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RESEARCH ARTICLE

# Germline Genome Editing Research: What Are Gamete Donors (Not) Informed About in Consent Forms?

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## Abstract

The potential for using germline genome editing (GGE) in humans has garnered a lot of attention, both for its scientific possibilities as well as for the ethical, legal, and social challenges it ignites. The ethical debate has focused primarily on the suggestions of using GGE to establish a pregnancy (i.e., to offer it in a clinical setting), which is, to date, illegal in many jurisdictions. The use of GGE in research (where a pregnancy would not be established) has received much less attention, despite the fact that it raises serious ethical and social issues as well. Herein, we report on the analysis of informed consent forms for egg and sperm donation used in a widely publicized study where genome editing was used to correct a disease-causing genetic mutation in human embryos. Importantly, embryos were created using eggs and sperm obtained specifically for these experiments. The analysis indicates deficiencies in how the forms addressed various issues, including limited and potentially misleading information about the sensitive nature of the study, the lack of an explicit mention of genomic sequencing, as well as the poor readability of the forms. Furthermore, the arguably high compensation of U.S.$5,000 for egg donors raises questions about undue inducement to participate in research. Moreover, since the procurement of eggs involves serious health risks, it may be questioned whether research requiring such a procedure should be pursued. If such experiments are continued, donors should be informed about all relevant aspects in order to make informed decisions about participating.

## Introduction

The CRISPR-Cas system was originally discovered as an adaptive immune response system in bacteria and was found to have very broad application in biotechnology, serving mainly as a precise, relatively inexpensive, and rapid genome editing (GE) tool (see Box 1 for explanations of biology terms).[1] This system, in particular CRISPR-Cas9, accelerated research in many organisms and on many types of cells. It is increasingly used in areas of gene-function studies, drug discovery,[2] agriculture,[3] gene therapies for human genetic diseases,[4] and others.[1] Among these studies, experiments using CRISPR-Cas9 in human embryos were conducted to correct disease-causing gene variants and to study the function of genes (Table 1). Some of these studies may facilitate the development of procedures that could be used in future clinical contexts (e.g., to correct a disease-causing gene variant in embryos in an *in vitro* fertilization [IVF] context). Such GE research in human embryos, first reported in 2015,[5] not only indicated a new area of potential clinical applications of GE, but also revealed scientific challenges, such as off-target effects and mosaicism. Moreover, it raised important questions about ethical, legal, and social issues (ELSI) in the research itself as well as related to the potential clinical offers.[6] While the suggested clinical use and related ELSI have garnered a lot of attention in the last four years[7]—for good reason, for example clinical use is currently illegal in many jurisdictions[8]—the ELSI of research on germline genome editing (GGE) seem to have been given less attention.

One of the ethical problems posed by GGE research is related to the use and destruction of embryos, which may

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**Box 1. Glossary.**

| | |
|---|---|
| CRISPR-Cas9 | Genome editing technology that allows for targeted, fast, and cheap modification of DNA. CRISPR-Cas9 system consists of a guide RNA molecule that identifies a targeted DNA sequence and Cas9 enzyme, which cuts the identified sequence. |
| Embryo | An early developmental stage of an organism, which starts after fertilization and lasts 7 weeks in humans. Experiments on human embryos are allowed until 14 days after fertilization. After this time, the embryos must be destroyed. |
| Gametes | Reproductive cells. Female gametes are called eggs or oocytes; male gametes are called sperm. Egg and sperm unite in the process of fertilization, which initiates the development of a new organism. |
| Genome editing | Technologies used to introduce changes to DNA, for example, to insert or delete a DNA sequence. |
| Germline | Refers to the cells that may pass on their genetic material to the offspring. Gametes and embryonic cells are examples of germline cells. Changes introduced to the DNA in germline cells are heritable. |
| Mosaicism | Occurrence of cells with different genotypes in one organism, for example, when a given gene is modified in some cells but not in all the cells of an organism. |
| Off-target effects | Unintended DNA modifications that occur outside of a targeted DNA sequence in a genome-editing process. |
| Oocyte | A female reproductive cell. |

be viewed as an even greater concern when embryos are created specifically for research (e.g., in the study by Ma *et al.*[9]).[10] The creation of embryos specifically for the purposes of research may have some advantages over using supernumerary embryos ''left over'' after *in vitro* fertilization procedures. Namely, GGE can be conducted at an earlier stage of development of an embryo, or even at the moment of fertilization, in order to avoid mosaicism.[9] In such cases, as well as in cases where gametes with specific genotypes are desired, sperm and/or oocytes may be obtained specifically for research.[a] Of note, oocyte procurement procedures are burdensome and involve serious health risks for women.[11,12] In order to understand further how GGE works, refine its functioning, and eventually evaluate the safety and efficacy when used to correct specific gene variants, large numbers of women would likely be required to undergo this invasive and risky oocyte retrieval procedure. Furthermore, given that, in each GGE study, genomes of embryos are sequenced to verify for off-target effects, there are also ethical questions related to informed consent for sequencing, return of sequencing results to research participants, and genomic data storage.[13] Ethical aspects pertaining to the handling of procured cells and tissue may also be raised in this context, specifically questions about the period of storage, future uses, access, creation of cell lines, and potential proprietary claims. In the case of research studies addressing potential clinical applications, there are concerns also about the uncertain medical need for such applications.[b] In particular, a very limited number of people may be in need of such procedures to address genetic conditions,[14,15] and it is questionable whether public resources should be used to try to address this (small) need with such a contentious procedure. Indeed, the uncertainties and the potential risks and harms involved, which include social and psychological harm as well as physical harm for the prospective children developed from genome-edited embryos, all contribute to the ethical challenges surrounding GGE in research.

**Table 1. List of published studies using CRISPR-Cas9 genome editing[a] on human embryos**

| *Year* | *Authors* | *Title* | *Type of modification* | *Embryos used* |
|---|---|---|---|---|
| 2017 | Ma *et al.* | Correction of a pathogenic gene mutation in human embryos | Correction of a mutation that causes hypertrophic cardiomyopathy | Viable[b] embryos created for the purpose of research (>100 embryos were created) using oocytes and sperm procured specifically for research |
| 2017 | Tang *et al.* | CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein | Correction of a mutation in *HBB* gene causing $\beta$-thalassemia and a mutation in *G6PD* gene related to a common enzyme deficiency | Viable embryos created for the purpose of research using oocytes and sperm from patients undergoing clinical IVF procedures<br>Non-viable tripronuclear embryos created in clinical IVF procedures |
| 2017 | Fogarty *et al.* | Genome editing reveals a role for OCT4 in human embryogenesis | Study of the function of the pluripotency transcription factor OCT4 during embryogenesis | Viable surplus embryos created in clinical IVF procedures |
| 2016 | Kang *et al.* | Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing | Introduction of an allele of the gene CCR5 associated with a resistance or slower progression of HIV infections | Non-viable tripronuclear embryos created in clinical IVF procedures |
| 2015 | Liang *et al.* | CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes | Modification of *HBB* gene, which when mutated causes $\beta$-thalassemia | Non-viable tripronuclear embryos created in clinical IVF procedures |

[a]Another GE approach called base editing has also been studied in human embryos. For a summary of base editing studies, see Lea and Niakan, 2019.
[b]Viable embryo can develop into a live birth; non-viable embryos do not have such ability due to various abnormalities.
HIV, human immunodeficiency virus; IVF, *in vitro* fertilization.

Given these concerns, related both directly to research and to potential clinical uses of GGE, it may be questioned whether GGE research on human embryos should be conducted at all. If allowed, there is a further question regarding what criteria should be followed. In 2015, a group of scientists (some involved in research on somatic GE) stated: ''At this early stage, scientists should agree not to modify the DNA of human reproductive cells.''[6] Many professional groups and individual authors who considered research involving GGE permissible nevertheless called for a moratorium on clinical uses of this technique.[16] Influential statements and guidelines, however, do not exclude, in principle, the potential future applications of GGE in the clinic.[17,18] Of note, these guidelines or statements often indicate that further research regarding safety concerns (and potential benefits) should be conducted. In addition, guidelines outline other conditions that should be met before such clinical applications should take place, for example, the need for public debate and/or societal consensus as well as appropriate oversight.[16]

In November 2018, despite these calls for caution, it was reported that GGE was conducted on human embryos, which were subsequently used to establish a pregnancy and developed into live births. He Jiankui, then an associated professor at a Chinese university, claimed that he modified the gene *CCR5* encoding a receptor that allows human immunodeficiency virus (HIV) to enter a cell, with the aim of introducing resistance to that virus.[19] This first use of GGE to establish a pregnancy, which importantly can be considered a type of enhancement and not a treatment,[c] met with strong objections and criticisms from the scientific community.[19] The ethical objections addressed to He were numerous, including the exposure of (future) offspring to unnecessary risks, lack of medical need for the use of GGE, the presence of alternative methods to prevent HIV from being contracted, questionable competences of He Jiankui himself to conduct such a procedure, undue inducements of the patients, inadequate informed consent documents, and breach of guidelines.[20] As a consequence, this widely condemned experiment has reinvigorated the debate on GGE.

Despite all the serious ethical concerns about the potential use of GGE to establish a pregnancy and studies on embryos using GE (which do not culminate in a pregnancy), such research has not been discouraged and appears to be continuing[21] (Table 1). Herein, we address some of the ethical aspects of GGE research, which have seemingly been overlooked or given less attention in ELSI discussions: the ethical issues surrounding the involvement of gamete donors in GGE studies. Given their direct engagement with this research, gamete and embryo donors may be considered a group of stakeholders who should be particularly involved in the dialogue on GGE. Simply put, GGE research can continue only if they agree to donate their gametes or embryos. Important questions may be posed about how genuinely informed they are about the impact and ethical dimensions of such studies, and whether their involvement in research is respectful of their autonomy. Since GGE studies involving oocyte donation for the purpose of research are particularly contentious from an ethical perspective, yet at the same time advantageous from a scientific point of view (see above), we believe that such studies deserve particular scrutiny. In order to gain insight into the consent processes of research participants who donated gametes for GGE research, we analyzed consent forms used in the study by Ma *et al.*,[9] which to our knowledge is the only study published to date (in English) in which oocytes procured specifically for research were used to study GGE.

## Methods

The consent forms were requested by email from an author of the study by Ma *et al*.[9] We received different consent forms for research participants: for oocyte donation, sperm donation, donation of discarded and/or excess materials from IVF,[d] blood/skin donation, and a flyer inviting participants to the study. In our study, we analyzed consent forms that were specifically used for oocyte and sperm donation; each of the consent forms also included information relevant for skin and blood donation.

We conducted a content analysis of these two forms, which involved careful and iterative perusal of the text. First, we conducted a deductive content analysis, whereby information relevant to the following predefined categories was identified: (1) the sensitive nature of the study, which was defined as any content with explicitly evaluative statements indicating that the nature of the study was sensitive; (2) compensation for participating in the study; and (3) whole genome/exome sequencing, including content not limited to information about the procedure of sequencing but also any information relating to the use of the genetic data.

The first category, sensitive nature of the study, was inspired by the requirement set by the Oregon Health and Science University regulatory framework, as specified in the methods section of article by Ma *et al*.[9] The category of information pertaining to whole genome/exome sequencing was chosen, as the authors noticed that few discussions of GE addressed the fact that subjects/patients of GE would inevitably have (part of) their genome sequenced, which raises a distinct set of ethical issues. Similarly, ethical issues related to the compensation of research participants, especially for egg donation in the

context of GGE, have not received much attention in the GE debate.

In a second step, all the information found for these three categories was scrutinised using an inductive approach, where researchers noted any themes of interest emanating from these sections of text. The content analysis was conducted by E.N. and verified by H.C.H.

Readability analysis was conducted using the SMOG test and software Readability Studio Professional Edition for Windows v2015 (Oleander Software Ltd., Vandalia, OH). To prepare for the readability analysis, the documents, which were originally in a portable data format, were saved as Word files and edited. Tables, logos, page numbers, and contact addresses were removed. The software was set to ignore lists and non-sentences (e.g., phrases that do not finish with a period). Links, email addresses, descriptions of lines for signatures, dates, and numerals were also ignored in the analysis. We also calculated the word count in the edited documents, when stripped of tables, logos, page numbers, and contact addresses, to indicate the time needed to read the forms.

## Results

### General characteristics of the forms

The consent forms had a content summary page and a page with the contact data of the principal investigator and co-investigators, the source of funding (Oregon Health and Science University), and the criteria of eligibility for participating in the study (either healthy adults or carriers of inherited disease-causing mutations in specific genes). The text of the forms was organized into sections with the following titles (verbatim from the forms): purpose, procedures, subject access to genetic information, risks and discomforts, benefits, alternatives, confidentiality and privacy of your protected health information, commercial development, costs, liability, participation, and signatures. The two forms analyzed herein differed in terms of the presence of information related to specific procedures of oocyte extraction and sperm donation and their implications.

### Content analysis

The sections of the forms that addressed the three chosen categories for analysis are presented verbatim in Table 2 and are discussed further in the discussion section. Only one paragraph was identified that complied with our criteria set for the category of ''sensitive nature of the study.'' With regard to compensation, we found that oocyte donors were compensated after each specified procedure, with the total compensation amounting to U.S.$5,000 (or U.S.$5,050 if a sample of skin was also donated). Meanwhile, sperm donors received U.S.$100 for semen donation and an additional U.S.$50 if a skin sample was donated. The content related to genomic sequencing, which is referred to only as genetic testing in the forms, contained information about the purpose of ''genetic testing,'' procedure, return of results, confidentiality and use of genetic information, and confirmation of clinically relevant results.

### Readability and word count

We found that the readability scores obtained in the SMOG test were 13.4 for the oocyte donation form and 12.9 for the sperm donation form. These numbers indicate years of education that an individual would have to complete to understand all of the text analyzed. In the United States, grade 12 refers to a high school senior, grade 13 to a university freshman (i.e., 1st year university), and grade 14 to a university sophomore (i.e., 2nd year university). The word counts on the forms were 4,295 and 7,506, respectively, for sperm and oocyte donors. Assuming the average pace of reading of 200 words per minute, one would need 21.5 and 37.5 minutes, respectively, to read these forms.

## Discussion

We present herein the first formal study to date of consent forms used in human GGE research. In her recent book, Baylis[7] discussed a few aspects of the consent forms used in the study by Ma *et al.*[9] Furthermore, consent forms for gamete donors have been studied in the context of IVF.[22] To our knowledge, however, there has been no content analysis of consent forms used for gamete donation for research on GGE. This context is particularly sensitive, as women undergo a risky and burdensome procedure specifically to enable scientific experiments (which is not the case when surplus oocytes or embryos created in clinical IVF procedure are used). Such engagement of women in research seems further problematized when gametes are donated for GGE studies, which are contentious for reasons described earlier, including the destruction of embryos and the (potential) fostering of future clinical applications for which medical need is uncertain and risks involved are significant.

### Consent to research of a sensitive nature

Valid lines of questioning remain with regard to the extent and nature of how participants should be informed about the ethical concerns related to human GGE studies. Interestingly, as outlined in the methods section of the article by Ma *et al.*,[9] ''The robust regulatory framework set forth by OHSU clearly specified that **informed consent**

**Table 2. Text verbatim corresponding to the three deductive categories identified in the consent forms for gamete donors from the study by Ma *et al.***

| *Category* | *Relevant quotations*[a] |
|---|---|
| Sensitive nature of the study | ''Germline gene editing is a controversial topic currently being discussed by a range of stakeholders; including scientists, national leaders, ethicists, academics, and many more individuals. Consensus amongst these groups calls for basic science experiments to be conducted in order to provide sufficient evidence regarding the safety and efficacy of gene editing tools. The knowledge gained from basic research studies, like this one, will add scientific data to the continued discussion of whether gene editing tools should be used in a clinical setting.'' |
| Whole exome/ genome sequencing | **Purpose:**[b]<br><br>*Form for oocyte donation:*<br>''During this study, your donated eggs, cumulus cells (the cells that surround your eggs), skin, fibroblasts from your biopsy and blood cells will undergo genetic testing. These tests will help researchers better understand human reproduction and development as it relates to embryonic stem cell research.''<br>''A portion of the blood collected for these hormonal assays will be used for genetic analysis and to confirm the presence of DNA mutations.''<br>*Form for sperm donation:*<br>''During this study, your donated sperm, skin fibroblasts from your biopsy, and blood cells will undergo genetic testing. These tests will help researchers better understand human reproduction and development as it relates to embryonic stem cell research.''<br>*Both forms:*<br>''Skin biopsy … Genetic tests will be conducted to verify or identify genetic disease.''<br>**Procedure:**<br>''We will draw blood from a vein in your arm. We will collect about 2 tablespoons of blood. Your sample may be frozen and later thawed and used for future experiments. Genetic tests will be conducted.''<br>**Return of results:**<br>''Subject access to genetic information:<br>The results of these studies will not be made available to you because the research is still in an early phase and the reliability of the results is unknown. If we discover new information that is important for your health care, either in this study or the future, you will be asked whether you wish to receive the results. You will be required to have the test repeated in a clinical laboratory; results from your donation are performed in a research laboratory and therefore are not considered a clinical diagnostic tool. If you choose to receive these results they will be presented to you by one of the physicians approved in this research protocol; because genetic information is complex and sensitive, the results should further be discussed with a genetic counselor or your primary care giver who can answer your questions or discuss your concerns. If you consent to this procedure, we may contact you again in the future to update your information or inquire about your specific health care history. |

(*continued*)

**Table 2. (Continued)**

| *Category* | *Relevant quotations*[a] |
|---|---|
| Whole exome/ genome sequencing | _____Yes, I would like to receive the results of this non-clinical laboratory results if it is important for my health care. I understand this is not a clinical diagnosis and must be repeated by my own health care professional.<br>_____No, I would not like to receive the results of this non-clinical laboratory results.''<br>**Confidentiality and use of genetic information:**<br>''Genetic Testing:<br>Although we have made every effort to protect your identity, there is a small risk of loss of confidentiality. If the results of these studies of your genetic makeup were to be accidentally released, it might be possible that the information we will gather about you as part of this study could become available to an insurer or an employer, or a relative, or someone else outside the study. Even though there are discrimination protections in both Oregon law and federal law, there is still a small chance that you could be harmed if a release occurred.<br>A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for most insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.''<br>''Confidentiality and privacy of your protected health information:<br>We will take steps to keep your personal information confidential, but we cannot guarantee total privacy. Neither your name nor your identity will be used for publication or publicity purposes. As part of this study we may share a small amount of information about your genetic code and mutation in papers we write about this study. This could mean that others could identify that you were in this study, but they could only do so if they also had your DNA so that they could ''match'' your genetic code to what was published. Other people would not be able to tell anything about you (such as your hair or eye color) from the small amount of your genetic code that we may publish. We will create and collect health information about you as described in the Purpose and Procedures sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form. The investigators, study staff, and others at OHSU may use the information we collect and create about you in order to conduct and oversee this research study and store in a repository for future research. We may release this information to others outside of OHSU who are involved in conducting or overseeing research, including:<br>• The Food and Drug Administration<br>• The Office for Human Research Protections, a federal agency that oversees research involving humans |

(*continued*)

**Table 2. (Continued)**

| *Category* | *Relevant quotations*[a] |
|---|---|
| Whole exome/ genome sequencing | Those listed above may also be permitted to review and copy your records, including your medical records. We may also share your information with other researchers, who may use it for future research studies. A code number will be assigned to you, your cells and genetic information, as well as to information collected about you. Only the investigators named on this consent and authorization form and their research staff will be authorized to link the code number to you. Other investigators who may receive samples of your tissue and genetic information for research will be given only the code number which will not identify you.''<br>''We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission. When we send specimens or information outside of OHSU, they may no longer be protected under federal or Oregon law. In this case, your specimens or information could be used and rereleased without your permission. We may continue to use and disclose protected health information that we collect from you in this study indefinitely.<br>Some of the information collected and created in this study may be placed in your OHSU medical record. While the research is in progress, you may or may not have access to this information. After the study is complete, you will be able to access any study information that was added to your OHSU medical record. If you have questions about what study information you will be able to access, and when, ask the investigator.''<br>''If you withdraw your consent prior to the usage of your donated material by the researchers, your unused samples will be destroyed. Your identity and the data obtained from this study will be kept strictly confidential. Only the investigators listed above and their research staff will have access to identifying information and the data will be maintained indefinitely.<br>If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to: … Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already acted based on your authorization.''<br>**Confirmation of clinically relevant results:**<br>''If the results are important for your health care, you will be asked to have the tests repeated in a clinical laboratory. The costs for the repeat testing and the counseling necessary to be certain that you understand what the results mean may be billed to you or to your third party carrier. Note that this will probably make the results available to the third party carrier and to your clinical record. You may choose to pay out of pocket instead.'' |
| Compensation | *Form for oocyte donation:*<br>Compensation Prorated Amount (information extracted from a table):<br>Screening: $50<br>Ovarian suppression $50, $250 (on the first and last visit for ovarian suppression, respectively) |

(*continued*)

**Table 2. (Continued)**

| *Category* | *Relevant quotations*[a] |
|---|---|
| Compensation | Ovarian stimulation: $1,500 (on the last, fifth visit for ovarian stimulation)<br>Egg retrieval: $3,000<br>Follow-up: $200<br>''Upon full completion of this study you will be paid $5,000 for egg donation and $50 for skin donation (if applicable) as compensation for your time and costs related to this study. If you stop participating or are removed from the study before all your visits are complete, a pro-rated portion of this amount based on the number of visits completed following enrollment, will be paid to you. Please see the table at the end of this form for details on how compensation will be prorated. For patients diagnosed with a DNA mutation enrolled in the current study, reimbursement for travel expenses incurred during the study participation period is negotiable and can be discussed and agreed upon during the initial screening process. No other compensation is offered.<br>You may receive payment via a debit card. There may be fees (for example, if the card is inactive for more than six months), which will be deducted from the balance on your card.<br>Details on how to use the card and any fees are included in the separate card member agreement and FAQ sheet.<br>Payment received as compensation for participation in research is considered taxable income for a research subject. If payments are more than $600 in any one calendar year, OHSU is required to report this information to the Internal Revenue Service (IRS). Research subject payments exceeding $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the research subject and a copy will be sent to the IRS.''<br>*Form for sperm donation:*<br>''Upon completion of this study you will be paid $100 for semen and $50 for skin donation (if applicable) as compensation for your time and costs related to this study. We will ask you for your social security number for this purpose. You may receive payment via a debit card. There may be fees (for example, if the card is inactive for more than six months), which will be deducted from the balance on your card. Details on how to use the card and any fees are included in the separate card member agreement and FAQ sheet.'' |

[a]Unless stated otherwise, the quotations were found in both forms: for oocyte and sperm donation.
[b]Headings in bold are sub-categories identified by the authors.

**could be obtained only if prospective donors were made aware of the sensitive nature of the study**.''[e] The authors then describe the information included in the informed consent forms:

> The consent form clearly presented the scientific rationale for the study; stating … that gene editing tools will be used on eggs, sperm, and/or embryos to evaluate the safety and efficacy of gene correction for heritable diseases. Additionally, consent form language clearly stated that genetic testing would be conducted in addition to creation of preimplantation embryos and embryonic stem cell lines for *in vitro* analyses and stored for future use. The incidental discovery of genetic information that might be important to the donors' health care is a possible outcome when engaging in this type of research. Informed consent documents provided the donor with the option to receive this information or not.[9]

Presumably, this fragment describes what the authors consider as elements of the study that have a sensitive nature, each of which raises ethical concerns. Yet, one may ask whether gamete donors should be informed more explicitly and comprehensively about the ethical issues

involved in research and the potential clinical uses of GGE. In our analysis of consent forms, which aimed to retrieve any content with explicitly evaluative statements indicating that the nature of the study was sensitive, we found one paragraph that complied with this criterion (Table 2). Relevant to category 1 (sensitive nature of the study), the paragraph contains three main messages: (1) GGE is a controversial issue currently discussed by relevant stakeholders (e.g., scientists, national leaders, ethicists); (2) there is a consensus among stakeholders that there is a need for basic research on GGE; and (3) this research would inform discussions on whether GGE should be used in the clinic by providing information about its safety and efficacy. The first statement rightly indicates that GGE is a disputable issue. Yet, there is no further explanation as to *why* this is the case. The second statement, meanwhile, appears misleading, since, as delineated in the introduction, there are groups of scientists and other experts who do not necessarily agree that proceeding with research on GGE in embryos is the right path.[6,23] Such a description of ''consensus'' support for studies on GGE may encourage potential participants to take part in research that they would not have participated in otherwise. Notwithstanding, in the remainder of the consent forms, the facts of embryo destruction and risks involved in egg donation are clearly articulated. Hence, *some* of the sensitive issues accompanying GGE research were communicated to the research participants. Furthermore, gamete donors were given a chance to ask questions to the project researchers, who, if requested, could have explained, for example, the controversy around GGE. Yet, given that consent forms do not describe other serious ethical concerns over GGE (e.g., the limited medical need, the fact that GGE to establish a pregnancy is currently illegal in many jurisdictions), research participants were unlikely to know about these at the time of consenting, unless they were told about these verbally or were *a priori* interested in the subject and made efforts to find out more about the problematic aspects of GGE research. We suggest that gamete donors, and especially oocyte donors, who undergo all the inconveniences and are exposed to serious health risks, should be explicitly informed about ethical concerns, including that it is uncertain and contentious whether the results of the research may benefit anyone in the future.[f] This is all the more important, given the risks involved, presence of alternative methods (preimplantational diagnosis), and other issues, some of which were discussed earlier in this article. Furthermore, given the current ethical controversies and legal prohibitions on the use of clinical GGE, it is possible that such tools may simply not be allowed and/or be allowed for a very small portion of cases. To respect these women (and men who donate sperm) and ensure that their decisions to participate in the research are informed, we believe that ethical issues surrounding the study should be explicitly articulated in the consent forms.

### Possibility of undue inducement and burden placed on women

Decisions to participate in a study may be significantly influenced by information of potential risks, benefits, as well as other aspects of research, including the monetary compensation offered to egg donors (e.g., U.S.$5,000 was offered to women who donated eggs in the study by Ma *et al.*[9]). The problems of egg donor compensation, possibility of undue inducement, exploitation, and body commodification are not new and have been discussed in the context of stem-cell research.[24] In response to these issues, various guidelines and legislation addressing this matter have been issued.[25,26] The recent guidelines of the International Society for Stem Cell Research (ISSCR)[25] warn of the possibility of undue inducement and exploitation of socially disadvantaged women. However, they also allow offering compensation:

> Compensation for oocyte providers' time, effort, and inconvenience, if permitted by local human subjects review committees, should be reasonably consistent with recompense levels for other types of research participation involving similarly invasive and burdensome medical procedures.[27]

The ISSCR's guidelines do not specify the amount that would comply with these requirements.[25,27] It may be argued that considering the serious inconvenience and burden placed on women, U.S.$5,000 (and even higher sums) is a fair compensation to offer. Yet, such a sum still prompts a question regarding whether a woman in a financially difficult situation would be compelled to take part in the study to earn this. Indeed, one may argue that it is hardly possible to fulfil both of these two conditions together, that is, of fair compensation and avoiding undue inducements. Notably, not all hold the view that compensation for inconveniences involved in oocyte donation should be offered. The National Academies of Sciences suggest that women donating oocytes for stem-cell research should be reimbursed only for ''direct expenses incurred as a result of the procedure.''[26] In the United Kingdom, oocyte donors receive relatively low compensation of £750.[28]

Interestingly, it seems that these issues have not received much attention in discussions of the ethics of GGE. The remark made by Dickenson when discussing stem-cell research seems to be equally relevant when it comes to GGE studies: ''In most commentaries and

debates, the women from whom the ova are taken have virtually disappeared from view.''[29] As of now, it seems that among studies in which GGE was used, only one involved oocyte procurement specifically for that research[9] (Table 1). Yet, given the interest in GGE applications, advantages of using freshly created embryos in GGE experiments, and calls coming from various expert groups to continue research in order to gain more information about safety and efficacy of GGE, more experiments requiring likely high numbers of ova can be expected in the future. In this context, where a burden is placed on women in order to conduct certain types of research, important questions to ponder include whether it is acceptable to conduct ethically questionable research that involves serious health risks to potentially (financially) vulnerable individuals. Oocyte donation for research (mainly in stem cell studies) has been practiced for well over a decade and is accepted by professional guidelines (e.g., ISSCR). Yet, from the ''traditional'' medical research ethics perspective, including guidelines outlined in landmark documents such as the Nuremberg Code[30] and the Declaration of Helsinki,[31] one could conclude that such research is not acceptable, given the serious risks involved and uncertain and limited benefits of the research.[g] The current practice may suggest that the principle of autonomy of the research participants has been given more significance than other traditionally upheld bioethical principles such as beneficence or non-maleficence. On the other hand, if the informed consent process is inadequate in terms of information provided, it may not fully respect the autonomy of the persons involved.

## Consent to genomic sequencing

Ma *et al*.[9] not only obtained gametes and blood/skin samples from some of the donors, but also generated large amounts of the donors' genomic data through the whole genome sequencing (e.g., of embryos) and exome sequencing (e.g., of blood cells). This was performed at various stages of the study (among other reasons, to check for off-target effects). The central question is whether gamete donors were aware that large parts of their genomes would be sequenced and analyzed and, importantly, the consequences of this. The consent forms contain a few sections related to genetic testing and to the handling of genetic information, including the purpose and procedure of genetic testing, data storage and sharing, confidentiality and related risks, and return of clinically relevant results. Yet, surprisingly, neither whole genome or exome sequencing nor any synonym of these or explanation that a large part of the DNA would be sequenced was mentioned. Therefore, unless explained verbally by the researchers, it is unlikely that the research participants were informed or understood that genomic sequencing took place. Such information may be relevant to decision-making of potential gamete donors, thus it should not be minimized in the context of wider research projects. Tabor *et al*. suggested that ''researchers should consider whether participants should be told specifically about ES/WGS during informed consent in order to maintain transparency and trust in the research enterprise.''[32] Furthermore, regarding the necessary elements of informed consent, the Common Rule[33] recently recognized the importance of explicitly communicating to research subjects when genomic sequencing may be conducted on their samples.

## Readability

In addition to the presence of certain elements of information in the consent forms, we analyzed how easily understandable the text of the forms might have been for research participants. The readability levels obtained in our analysis (in both forms around 13), indicate that a person would have to complete 13 years of education (e.g., to 1st year university in the United States) to understand the text fully; this is significantly above the grade level of 8, recommended by U.S. medical schools.[34] The difficulty and length of the forms (the estimated time needed to read the oocyte donation form is roughly 40 minutes) may potentially be factors deterring people, especially without previous knowledge of genetics, from reading it thoroughly. Even if research participants had taken the time to read all of the forms, it is questionable whether they were able to understand all of the content.

The problems with communication about genomics have been identified previously, including in the context of informed consent forms for genomic sequencing.[35] Consent to genomic sequencing exposes a tension identified in other contexts, that is, between the requirement of specific consent, which entails that the numerous aspects (potentially) relevant to decision making should be explained, and the aim of obtaining truly informed consent, which is contingent upon comprehension of the information received. The latter condition requires that information is presented in an understandable, accessible, and ideally concise manner. Genomic sequencing (and editing) and its implications are complex matters to convey, and efforts need to be taken to find the proper vocabulary to communicate with people who do not have expertise in this area. Adding in the scientific and ethical complexity of GGE should only make us more vigilant in creating consent forms and consent processes that participants can understand. Otherwise, obtaining consent becomes a mere administrative detail to check off and not a communication process that helps individuals

understand the consequences of their participation and in this way protects against potential abuse and facilitates informed decision making.

## Conclusion

In conclusion, our study indicates deficiencies in how the consent forms addressed various issues, in particular, limited and seemingly misleading information about the sensitive nature of the study, a lack of an explicit mention of genomic sequencing and general low readability of the forms. While our study could not assess whether the first two issues were addressed verbally during the consent process, there are good reasons (e.g., complexity of the science and ethical issues) for such information to be included in writing in the forms. Efforts to communicate to research participants effectively and to provide them with comprehensive information about GGE studies, including about their ethical implications, should be undertaken seriously to ensure that these individuals are engaged in a respectful way and that their consent is informed. This issue seems particularly urgent in light of the numerous calls for inclusive debate and public engagement regarding the use of GGE. Arguably, gamete donors, in particular oocyte donors, are currently the most affected group by GGE research, especially in studies that require gamete donation outside of the IVF context. Therefore, they should be recognized and acknowledged as particularly important stakeholders, and communication with them should be done thoughtfully. It is important to note that such improvements in engagement and communication is an ongoing process that ultimately is the responsibility of many parties, not just the scientists or even the ethics committees. The authors of the study addressed herein explicitly mention that they actively engaged with and followed their ethics' committee guidance. Hence, we do not highlight weaknesses in the consent forms to point a finger, but rather to identify the cracks in the system with the aim of helping stakeholders reflect on an ethically challenging field.

Finally, we highlight the question of the necessity and acceptability of research that poses serious (short- and long-term) health risks to potentially vulnerable women and which may foster future clinical uses for which medical need is doubtful and involving numerous serious concerns. While some expert guidelines call for continuation of GGE research, it is valid to question whether they adequately recognize and acknowledge that some types of research would put a particularly grave burden on (vulnerable) women. As stakeholders in genomics, we should aim to uphold high ethical standards for research so that the progress in science is truly for benefit, and not to harm, especially when it comes to the most vulnerable.

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## Endnotes

[a]An alternative to gamete extraction for the purpose of research is the use of leftover gametes derived from IVF procedures. Yet, in this case, gametes with a genotype desired by researchers may not be available, and recruitment of gamete donors meeting specific criteria may be the only possibility to conduct a planned experiment.

[b]There are at least three situations in which GGE could be applied in a clinical context. In each of these situations, the goal would be to obtain genetically related offspring that possess certain traits (e.g., not being affected by a disease). (1) Very rare cases of couples who carry gene variants in configuration that will cause a monogenic disease in all their children. There is no alternative approach for them to have children genetically related to both parents and not affected by disease. (2) Couples who carry gene variants that will likely result in a portion of their offspring having a disease and a portion without disease. In such cases, preimplantation genetic diagnosis (PGD) may be currently used to identify embryos *in vitro* that do not have a disease variant and implant these to establish a pregnancy. (3) Enhancement purposes, for example increase of resistance to a given disease; see the study of He Jiankui as an example (described in Introduction).

[c]While elaborating in depth on the debate on the distinction between therapy and enhancement goes beyond the scope of this article, we can briefly highlight that part of the debate around the potential use of human GGE and the use of somatic GE focuses on the purpose

of the editing. For example, the National Academies of Sciences, Engineering, and Medicine admits that drawing a clear line between treatment and enhancement is challenging and recommends that GE should not be used ''for purposes other than treatment or prevention of disease or disability.''[17]

[d]The form for donation of discarded and/or excess materials from IVF refers to eggs and embryos obtained in IVF procedures. From the description in the methods section in the article by Ma *et al*.[9] it is not clear if ''spare'' oocytes obtained in the IVF procedures were used in the study in addition to oocytes retrieved specifically for the research. While discussion of the use of such ''spare'' oocytes in research is beyond the remit of this article, we want to highlight that such practice raises ethical issues as well (see, e.g., Baylis[7]).

[e]Emphasis added by authors.

[f]The consent forms state: ''…by serving as a subject, you may contribute new information which may benefit patients in the future.''

[g]For example, the Declaration of Helsinki states: ''Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects … All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.'' Similarly, the Nuremberg Code outlines: ''The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.''

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