

**Genome Editing in Clinical Genetics, Points to Consider:
A Statement of the American College of Medical Genetics and Genomics**

BETHESDA, MD – January 26, 2017 | The American College of Medical Genetics and Genomics is weighing in on the genome editing/CRISPR debate with a new Points to Consider statement, “Genome Editing in Clinical Genetics.” Genome editing, including CRISPR/Cas9, is a new and notable technology that enables geneticists and researchers to edit parts of the human genome. ACMG recognizes that genome editing offers great promise for the future treatment of individuals and families with genetic disorders, but also raises major technological and ethical issues that must be resolved before clinical application. The potential for rapid advance of this approach, and the pressure to apply it clinically, should not be underestimated. The ACMG Board of Directors strongly encourages broad public debate regarding the clinical application of genomic editing and will appoint an ad hoc committee to recommend specific areas where it can contribute to this debate.

ACMG President Gerald Feldman, MD, PhD, FACMG said, “ACMG is excited about the vast potential for genome editing that will benefit patients with rare genetic disorders, not to mention other conditions such as cancer. We are aware that there are clinical trials already ongoing in treatment of cancer and others likely to be launched in the near future, including for genetic conditions. Our goal in this statement is to draw attention to the opportunities for treatment of genetic conditions, some of the challenges that are being actively addressed, and the ongoing concern about even greater challenges associated with germline, as opposed to somatic, genome editing. We look forward to facilitating in any way we can the rapid and safe transfer of this important technology to clinical application.”

Background

Medical geneticists provide diagnosis, counseling, management, and treatment for individuals and families affected by genetic disorders. These disorders are due to genetic variations that may range from gain or loss of entire chromosomes to alterations involving only a single DNA base pair. Management and treatment options have typically included anticipatory guidance, surveillance for complications, surgery, dietary management, medications, and in some recent instances, gene replacement therapy. Progress in these areas has brought comfort, hope and relief to many patients and families who live with genetic conditions, some of which have devastating effects on health and well-being.

Because the underlying causes of these conditions may be changes in the structure of a gene or a region of the genome, the question has been raised whether it is possible to alter the genetic code in an affected individual to alleviate the pathology. In principle this could be done in somatic (nonreproductive) cells to restore function at the tissue level, or it could be done in the embryo, both to treat that individual and to remove the variant from the germline (reproductive cells) of that individual. Until recently, this kind of approach was technologically out of reach, but with the advent of genome editing approaches, especially CRISPR/Cas9, it is becoming increasingly feasible.

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Genome editing is an area of very rapid technological change, so what is not possible today could well become a reality in the very near future. As a consequence, although ACMG is focused on current clinical practice, the ACMG Board of Directors felt compelled to issue these points to consider on the potential clinical application of genome editing.

ACMG's Points to Consider

1. ACMG applauds the research applications of genome editing technologies, which are proving to be of great value in developing disease models and studying disease mechanisms. However, the current limitations in these technologies — such as off-target effects — must be overcome prior to any clinical application.

2. Application of genome editing technologies to alter pathogenic variants in somatic cells offers promise in the treatment of individuals with disorders due to single gene variants that primarily affect specific tissues, such as liver or blood cells. As with any new clinical intervention, clinical application of genome editing technology will require stringent medical and genetic review.

Among the concerns that must be addressed are the need to assure that:

- a. the underlying pathogenic variant has been corrected to a form that will not be pathogenic;
- b. no other genetic variations have been introduced in the process of editing the pathogenic variant;
- c. the cells that have been edited have not acquired other genetic variants as part of the process of treatment, for example during cell culture; and
- d. the cells treated do not have epigenetic marks that will result in abnormal function if transplanted back into an individual.

3. Application of genome editing at the level of the embryo raises many technical and ethical concerns, including:

- a. The risk of off-target effects of genome editing may have unpredictable consequences to the embryo and, since the germline is involved, to future generations as well. Any potential adverse effects could have far-reaching consequences that could take years or even decades to recognize.
- b. The consequences of editing a pathogenic variant may have unknown epigenetic effects that may alter normal patterns of gene expression in some tissues.
- c. The decision as to which specific genetic variants should be subject to genome editing needs further discussion at a societal level. Some variants that are associated with highly penetrant disorders with major adverse effects on health and quality of life might seem like compelling candidates for therapeutic editing. It is inevitable, however, that consideration will also be given to editing variants associated with phenotypes that are not fully penetrant and for which effects on quality of life are less clear. Ultimately, one can foresee efforts to edit variants associated with non-disease traits or contribute to multifactorial disorders in unpredictable ways. Such issues are not typically of concern in the management of children or adults with genetic conditions, but will become critical if gene editing in the embryo is contemplated.

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In light of these potentially serious and far-reaching concerns, the ACMG Board of Directors believes that genome editing in the human embryo is premature and should be subject to vigorous ethical debate and further refinement of technological issues. The ACMG will appoint an ad hoc committee to recommend specific areas where it can contribute to this debate.

The new ACMG Points to Consider statement is available at:

<http://www.nature.com/gim/journal/vaop/ncurrent/full/gim2016195a.html>

About the American College of Medical Genetics and Genomics (ACMG) and ACMG Foundation

Founded in 1991, ACMG is the only nationally recognized medical society dedicated to improving health through the clinical practice of medical genetics and genomics. The American College of Medical Genetics and Genomics (www.acmg.net) provides education, resources and a voice for 2000 biochemical, clinical, cytogenetic, medical and molecular geneticists, genetic counselors and other healthcare professionals, nearly 80% of whom are board certified in the medical genetics specialties. The College's mission is to develop and sustain genetic initiatives in clinical and laboratory practice, education and advocacy. Three guiding pillars underpin ACMG's work: 1) Clinical and Laboratory Practice: Establish the paradigm of genomic medicine by issuing statements and evidence-based or expert clinical and laboratory practice guidelines and through descriptions of best practices for the delivery of genomic medicine. 2) Education: Provide education and tools for medical geneticists, other health professionals and the public and grow the genetics workforce. 3) Advocacy: Work with policymakers and payers to support the responsible application of genomics in medical practice. *Genetics in Medicine*, published monthly, is the official ACMG peer-reviewed journal. ACMG's website (www.acmg.net) offers a variety of resources including Policy Statements, Practice Guidelines, Educational Resources, and a Find a Geneticist tool. The educational and public health programs of the American College of Medical Genetics and Genomics are dependent upon charitable gifts from corporations, foundations, and individuals through the ACMG Foundation for Genetic and Genomic Medicine (www.acmgfoundation.org).

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