



Published in final edited form as:

*Circ Cardiovasc Genet*. 2017 October ; 10(5): . doi:10.1161/CIRCGENETICS.117.001910.

## What do we really think about human germline genome editing, and what does it mean for medicine?

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### Abstract

Genome editing has captured widespread attention due to its potential therapeutic applications. Early studies with human embryos have established the feasibility of human germline genome editing but raise complex social, ethical, and legal questions. In light of the potential impact of genome editing on the practice of cardiovascular medicine, we surveyed ≈300 attendees at a recent American Heart Association conference to elicit their opinions on somatic and germline genome editing. The results were revealing and highlight the need to broadly engage the public and solicit the opinions of various constituencies before proceeding with clinical germline genome editing.

### Keywords

Genetics; gene therapy; CRISPR; Cas9

Genome editing with clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated 9 (CRISPR-Cas9) has proven so effective in vitro and in vivo that human therapeutic applications are already under pursuit. Clinical trials for somatic genome-editing therapies, i.e., modification of cells, tissues, and organs in living people, have been announced in the U.S. and China. The first reports of human germline genome editing (GGE), i.e., embryo modification, were published in 2015 and 2016, although those studies used nonviable embryos and relatively crude first-generation CRISPR-Cas9 tools. A more recent report in August 2017 of GGE to correct a disease-causing gene mutation in viable human embryos that, in principle, could have been carried to term and resulted in healthy offspring was widely heralded in the press as a breakthrough and drew considerable

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### Disclosures

None.

attention.<sup>1</sup> What was particularly notable about this study was that the correction of the mutation was efficient and specific—unlike the earlier studies, unintended mutations were not observed elsewhere in the genome (off-target effects) in edited embryos, and mosaicism (mutations present in some cells in the embryo but not in other cells) was largely eliminated. Furthermore, the relevance to cardiovascular medicine was unambiguous, since the sperm used for the study originated from a man with severe hypertrophic cardiomyopathy, with the corrected mutation being in the cardiac myosin-binding protein C (*MYBPC3*) gene. In light of this study, it is clear that human GGE is now feasible and might be achieved for some genes without off-target effects. In addition to remaining safety concerns, the path to clinical use will now have to contend with important social, ethical, and legal issues. The future is upon us, whether we like it or not.

Recognizing the relevance and potential impact of these issues on the future practice of cardiovascular medicine, the American Heart Association's Council on Functional Genomics and Translational Biology co-sponsored a plenary session entitled "Scientific, Clinical and Ethical Implications of Genome Editing" at ATVB|PVD Scientific Sessions in Minneapolis, Minnesota, in May 2017. The objective of the session was to provide attendees with sufficient background regarding CRISPR-Cas9 genome editing so that they could then meaningfully explore and discuss how genome editing might be relevant to clinical practice. We (the authors) gave short presentations that covered: the basic concepts of CRISPR-Cas9 genome editing; how CRISPR-Cas9 has transformed the way in which mouse models of human physiology and disease are made, making the process far more rapid and efficient;<sup>2</sup> proof-of-concept studies demonstrating that CRISPR-Cas9 targeting of genes in the mouse liver can beneficially modify lipid traits, heralding possible one-shot, lifelong treatments for dyslipidemia and coronary heart disease;<sup>3, 4</sup> potential dangers of genome editing (e.g., unintended mutations) and strategies to reduce those dangers;<sup>4, 5</sup> potential clinical scenarios in which one might contemplate performing GGE, including the preemption of devastating genetic diseases in one's offspring, the reduction of risk of common disorders such as coronary heart disease and Alzheimer disease, and the addition of desired non-medical traits ("enhancements"); the possibility of implementing GGE not in embryos but rather in germ cells such as sperm and oocytes, which might be less morally objectionable to some people; and potential adverse consequences of modifying the human germline, such as spreading susceptibility to certain diseases or exacerbating societal inequities. In particular, it was pointed out that although many commentators have noted that in vitro fertilization paired with pre-implantation genetic diagnosis can often avoid any need for GGE, there are situations where all unmodified embryos will yield offspring with disease—two parents with a recessive disorder such as sickle cell disease or cystic fibrosis, or a parent homozygous or compound heterozygous for dominant mutations such as the Huntington disease repeat expansion. In these cases, GGE might be the only way for parents to have a healthy, genetically related child.

After the presentations, we used an audience response system to gauge opinions on a variety of questions related to somatic genome editing and GGE (Table), with responses from a total of 301 attendees. The survey was followed by a "town hall" style discussion. Most of the respondents were basic scientists or clinical researchers, with a small proportion being clinical practitioners. A strong majority (80%) supported the use of somatic genome editing

in adults to prevent serious diseases; indeed, 69% would opt to themselves receive a safe, one-shot genome-editing therapy that would permanently reduce the risk of coronary heart disease. In stark contrast, the vast majority (83%) was opposed to the notion of using somatic genome editing to acquire desired traits such as athletic ability.

With respect to human GGE, a substantial majority (68%) supported in vitro research that would not culminate in pregnancy—studies like the one published in August 2017 in which *MYBPC3* gene correction was performed in embryos. This is notable because numerous official statements have also endorsed such research, including ones from the U.S. National Academies of Sciences, Engineering, and Medicine<sup>6</sup> and the American Society of Human Genetics.<sup>7</sup> A substantial majority of our respondents also supported public (government) funding of in vitro research that would not culminate in pregnancy. Although this is probably a non-starter in the U.S. for the foreseeable future, it accords with the call from the American Society of Human Genetics that there be no prohibition on public funding of in vitro research.<sup>7</sup>

With respect to clinical uses of GGE, a majority (61%) supported its use by parents if there were no other means to have a healthy biological child. Opinions were fairly evenly split as to whether it was acceptable for GGE to be used to reduce the risk of a child having a serious medical condition (45% yes, 40% no); of note, a Pew Research Center survey in 2016 found a similar split among U.S. adults when asked if “the possibility of gene editing to give healthy babies a much reduced risk of serious diseases is something they would/would not want for their baby” (48% yes, 50% no).<sup>8</sup> In stark contrast, our respondents were almost universally opposed to the notion of using GGE to increase the odds of a child having a desired trait, such as athletic ability.

Assuming that clinical use of GGE was to proceed, a substantial majority (68%) was supportive of the costs being covered by public (government) health care to ensure broad access. Finally, and perhaps most crucially, our respondents overwhelmingly were opposed to GGE if the public was not asked about their opinion on the issue (although, curiously, fewer respondents were opposed if the public had been asked but was not supportive). This appears to reflect a general sentiment that the public should be consulted before any clinical application of GGE proceeds.

We note the obvious limitation that our respondents, all of whom were attendees at a scientific conference, might not be representative of the “public.” Indeed, the “public” itself is a highly heterogeneous entity comprising a variety of constituencies. Nonetheless, we felt that the plenary session was an example of a meaningful consultation with an important constituency, one that could be replicated in some format in many settings with many different constituencies. In light of the American Society of Human Genetics statement’s call for “a transparent public process to solicit and incorporate stakeholder input,”<sup>7</sup> we urge health advocacy organizations like the American Heart Association to foster and participate in that process.

## Acknowledgments

We thank the organizers of ATVB|PVD Scientific Sessions 2017 and the American Heart Association staff for their support of the plenary session and the use of the audience response system.

## Abbreviations

**GGE**      germline genome editing

## References

1. Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, et al. Correction of a pathogenic gene mutation in human embryos. *Nature*. 2017; [Epub ahead of print]. doi: 10.1038/nature23305
2. Miano JM, Zhu QM, Lowenstein CJ. A CRISPR Path to Engineering New Genetic Mouse Models for Cardiovascular Research. *Arterioscler Thromb Vasc Biol*. 2016; 36:1058–1075. [PubMed: 27102963]
3. Ding Q, Strong A, Patel KM, Ng SL, Gosis BS, Regan SN, et al. Permanent alteration of PCSK9 with in vivo CRISPR-Cas9 genome editing. *Circ Res*. 2014; 115:488–492. [PubMed: 24916110]
4. Jarrett KE, Lee CM, Yeh YH, Hsu RH, Gupta R, Zhang M, et al. Somatic genome editing with CRISPR/Cas9 generates and corrects a metabolic disease. *Sci Rep*. 2017; 7:44624. [PubMed: 28300165]
5. Chadwick AC, Wang X, Musunuru K. In vivo base editing of PCSK9 (proprotein convertase subtilisin/kexin type 9) as a therapeutic alternative to genome editing. *Arterioscler Thromb Vasc Biol*. 2017; [Epub ahead of print]. doi: 10.1161/ATVBAHA.117.309881
6. National Academies of Sciences, Engineering, and Medicine. Human Genome Editing: Science, Ethics, and Governance. Washington, DC: The National Academies Press; 2017. Available from: <https://doi.org/10.17226/24623>
7. Ormond KE, Mortlock DP, Scholes DT, Bombard Y, Brody LC, Faucett WA, et al. Human germline genome editing. *Am J Hum Genet*. 2017; 101:167–176. [PubMed: 28777929]
8. Pew Research Center. U.S. Public Wary of Biomedical Technologies to ‘Enhance’ Human Abilities. 2016. Available from: [http://assets.pewresearch.org/wp-content/uploads/sites/14/2016/07/02120148/PS\\_2016.07.26\\_Human-Enhancement-Survey\\_FINAL.pdf](http://assets.pewresearch.org/wp-content/uploads/sites/14/2016/07/02120148/PS_2016.07.26_Human-Enhancement-Survey_FINAL.pdf).

**Table 1**

Survey results from 301 total respondents at a plenary session on genome editing at ATVB|PVD Scientific Sessions 2017

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Which of the following best describes your primary occupation?
Basic scientist = 74%
Epidemiologist = 1%
Clinical researcher = 12%
Clinical practitioner = 6%
Other = 7%
If you had the opportunity to receive a one-shot somatic genome-editing therapy that would permanently reduce your risk of coronary heart disease, would you do so (assuming the therapy is 100% safe)?
Yes = 69%
No = 19%
Don't know = 12%
Would you support basic in vitro human germline genome editing research that would not culminate in pregnancy (e.g., to study developmental biology)?
Yes = 68%
No = 22%
Don't know = 10%
Would you support public (government) funding of basic in vitro human germline genome editing research that would not culminate in pregnancy?
Yes = 71%
No = 20%
Don't know = 10%
Do you think it would be acceptable for parents to use human germline genome editing to have a healthy biological child when there is no other means to do so?
Yes = 61%
No = 28%
Don't know = 11%
Do you think it would be acceptable for parents to use human germline genome editing to reduce the risk of their child having a serious medical condition (e.g., premature coronary heart disease or Alzheimer disease)?
Yes = 45%
No = 40%
Don't know = 15%
Do you think it would be acceptable for parents to use human germline genome editing to increase the odds of their child having a desired trait (e.g., athletic ability)?
Yes = 2%
No = 95%
Don't know = 3%
Do you think it would be acceptable for an adult to receive somatic genome editing to acquire a desired trait (e.g., athletic ability)?
Yes = 13%
No = 83%
Don't know = 4%
Do you think it would be acceptable for an adult to receive somatic genome editing to reduce the risk of having a serious medical condition (e.g., premature coronary heart disease or Alzheimer disease)?

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Yes = 80%  
No = 13%  
Don't know = 7%

Would you support clinical applications of human germline genome editing if the public was not asked about their opinion on the issue?

Yes = 19%  
No = 72%  
Don't know = 9%

Would you support clinical applications of human germline genome editing if the public was asked about the issue but was not supportive?

Yes = 36%  
No = 49%  
Don't know = 15%

Would you support the costs of clinical applications of human germline genome editing being covered by public (government) health care to ensure broad access?

Yes = 68%  
No = 25%  
Don't know = 7%

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