deficits, and emerging concerns about issues surrounding enhancement." This survey is a contribution to understanding the practical and contextual dimensions of the ethical question; how can gene-editing technology contribute to human flourishing?

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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George Gaskell[1], Imre Bard[1], Agnes Allansdottir[2], Rui Vieira da Cunha[3], Peter Eduard[4], Juergen Hampel[5], Elisabeth Hildt[6], Christian Hofmaier[5], Nicole Kronberger[7], Sheena Laursen[4], Anna Meijknecht[8], Salvör Nordal[9], Alexandre Quintanilha[3], Gema Revuelta[10], Núria Saladié[10], Judit Sándor[11], Júlio Borlido Santos[3], Simone Seyringer[7], Ilina Singh[12], Han Somsen[8], Winnie Toonders[13], Helge Torgersen[14], Vincent Torre[15], Márton Varju[11] & Hub Zwart[13]

[1]Department of Methodology, London School of Economics, London, UK. [2]Toscana Life Sciences Foundation, Siena, Italy. [3]Institute of Molecular and Cellular Biology, Porto, Portugal. [4]Experimentarium, Science Communication Centre, Copenhagen, Denmark. [5]Center for Interdisciplinary Risk and Innovation Studies, Stuttgart University, Stuttgart, Germany. [6]Center for the Study of Ethics in the Professions, Illinois Institute of Technology, Chicago, Illinois, USA. [7]Department of Social and Economic Psychology Johannes Kepler University, Linz, Austria. [8]Tilburg Institute for Law, Technology, and Society, Tilburg University, Tilburg, The Netherlands. [9]Centre for Ethics University of Iceland, Reykjavik, Iceland. [10]Centre on Science, Communication and Society Universitat Pompeu Fabra, Barcelona, Spain. [11]The Center for Ethics and Law in Biomedicine Central European University, Budapest, Hungary. [12]Department of Psychiatry and Oxford Uehiro Centre University of Oxford, Oxford, UK. [13]Institute for Science, Innovation and Society Radboud University of Nijmegen, Nijmegen, The Netherlands. [14]Institute of Technology Assessment Austrian Academy of Sciences, Vienna, Austria. [15]Centre for Neurobiology, International School for Advanced Studies, Trieste, Italy.
e-mail: g.gaskell@lse.ac.uk

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Query the merits of embryo editing for reproductive research now

To the Editor: Recently, a team from the United States used CRISPR–Cas9 on viable human embryos to correct a gene mutation that causes hypertrophic cardiomyopathy, a heritable heart condition in which the ventricle walls thicken to hinder proper blood flow[1]. For many, this announcement brings closer to reality the prospect of editing disease-associated mutations in fertility clinic embryos intended for reproductive use. The study certainly raises many scientific uncertainties and questions. But we contend that it also brings to light some questionable value assumptions that have largely flown under the radar in the social discourse around embryo editing. Here, we call attention to some of these assumptions and suggest that additional human embryo editing research may not be adequately justified until these issues have at least been openly acknowledged and debated. To be clear, our discussion is meant to apply only to 'preclinical' embryo editing research: that is, to corrective nuclear genome editing research performed *in vitro* with an eye toward eventual reproductive use under favorable regulatory circumstances. Our points do not necessarily apply to human embryonic genome editing studies for fundamental research aimed at silencing genes to understand their function in early development.

Gaps in current ethical standards

Although the US team abided by the most recent ethical standards for human genome editing, there remain critical gaps in these standards. According to guidelines issued last year by the US National Academy of Sciences (NAS; Washington, DC) and the International Society for Stem Cell Research (ISSCR), germline editing of nuclear DNA is permissible only if scientific work is limited to *in vitro* embryo research; no edited human embryos ought to be implanted for reproduction at this time[2,3]. Unlike the ISSCR, however, the NAS goes further to specify ten necessary conditions under which, in the future, *in vitro* germline editing research might be permitted to cross over into first-in-human clinical trials for reproduction (see **Table 1**).

Among these requirements, we highlight the following three: (1) that there must be no reasonable alternatives to reproductive embryo editing; (2) that embryo editing be done only to prevent a serious disease or condition; and (9 in **Table 1**) that there be "continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public."

We believe these additional NAS conditions are significant not only because they allow for the very possibility of reproductive embryo editing in the future, but also because they offer guidance *now* for scientists pursuing *in vitro* embryo editing research aimed at possible future reproductive use. Conditions (1) and (2), for instance, should motivate researchers to deliberate carefully about which genetic diseases to target in their *in vitro* embryo editing studies. Researchers investigating the technical feasibility of reproductive embryo editing must first select a specific disease and then stick with it for the long haul. They cannot jump from one disease to another and still hope to have all the preclinical safety, efficacy, and proof-of-concept data necessary for the regulatory approval of any particular intervention. For example, if the US Food and Drug Administration (FDA; Rockville, MD) ever allows germline editing trials, it is likely to do so for a very specific guide RNA sequence on a CRISPR–Cas9 construct intended to correct a particular gene mutation. The FDA will not give researchers carte blanche to pursue just any generic approach to CRISPR–Cas9 germline editing in a clinical trials context. Therefore, disease selection and specialization at the very start of *in vitro* research is crucial for teams aspiring to develop any future embryo editing intervention.

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Table 1 NAS recommendations for clinical trials using heritable human germline genome editing

Recommendation	Description
1	The absence of reasonable alternatives
2	Restriction to preventing a serious disease or condition
3	Restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to that disease or condition
4	Restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects
5	The availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures
6	During the trial, ongoing, rigorous oversight of the effects of the procedure on the health and safety of the research participants
7	Comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy
8	Maximum transparency consistent with patient privacy
9	Continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public
10	Reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition

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But how will teams decide which genetic diseases to target? According to the NAS, reproductive embryo editing should be reserved only for cases where there is "the absence of reasonable alternatives" for affected persons hoping to rear healthy children. At first glance, this requirement makes sense only if we exclude as "reasonable alternatives" child adoption and the use of healthy donor sperm or eggs—all of which are safe options for prospective parents at risk of transmitting genetic harms. Perhaps one could argue that these alternatives fail to be 'reasonable' because they are not always affordable or available for those hoping to pursue them. This is an important point, and we shall return to the issue of affordability and availability of options below.

On closer inspection, this first NAS requirement is premised on the condition that there must not be any reasonable alternatives for those who want a healthy child that is *genetically related to oneself and one's partner.* We emphasize that it is this very personal desire—the desire to have a genetically related child—that reproductive embryo editing research must promise to fulfill.

But the problem here is that there *already exists* a proven alternative for couples who want to have genetically related children without transmitting a large range of harmful genetic conditions, including—importantly—any conditions that could in principle also be edited from the germline. Pre-implantation genetic diagnosis (PGD) is an early-stage embryo screening process that allows couples to select healthy, genetically related embryos for implantation after *in vitro* fertilization (IVF). This is an crucial fact, made all the more significant if PGD becomes a future standard of care within the context of reproductive embryo editing, specifically for quality control before the uterine transfer of edited embryos. Under these imagined circumstances, the 'most reasonable' alternative for affected couples may simply be to use PGD alone, without first burdening their pre-implantation embryos with the technical complexities and unknown risks of genome editing.

In light of these observations, we believe the real merits of reproductive embryo editing must be found in more narrowly defined situations in which germline genome editing promises to achieve something that PGD itself cannot. Along these lines, one possible rationale might be that embryo editing could benefit couples by increasing the overall number of healthy embryos available for implantation. For instance, if one parent has a deleterious copy of a gene, then on average 50% of the couple's embryos could inherit the mutation. Germline editing, however, could offer couples a greater number of healthy embryos for implantation, a point that was strongly emphasized by the authors of the US study.

But notice that this rationale is essentially an appeal to *efficiency*, quite distinct from the justification that embryo editing is necessary to enable affected couples to have healthy genetically related children *at all*.

Add to this a further complication. If CRISPR–Cas9 is introduced at the time of fertilization to avoid genetic mosaicism (as the US team did), then this technical approach could result in the wholly unnecessary editing of unaffected embryos, imbuing them with all attendant risks and no offsetting benefits. What effects might 'gene correction' have on normal embryos? Can an appeal to improved efficiency sufficiently outweigh concerns about unknown health risks to the child to be and potential social harms? These are important questions.

Of course, a final rationale for reproductive embryo editing is that PGD will not be effective in special cases where *all* of a couple's embryos are guaranteed to carry a harmful mutation. Perhaps, as the NAS points out, patients with recessive diseases like cystic fibrosis might meet through patient support groups and become life partners. Or one prospective parent could be homozygous for a dominant late-onset disease like Huntington's. Or there may be very rare circumstances in which both intended parents could have dominant-negative mutations. In such cases, embryo editing could be the only way for partners to have healthy children who are genetically related to both of them. As a pragmatic matter, however, we wonder whether the actual number of patients facing these unique reproductive situations—if they can even be identified *ex ante*—would be sufficient to mobilize research investment in a germline editing solution targeting a specific genetic condition. This is a practical challenge for translational investigators.

In any case, contemplation of these special scenarios recalls the central questions underlying all embryo editing. Does the desire to have healthy genetically related children justify the pursuit of reproductive human germline engineering? What about a couple's desire to have more embryos available for uterine transfer, especially in light of the fact that IVF is already financially inaccessible to most couples? These questions must be faced squarely if further embryo editing research is to be justified.

Socio-historical factors must be addressed for embryo editing to proceed

We believe the time is now to discuss the merits of reproductive embryo editing. A recent American poll suggests that most people are willing and eager to have a discussion[4]. Below, we provide some important considerations for such a discussion.

Discourse should not be initiated simply to determine whether specific disease cases are ready for clinical investigations regarding safety and consistency challenges.

Waiting until after the preclinical stages of research are well under way bypasses discussion about the philosophical and

ethical wisdom of even pursuing clinical embryo editing in the first place. For example, concerns about the focus on genetically related children or evaluations of disease seriousness cannot be addressed by discussions of research subject consent or methods to reduce off-target effects of editing.

Discussions about the merits of embryo editing should include the perspectives of fertility specialists and prospective parents likely to utilize PGD because these persons are the most proximal potential beneficiaries of the clinical translation of preclinical embryo editing research to facilitate the conception of genetically related children. These parties have been largely absent from previous policy discussions, international forums, and professional society working groups addressing the ethics of genome editing.

Additional data into how fertility specialists and PGD patients conceptualize what constitutes "reasonable alternatives" or "serious diseases" must be evaluated before further investment of germline editing research resources is made in this area, including the use of human subjects who must endure the burdens of egg and embryo donation[5].

It should be noted, however, that intended parents' varied desires for the translation of scientific research into improved clinical technologies may reflect a specific cultural view of genetic kinship, which, though shared by many scientific and ethical gatekeepers, cannot be assumed to be universal[6].

Nor can one assume that different people's conceptions of "serious" genetic conditions will be the same. As global experiences with PGD suggest, embryo selection practices can reveal culturally variable tolerance levels regarding the characteristics deemed suitable for preclusion, such as sex, congenital deafness, and Down's syndrome—characteristics that are far more readily selected against in China than, say, in the UK. We must not forget that PGD itself remains a controversial and complex practice, and that it may pose some inherent risks to screened embryos[7].

Finally, discussions over the merits of embryo editing should also include social justice arguments about the distribution of clinical techniques and their relative benefits to society. In the United States, the NAS defines procreative liberty as a negative right whereby individuals cannot expect to have their reproductive desires met by the state. This perspective does not consider government services providing family planning resources to populations whose reproduction has historically been envisioned as problematic or undesirable[8]. It is easy to assume that the importance placed on having genetically related children validates the pursuit of clinical study. Interestingly, when the desire to have genetically related children is held by those without the financial means to access assisted reproduction, the inability to have a genetically related child is quickly reframed as an irrelevant economic artifact[9].

Although they acknowledge that cultural values shape genome-editing policies, the NAS guidelines provide little acknowledgment of how the report itself reflects a specific cultural perspective. The simultaneous valuing of genetic parenthood for those who can afford it and dismissal of genetic parenthood desires for those who cannot has a specific sociopolitical context that is easier to recognize when the participating voices are more diverse. If scientific organizations truly seek to gauge *whether* to proceed to clinical applications rather than *how* to proceed, they must assess the diverse societal values regarding the types of reproductive options considered "reasonable," the way that disease seriousness is conceptualized, and the uneven accessibility of increasingly sophisticated services.

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Insoo Hyun[1] & Catherine Osborn[2]

[1]Department of Bioethics, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA. [2]Department of Anthropology and Dittrick Medical History Center, Case Western Reserve University, Cleveland, Ohio, USA.
e-mail: insoo.hyun@case.edu

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