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INTERGENERATIONAL MONITORING IN CLINICAL TRIALS OF GERMLINE GENE EDITING:

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Abstract

Design of clinical trials for germline gene editing stretches current accepted standards for human subjects research. Among the challenges involved is a set of issues concerning *intergenerational monitoring* – long-term follow-up study of subjects and their descendants. Because changes made at the germline would be heritable, germline gene editing could have adverse effects on individuals' health that can be passed on to future generations. Determining whether germline gene editing is safe and effective for clinical use thus may require intergenerational monitoring. The aim of this paper is to identify and argue for the significance of a set of ethical issues raised by intergenerational monitoring in future clinical trials of germline gene editing. Though long-term, multigenerational follow-up study of this kind is not without precedent, intergenerational monitoring in this context raises unique ethical challenges, challenges that go beyond existing protocols and standards for human subjects research. These challenges will need to be addressed if clinical trials of germline gene editing are ever pursued.

Keywords

gene therapy/transfer; clinical trials; reproductive medicine; genetic counseling/prenatal diagnosis; research ethics

INTRODUCTION

The use of gene editing techniques to make modifications in human embryos has shown great promise in recent years.[1–2] Germline gene editing (GGE) is still nowhere near ready for clinical use, but potential clinical applications are beginning to take shape. Recent experimental successes in research on human embryos have shown that it is, in fact, possible to make heritable changes at the germline for purposes of treating genetic disease,[2] and the unregulated (and, in the judgment of many, unethical) creation of a pregnancy from edited embryos in China has – unfortunately – served as the first "live fire" exercise of gene editing at the germline.[3] Should therapies that involve germline gene editing ever become serious candidates for clinical application, there will need to be earnest consideration of a number of ethical issues involving human subjects research, clinical application and justification, and regulation of clinical use.

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Among these issues will be design of clinical trials.[4] A central question in design of clinical trials for GGE concerns *intergenerational monitoring* of subjects and their descendants. Unlike with other assisted reproductive technologies (ART), or with somatic gene editing, any changes made through GGE would be heritable, and risks could be passed on to future generations. Follow up study of initial subjects may not be enough; in order to adequately gauge risks and benefits from GGE in reproductive medicine, multiple generations may need to be monitored. For this reason, various advisory bodies and professional medical organizations have stated that any future clinical trial of GGE may need to include long-term, multigenerational follow-up study of the subjects, their children, and potentially even grandchildren to determine long term risks and effectiveness of GGE. Recent reports on gene editing from advisory bodies and professional medical organizations have called for intergenerational monitoring as part of any translational pathway for GGE. In their recent report on gene editing the National Academies of Science, Engineering, and Medicine (NASEM) stated:

> As with any new procedure, carefully monitored clinical trial protocols would be required for heritable genome editing…Unlike conventional clinical trials, heritable genome editing trials would likely require long-term prospective follow-up studies *across subsequent generations*. This follow-up would entail study of the future children affected by the intervention, none of whom would have been party to the initial decision to participate in a research trial (my emphasis).[5]

This was echoed in the recent Nuffeld Council Report on gene editing.[6] Statements from other professional organizations on technical and ethical aspects of GGE have pointed out the potential need for and difficulty of conducting intergenerational monitoring in this context,[7] and have called for evidence in support of clinical efficacy and safety of GGE that will be difficult to attain without intergenerational monitoring.[8]

The aim of this paper is identify and argue for the significance of a set of ethical issues raised by intergenerational monitoring in future clinical trials of GGE. Though long-term, multigenerational follow-up study of this kind is not without precedent, intergenerational monitoring in this context raises unique ethical challenges, challenges that go beyond existing protocols and standards for human subjects research. These challenges will need to be addressed if clinical trials of GGE are ever pursued. In brief, these are: (1) justification for type and degree of monitoring and collection of specific information; (2) communication of findings, counseling, and management of future risks; and (3) the relationship between researcher and subjects. Each of these is a familiar issue to bioethicists. However, as I will argue here, each of these poses unique issues for intergenerational monitoring in clinical trials of GGE. Though these challenges are not necessarily intractable, they are significant, and any discussion of a responsible translational pathway for GGE will need to tackle the problems of intergenerational monitoring in full.

In the next section I will briefly review the current state of research into clinical applications for germline gene editing in reproductive medicine, and then consider some reasons why intergenerational monitoring may be necessary. In section 3 I will discuss and argue for the importance of each of the three families of issues listed above, before a brief conclusion in section 4.

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GENE EDITING IN THERAPEUTIC CONTEXT

The germline is the set of cells that are responsible for passing on genes to children in the normal course of reproduction. In humans, the germline includes sperm cells and oocytes (egg cells). GGE involves editing of these cells. As opposed to somatic gene editing, which targets genes in large sets of cells in a developed or developing organism (potentially billions of cells), GGE targets genes only in a small set of germ cells, most usually a fertilized zygote.[1] This has a number of potential benefits over somatic gene editing for certain kinds of diseases,[1] but crucially it means that any changes made will be heritable. This raises significant technical and ethical issues for any potential clinical use of GGE.

It is early days in research into human GGE, but there are a few notable points to take away from the experiments on human embryos that have been done. The first is that GGE is nowhere near ready for clinical use, and even if GGE meets some important targets for safety and efficacy, will likely still be far more risky than other options, such as preimplantation genetic diagnosis (PGD), over the near term. Translational research on GGE to date has focused on use of gene editing techniques to correct pathogenic mutations that lead to monogenic, autosomal inherited disorders. Most of the experiments have been on non-viable embryos and have resulted in large amounts of off target effects (meaning, edits to parts of the genome that were not intended).[2] A recent experiment conducted at Oregon Health and Science University (OHSU) achieved notable success in reducing off target effects.[9] This has been the standout research result so far and interpretation of the data from the study is disputed.[10] Other studies on the use of the same CRISPR gene editing technique utilized by the OHSU team showed large rates of off target effects and unintended mutations.[11]

The small batch of experiments on GGE in humans constitutes an important ‘proof of concept’ for something that had been, up to recently, largely a matter of speculation. Though this has caused a great deal of consternation in scientists and ethicists alike, the clinical potential for GGE appears – at least for now – to be quite limited. None of the experiments involve the kinds of editing that would result in changes to significant, complex traits.[12] All experiments on humans have involved changes to single genes, and moving to edits to multiple genes looks technically very difficult. The most likely clinical use for GGE in the future will be in the treatment of monogenic, autosomal inherited disorders such as hypertrophic cardiomyopathy or spinal muscular atrophy.[1] PGD can already ensure individuals who carry these diseases can have biologically related children free of them. The main benefit of GGE will be for the proportion of the population for whom PGD is not an acceptable therapeutic option.[1, 8, 13]

Because changes made at the germline are heritable, determining that GGE is safe and effective may require monitoring not only individuals that result from pregnancies created with edited embryos, but also their descendants. This is a departure from follow-up study of other ART and even the limited follow up study of subjects of mitochondrial replacement therapies (MRT), in which only initial subjects are monitored. This is for a number of reasons. First, there may be adverse effects that only manifest after an individual has reached reproductive age, which could be passed on to children and grandchildren. The only way to

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determine whether a heritable change is the result of the editing process or some other factor of an individual's biology would be to monitor their descendants. Second, unlike with mitochondrial DNA, consequences of GGE could be very wide ranging and could affect a large set of an individual's resulting traits. Effects, intended or otherwise, of GGE cannot just be determined through limited monitoring of a set of health indicators over the course of an initial subject's lifetime, as has been done with follow up study of MRT.[14] Though MRT is (arguably) a form of germline intervention, MRT is an imperfect analogue for the challenges of human subjects research with GGE. Mitochondrial DNA has different and more limited effects on an individual's health and makeup than nuclear DNA, and so MRT has a more limited set of effects than GGE and, crucially, less of a potential for ethically fraught effects (such as unintended consequences for an individual's cognitive development). Because of this, the kind of follow up study required to determine whether MRT is safe and effective is *different in kind* from what will be required for GGE.

Preclinical research and further animal model testing will shed light on many of these potential risks. There are a number of questions that animal model testing will need to answer, such as the possibility of de novo mutation between generations that erases the correction of pathogenic genotypes via GGE. Given standards for approval of something like GGE, much of the potential risks would have to be ruled out anyway in order to proceed with human subjects research. But even if this is so, it is just unlikely, given the complexity of human biology and our current state of knowledge about morphogenesis, development, and gene expression over the lifespan, that we can totally rule out the possibility that there could be adverse effects to health that are heritable and that only manifest after an individual reaches reproductive age. Lessons here should be drawn from the unexpected and troubling evidence that conception via ART can have unforeseen effects on health.[15–16] Gene expression over the lifespan plays a major role in health, especially in the etiology of chronic diseases,[17] and there is evidence to suggest that, among the factors that can affect gene expression, conception via ART can have significant effects.[15]

Whether or not there *could* be *enough* preclinical data to justify human experimentation *unless* such unintended consequences can be definitively ruled out is a significant ethical question in its own right, and one that will need to be confronted and discussed before human subjects research proceeds. An argument would have to be made that monitoring, and treatment and counseling should future adverse effects manifest, is sufficient to manage the risks of any such effects. The heritability of any risk in this context compounds the risk of any future adverse effects, and so raises higher barriers. Before responsible human subjects research can commence, we will have to consider in depth whether the possibility of such unintended consequences raises too high an ethical barrier. We may well get to the point where clinical trials of GGE are a real possibility, without being able to rule out the potential for heritable effects on an individual's health that result from the editing process, but only manifest after they reach reproductive age. In such a situation, intergenerational monitoring may be required.

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CHALLENGES

Intergenerational monitoring in clinical trials of GGE is not completely unprecedented. There are analogous kinds of research; long-term follow-up studies for ART, for instance, are common, as are cohort studies involving biobanked genetic material.[18–20] The Framingham study of cardiovascular disease in the United States is another example.[21] Long-term follow up with MRT is perhaps the closest (though, as argued above, imperfect) analogue,[22, 14]. But intergenerational monitoring in clinical trials of GGE poses some special, and especially thorny, ethical challenges that go beyond what is faced in other cases. Ethical conduct of intergenerational monitoring will need to resolve a set of questions in three problem areas.

Justification for Type and Degree of Monitoring and Collection of Specific Information

Researchers will need to consider carefully exactly what information is required from future subjects, how many generations will need to be monitored, and most importantly *why* this specific information is required. The more generations are required for monitoring, the more invasive the monitoring necessary, and the more and different kinds of information needed, the more difficult it will be to carry out an ethical and effective clinical trial.[22] The type of information necessary will depend in part on the genes targeted in the editing process. For example, use of editing to correct a pathogenic *MYBPC3* gene to treat hypertrophic cardiomyopathy, as in the OHSU study,[9] will require monitoring a subject's cardiovascular health, and potentially continuous genetic screening to ensure that the editing is still effective over their life. But genes that are involved in multiple parts of human development will likely require monitoring of other parts of a subject's health. How widespread the effects on a subject could be, and so the scope of monitoring required, may be a good litmus test for appropriate clinical targets. If a gene is thought to have effects on many parts of a subject's physiology, thus requiring extensive and thorough monitoring, this may indicate that this is not a good target for GGE (at least in the early stages of human subjects research).

Researchers and ethicists need to carefully consider what kinds of information would be necessary to show that GGE is safe and effective. For some types of GGE, more limited monitoring may be sufficient. In the case of correction of a pathogenic gene where the aim of the editing is to restore the individual's genotype to the "wild type" already possessed by the rest of the population, since most people have the "wild type", the health effects of the genotype are (likely) well known.[1] For other targets, this may not be the case, and of course the potential for the kinds of unintended consequences outlined in the previous section will need to be considered as well.

An absolutely crucial question here will be how many generations will be required to ensure a sufficient sample. Trial design will need to take into account what level of participation is necessary. It is entirely possible that not all subjects will submit to monitoring or will continue for the length of the study. Participation rates in follow up studies of other ART vary.[14] Experience with follow up study following MRT has been relatively high,[14] but as discussed above, MRT is an imperfect analogue for GGE, and none of these studies involved intergenerational monitoring or the kinds of medical testing likely required in

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follow up study for GGE. Consent to participate before studies begin has been an imperfect instrument to ensure participation in follow-up study of MRT.[23] Given the history of follow up study with ART, great care will need to be taken to ensure adequate participation to get a robust set of data on the intergenerational effects of GGE.

Communication of Findings, Counseling, and Management of Risks

Suppose that during the course of long-term follow-up study, researchers identify a serious, potentially heritable health risk. Researchers will need to contact subjects, communicate this information, and offer counseling on management of the risk. If the study does reveal a threat to an individual's health that manifests only after they withdraw from the study, subjects may need to be contacted anyway and offered treatment and, if the risk is heritable, reproductive counseling. This could come with serious risks to subject's health and well-being. This notification requirement means researchers would need to keep tabs on subjects when they have withdrawn from the study, potentially *without their knowledge*. If a subject chooses to cease participation, has children, and then passes away without their children knowing that their parent was the result of a pregnancy created from an edited embryo, researchers will need to have information about the whereabouts of this subject's children and other descendants without these children knowing it. Communication, even just a simple notification that subjects may be contacted about health information in the future and can in turn contact researchers for questions about their health, involves a de facto disclosure (a) of information about parentage and (b) of information about health that a parent may choose not to share with them.[4]

The exigencies of managing risks and communicating adverse findings with subjects means that, in any situation where intergenerational monitoring is required, a decision to conceive a child from an edited embryo in a clinical trial of GGE involves *a limited waiver of privacy*, for certain key parts of that child's life, and for potentially multiple generations of one's descendants. This raises some enormously difficult issues involving informed consent.[24–25] Though parents can consent for their children, they cannot consent to enroll their children and descendants perpetually, and cannot consent in a way that binds their children past the age in which children can exercise their own judgment about whether to continue.[26] Great care will need to be taken to ensure that decisions to withdraw from a study, or not to participate in the case of a descendant of an initial subject, can be honored without compromising the integrity of the study.

This also means that researchers running the trial have been entrusted with information about not just their subjects and their subject's health, but also extremely intimate information about parentage, sexual history, and much more.[27] And this is not just "virtual" information, in the sense that it is information that could be extracted from a set of banked, de-identified genetic samples. Rather, researchers will need to know this about their subjects, or at least have permissible access to this information, if monitoring and notification are required.

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The Researcher-Subject Relationship

Researchers in clinical trials of GGE may have more significant obligations towards subjects than researchers in other cohort studies. Individuals who are part of something like a cohort study can withdraw at will. In keeping with a fundamental principle of clinical research ethics, an individual can discontinue their participation and, upon doing so, their involvement with the study and with the researchers involved ceases. This is not (or at least not terribly) problematic for something like the Framingham study, because any risks to the individual's health from ceasing their involvement with the study were already there before they enrolled. If the individual had a certain baseline risk for, say, cardiovascular disease, then that risk was not altered by participation, and any increased risk to the individual (terminating whatever care they were receiving as a member of the cohort) was the result of their decision to end participation. This is slightly trickier with a long-term follow-up for ART, as any risks to the child are the result of the ART, but presumably the decision to conceive through ART was external to participation in the study and so, again, participation does not change the risk to the subjects.

With GGE this would be different. For the first cadre of subjects, any risks to children would be the result of the editing process. Since going through the editing process requires enrolling in the study, these risks would be *created* by the decision of the children's parents to participate. In a very real way, the researchers conducting the study have generated risks for the edited subjects *and their descendants*. This has several consequences. First, it may create an obligation, on the part of the researchers, for certain key aspects of subjects' health (Barbra Rothschild, personal communication, 2018). These obligations may last for two generations (depending on how many generations will need to be monitored in order to determine that the procedure is safe), involving not just the original subjects but also an indefinite number of their descendants. Second, this complicates withdrawal from and participation in the study. Children and grandchildren will need to be counseled and socialized by their families into participation.[26] It is possible (maybe even likely) that some will withdraw and cut off contact, thus breaking the chain of participation. For other sorts of long-term follow-up study this would terminate both researchers' involvement with the subject and any obligations they may have to them. But in this case, obligations may continue. Studies will have to be designed to allow withdrawal from the study, while at the same time ensuring obligations for these individuals' health that fall on the researchers can be met.

CONCLUSION

GGE, for the treatment of a certain class of diseases, has revolutionary clinical potential, and can offer a series of benefits over alternatives such as early life gene therapy or PGD.[1] Potential clinical applications, though, are limited; for most individuals with a family history of genetic disease, PGD is and will likely remain the best option, and the continuing development of pediatric gene therapies, such as the recent introduction of onasemnogene abeparvovec for the treatment of spinal muscular atrophy,[28] could offer a better therapeutic option down the road. And of course there are familiar worries about the ethics of mucking about at the germline to begin with, such as worries about the use of GGE for

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non-therapeutic purposes such as biomedical enhancement. There is, and will remain for the foreseeable future, real questions about whether GGE *should* be done at all.

In an important sense the broader question about whether GGE *should* be done is secondary to questions about whether it *could* be done. The possible need for intergenerational monitoring raises serious questions about whether GGE *could* be done ethically, and whether clinical trials of GGE could meet current standards in clinical research ethics. If no ethically acceptable clinical trial of GGE is possible, because of something like the challenges and complications involved in intergenerational monitoring, then broader social and philosophical questions are moot – we simply can't do it, even if GGE is technically possible. At the least, what such a situation would mean is that we may need to reconsider key parts of accepted clinical research ethics codes, decide whether these can be restructured, and reassess their importance in light of whatever benefits there will be from some future GGE. These will be difficult debates and the stakes will be extremely high. The consequences if mistakes are made could be tragic. There is great need for attention to these questions about whether and how GGE could be done ethically, in addition to questions about whether it should be done at all. Part of this set of issues requires serious consideration of protocols for the ethical conduct of intergenerational monitoring in future clinical trials of GGE.

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Competing Interests

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