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## Justice in CRISPR/Cas9 Research and Clinical Applications


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**Abstract**

CRISPR/Cas9 is a rapidly developing gene editing technology that will soon have many clinical applications. As with many other new technologies, somatic gene editing with CRISPR/Cas9 raises concerns about equitable access to therapies by historically disenfranchised racial and ethnic minorities. We describe justice concerns related to CRISPR/Cas9, including its potential impact on historically mistreated populations through underrepresentation of minorities in genomic databases and the potential for disparate access to somatic gene therapies when they become clinically available. We then describe ongoing work that aims to address these justice concerns. We conclude by highlighting important considerations to ensure equitable access to therapies going forward, including enhancing diversity in genomic sequencing efforts, improving education and transparency, and building partnerships with underserved and socially disenfranchised communities.


### Introduction

Gene editing has been possible for years with tools such as Zinc-finger nucleases and TALENs (transcription activator-like effector nucleases).[1] CRISPR/Cas9 is one such adaptable and specific tool in which an RNA "guide" binds to a specific stretch of DNA and directs the Cas9 nuclease to introduce a cut in the genetic sequence. Other functional groups can be added to further alter the stretch of DNA.[2,3] CRISPR/Cas9 has many potential clinical applications. The initial focus has been on cancer immunotherapy and correction of single gene disorders.[4-6] For example, several teams have used the CRISPR/Cas9 system to correct pathogenic variants underlying beta thalassemia, a hemoglobinopathy.[7] CRISPR/Cas9 offers multiple options to correct such defects, including changing the genetic code at the locus containing the pathogenic variant or creating an alternate hemoglobin product that can reduce severity of disease. With the

advent of CRISPR/Cas9 come new considerations of when and how this technology should be applied in the clinical setting.

A key ethical distinction in discussions of human genome editing is that between germline applications (alterations that will be passed down to future generations) and somatic applications (those that will not be passed down),[8] which is addressed in detail in the consensus report of the International Summit on Human Gene Editing.[9] Germline editing is controversial because of ethical and clinical risks inherent in making a genetic change that would be inherited. Although the National Academies of Sciences, Engineering, and Medicine (NASEM) have recently begun to discuss criteria for ethical germline editing,[10] most professional societies—including the NASEM, the American Society of Human Genetics, the European Society of Human Genetics, and the American College of Medical Genetics and Genomics—currently forbid germline gene editing.[9,11-13] For this reason, this discussion will be limited to somatic gene editing only.

For CRISPR/Cas9 to be maximally beneficial to all communities—and to potentially mitigate, rather than exacerbate, health care disparities—equitable opportunities to participate in and benefit from research are paramount. This article will detail several barriers to equitable participation in and benefit from this kind of research and opportunities to overcome these barriers.

**Barriers to Equitable Participation in and Benefit from Research**

*Mistrust of research.* Minority groups in the United States have repeatedly experienced unequal and unethical treatment in research, ranging from participation without adequate informed consent to forced or coerced participation in treatments and studies. This mistreatment is perhaps most notable among African Americans in light of transgressions such as those in the US Public Health Service Tuskegee Syphilis Study, but numerous other groups have experienced similar mistreatment.[14-16] Scars from this mistreatment still create mistrust of the medical and scientific community, as evidenced by low enrollment rates of African Americans and other minority groups in many research studies.[14,17,18] Furthermore, minority communities are aware of health disparities and that they often receive inferior care compared to wealthier, nonminority groups.[19,20] Concerns of minority groups in the US include unjust distribution of new resources and the potential for genetic enhancements to actually exacerbate disparities.[21] These concerns must be addressed in the enrollment phase of new trials of CRISPR/Cas9 to ensure adequate representation of minority patients and adequate protection of these historically mistreated groups.

*Underrepresentation in research.* A second barrier to equitable participation in research is underrepresentation of minority patients in genetic databases that inform future research. While the National Institutes of Health (NIH) Human Genome Project and the United Kingdom's 100,000 Genomes Project have expanded general knowledge of the

human genome, overall there has been a lack of diversity in large-scale genome projects.[22,23] Recent work estimates that only 3% of participants in genome-wide association studies (GWAS) published in the GWAS catalogue are of African descent.[24,25] These studies are crucial for understanding associations between genetic variants and disease within specific populations. Without adequate understanding of the range of clinical variants, it will be harder to tailor therapies specifically to minority populations if less is known about their genomic makeup. Consequently, underrepresented minorities will likely miss out on potential gene therapy benefits.[26]

*Disparate access to research benefits.* Racial and ethnic minorities in the US have very disparate health outcomes and access to health care. In this country, socioeconomic status is strongly associated with race and ethnicity,[27,28] raising concerns that the benefits of gene therapy will prove unavailable to some of the neediest groups for financial reasons.[29,30] Gene therapy treatments might initially be funded through research, but these are likely to be prohibitively expensive for many once commercially available. When such new therapies are introduced to the market, minority populations are less likely to have access to them.[31] Some of this inequity in access is hypothesized to be a result of overt or subconscious racism and differential treatment in medicine.[17,32] There is likely also a disincentive to participate in research if potential participants perceive that benefits of research might not be available to them, although research is needed to support this hypothesis.

**Taking Steps Forward**

To overcome the aforementioned barriers to minorities' participating in and benefiting from research, the scientific community must ensure diversity in genomic sequencing, build trust and partnerships, and advocate for equitable access to emerging therapies. An early attempt to address the lack of diversity in genomic databases was the Human Genome Diversity Project, through which human genomes from around the globe were sequenced in order to better understand genomic diversity.[33] A further step is the NIH's All of Us research project, a national effort to enhance diversity in genome sequencing in part through partnerships with numerous hospital systems and community health advocacy groups such as the Black Women's Health Imperative.[34] This work and that of other organizations has promise as a step toward making clinical applications of gene editing more equitable across all populations, but further work is necessary.

Increasing diversity of genomic databases is necessary not only to produce more relevant research and clinical applications, but also to create a sense of inclusion and trust among historically disenfranchised minority communities. Establishing such partnerships in somatic gene therapy research and its clinical applications must happen on a health systems level, not just on a patient-clinician level. The duty of balancing risks and ensuring informed consent cannot solely be fulfilled by adhering to the normal human subjects protections procedures provided by institutional review boards.[16]

Medical and research communities need to prove to the public that inclusion of minority groups in genetic research and equal access to the benefits of this research are high priorities and that opinions and concerns of minority communities are considered when designing protocols and developing new therapies.[14] Input from stakeholder groups—both experts and laypeople—tasked specifically with considering long-term implications of somatic gene therapy for minority groups is crucial. These stakeholder groups should be assembled from communities that will face the direct risks and potential benefits of research. If a gene editing study for sickle cell disease (SCD) is conducted, for example, input should be sought from patients with SCD and from advocacy groups like the Sickle Cell Disease Association of America to promote equitable access to somatic gene therapy upon its arrival in the clinic.

Partnerships with minority communities must involve transparency, education of the public about gene editing and research studies design, and meticulous informed consent.[6,35] The National Human Genome Research Institute has several groups dedicated to exploring health disparities in genomics along with avenues of engaging minority groups and the public.[36-38] These initiatives should be expanded and serve as models for larger-scale efforts to engage minority groups and build trust. Transparency will require translating published materials of relevant studies into language interpretable by the public and making discussions of the ethics and science related to applications of gene editing available outside academic medical centers and scientific journals. The scientific community should devote resources not only to engage and educate the public but also to study the effectiveness of these interventions. The same methodological rigor that is applied to the science of gene editing must be applied to public education and dissemination of research results.

Conversations about the ethics of clinical applications of gene editing and its potential impacts on minorities have been happening for years.[9,11,39] These conversations should continue to move into the public sphere. NIH funding is now available to study the ethics of genomics and its applications; the issues of access and justice need urgent exploration.[40] It will be important to reach out to minority communities directly to ascertain their specific concerns. One such study, examining perspectives of SCD patients on gene editing in SCD, is already underway.[41]

**Conclusions**

To ensure just distribution of risks and benefits of research, the medical-scientific community must foster trust and open communication with historically disenfranchised groups. Basic scientists, physicians, and health policymakers must work to ensure justice in gene therapy locally and worldwide. While gene editing poses a risk of maintaining or even widening health inequities, it could also be a tool to reduce them. One main goal of CRISPR/Cas9 somatic gene therapy can and should be its use as a form of preventive medicine to address specific racial and ethnic disparities in health outcomes. Toward this

end, researchers and clinicians must continue to act as educators, builders of community partnerships, and advocates for just and equitable access to these new technologies.

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