*, 2019), sometimes called enhancement. There are serious ethical concerns about enhancing or selecting 'desirable' human qualities (e.g. intelligence) in IVF babies, but this is a very difficult endeavor and is likely to be strictly regulated by ethics committees in transparent and continued discussion with all stakeholders to determine permissibility limits. Both HHGE and FGT offer far more potential benefits that should shift opinion firmly toward supporting research into, and eventual clinical translation of, these technologies.

Lifting barriers to HHGE

Advocates of HHGE or FGT believe that parents have a right to having children free of certain genetic diseases, and understand that the path to this ultimate goal is long and complex, not least because the current barriers, placed with the intention of avoiding harm, may end up impeding any realistic chance of clinical translation. As Hermerén (2012) espoused, employing the safest alternative because of 'knowledge gaps and uncertainties in the wake of new and emerging technologies' may derail innovative research. The Report illustrates a willingness to lift existing barriers to HHGE research, and this is supported by new governance statements from the International Society for Stem Cell Research (ISSCR) supporting categories of research involving extended embryo culture and chimeric embryo development *in vitro*, though not editing of human embryos for reproduction owing to unproven safety and insufficient scientific rationale (Lovell-Badge *et al.*, 2021). Eventually, progressing to clinical HHGE will require further lifting of restrictions, particularly enabling extended embryo culture beyond the current limitation of <14 days (before gastrulation). In the event that all implantable embryos generated by IVF-PGT-M carry the mutation, the best embryos will be subjected to microinjection of editing tools, repeat biopsy to confirm correction and prolonged embryo culture while awaiting molecular analyses. The UK Human Fertilisation and Embryology Authority currently stipulates that *in vitro* embryo culture not exceed 14 days, which limits the number of biopsies that can be conducted in this time (Chan, 2018). Embryos can be cryopreserved during molecular analyses and correctly edited embryos transferred in a future natural cycle (Bourdon *et al.*, 2021). NASEM and ISSCR make an important point that researchers should maintain transparency and open public discourse on ethical, moral and societal limits to guide permissibility of germline editing. We believe that public dialogue on acceptable human germline modifications and the permissibility of influencing future generations' genetic makeup should develop in tandem with a broad consensus on diseases that should be tested for by PGT-M.

If the ethical and technological hurdles to germline modification prove insurmountable, a practical way to achieve HHGE may be to focus on deriving functional gametes from reprogrammed gene-edited stem cells. *In vitro* gametogenesis (IVG) has seen significant progress in derivation of gametes from embryonic and induced pluripotent stem cells in mice (Gupta *et al.*, 2021), but progress in human cells is necessarily restrained by regulations prohibiting formation of embryos following IVG because of unresolved safety issues (Clark *et al.*, 2021). Any progress in this field will require the same stringent ethical oversight and is subject to similar restrictions as current HHGE; research in IVG and HHGE for reproductive purposes is currently prohibited, pending convincing safety and efficacy data (Lovell-Badge *et al.*, 2021).

Can HHGE and FGT co-exist?

It is important to recognize the nuanced difference between HHGE preventing disease but not directly saving lives, and FGT which can potentially save a life where there is a lethal disease (Ishii, 2017; Rulli, 2019). This could influence allocation of research funds (Rulli, 2019). Scientific aims, technical advances and ethical boundaries must be considered in tandem, as the science cannot rightfully advance without the ethics. Similarly, to discuss HHGE in isolation without a balanced comparison to perinatal interventions is to limit appreciation of its role and acceptance of its place in reproductive and perinatal medicine (Fig. 1). For physicians who will counsel prospective parents on GMT, perform personalized ART or monitor treated offspring, an appreciation of these issues will aid in selecting the appropriate application for the specific indication (Critchley *et al.*, 2018). HHGE requires specialized skills for IVF-PGT, which is inherently labor-intensive, costly and resource-heavy, and may not be readily accessible in some at-risk communities; access inequalities should be urgently addressed prior to clinical introduction of HHGE (Pennings *et al.*, 2008). FGT requires skills in fetal blood sampling and intrauterine transfusions, thus we anticipate higher adoption in at-risk communities with access to these specialized fetal services. Substantial progress in fetal surgery (e.g. meningomyelocoele) and intrauterine SCT (for ATM, osteogenesis imperfecta), illustrate the growing regard of the fetus as a distinct entity deserving of the highest duty of care (Williams *et al.*, 2001), and increasing acceptance of fetal interventions to overcome devastating congenital conditions (van Lith *et al.*, 2013; MacKenzie *et al.*, 2015; Sagar *et al.*, 2020). For HHGE to be implemented, rigorous decades-long surveillance is required to study long-term genotoxicity to assess the full intergenerational impact. Protection of the future person's autonomy vis-à-vis collection of personal medical data in the interests of future beneficiaries versus the right to privacy, medical infrastructure and equitable access to healthcare for all affected generations, could drive the costs of HHGE far beyond those of IVF-PGT-M and GE (Pennings *et al.*, 2007, 2008; Howard *et al.*, 2018).

Conclusion

Owing to the rapid flux of scientific advancements in genetic medicine, temporal aspects will influence the benefit-risk ratio of HHGE and FGT. Presently, as a result of the wealth of evidence from animal studies, FGT is in a more advanced position for clinical translation, and less

ethically contentious as it avoids germline targets. HHGE is nascent technology around which the ethical considerations will evolve with time and greater understanding. Evidence on its feasibility is still at a very early stage and the ethics remain controversial. Eventually, HHGE may be in a similar position backed by scientific evidence of editing efficiency, minimal off-target effects and *in vivo* safety, but preferable precisely because of germline modification that allows future generations to inherit the corrected gene and also avoids maternal bystander effects. Thus the balance of favor in the long term may shift from FGT to HHGE, with technical advancements and greater acceptance of germline targeting within specified limits. The Report serves as an invitation to a larger conversation on human GE and concurrent public dialogue on the ethical implications of this technology is imperative. It is conceivable that at-risk parents will be open to HHGE or FGT knowing the medical burden that can be avoided (Wertz *et al.*, 1991). Physicians involved in patient care must remain well-informed of the rapidly-evolving scientific, ethical and legal landscape pertaining to prenatal GMT. Genome modifications made in the best interest of the child must focus on curing disease rather than selecting preferred physical traits—this guiding ethical principle should be honed by the particular community it serves.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

There are no new data associated with this article.

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Authors' roles

C.N.Z.M. co-developed the argument, performed the literature search, took the lead role in writing the paper and designed the figures and table. M.K.L. co-developed the argument, performed the literature search and substantially revised the manuscript. T.N.L. co-developed the argument, performed the literature search and assisted in revising the manuscript. P.S.L. co-developed the argument and guided the authorship team in substantially revising the manuscript.

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Conflict of interest

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