

# HUMAN GENOME EDITING FAQ

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## DEFINITIONS

### What is a genome?

A genome is the instruction book of a cell that is encoded by four letters found in DNA (A, G, T & C, also known as bases). The order, or sequence, in which these letters are written are translated by cells ultimately leading to the manufacture of proteins which enable cells to grow, survive & communicate with other cells.

The genome can be broadly broken into two components 1) coding DNA called genes that encode the proteins and 2) non-coding DNA which regulates when and how genes are turned on within the cell. Within humans there are approximately 20,000 genes that encode the human body. Of those 20,000 genes there are more than 6,000 genetically based diseases identified so far where the DNA sequence has been changed in such a way as to result in abnormal protein levels or function.

### What is genome editing and how does it work?

Genome editing is a process by which a DNA sequence is modified to elicit a desired outcome within a living cell. Though DNA modification techniques have existed for decades, recent advances in genome editing technology have provided scientists and researchers with far more precise and efficient genome editing tools. Scientists are exploring myriad potential uses for these tools, including agricultural, environmental, and clinical applications. In basic research, genome editing is being used to determine the roles different genes play in disease. Medical researchers are exploring ways to use genome editing to treat or prevent genetically-defined human diseases.

Genome editing is based on a naturally occurring system that directs a molecular scissors, called a nuclease, to a target region of DNA. The DNA is targeted by a recognition signal that is specific to a fragment of DNA. Once the nuclease has been directed to the appropriate region of DNA it cuts the DNA. The DNA is then repaired by a process found naturally in every one of our cells. This repair machinery is there to repair any break that may occur within your DNA.

Once the DNA is cut, the cell can be directed to repair that region of DNA in three different ways:

1. Insertion of a DNA sequence, when a template DNA is provided to the cell in parallel with the targeted cutting.
2. Deletion of a DNA sequence, when two regions of DNA are cut.
3. Change of a DNA sequence, when a corrective template DNA is provided.

### What is the difference between somatic cell and germline genome-editing?

**Somatic cells** are cells whose genetic material *cannot be passed on to future generations of people*. The vast majority of cells in the human body are somatic cells, examples of which include the tissues that make up our skin, muscles, lungs, liver, and heart as well as blood cells. Changes to somatic cells will only impact an individual patient who consents to participate in a genome editing procedure. Current therapeutic applications of genome editing focus on somatic cells.

**Germline cells** (or germ cells) are any cells in multicellular organisms whose genetic information may be inherited by future generations of that species. In humans, examples of germ cells include sperm or egg cells, fertilized embryos, or

reproductive stem cells. As such, any genetic manipulations in germ cells could be passed down to future generations if they resulted in a pregnancy that came to term. Such changes would then be introduced into the human gene pool, or total collection of heritable human genetic information.

### How many kinds of genome editing technologies exist, and how do they differ (TALENs, Zinc Fingers, and CRISPR)?

Broadly speaking, there are three major genome editing technologies in use today to make targeted DNA edits. Although each works slightly different, all of them rely on nucleases—proteins that cut DNA—and they can all bind to and edit targeted genes. These include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the more recently discovered Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) nucleases.

**Meganucleases** represent a fourth category, but are not as widely used for potential clinical applications. The decreased cost and increased speed of making specific DNA and RNA has greatly improved the efficiency of these technologies.

All genome editing technologies can be used to delete, insert, or repair the sequence of DNA with the use of a nuclease enzyme. Once optimized for cell type, these nucleases can work on any type of DNA including that of humans, animals, plants, or microorganisms like bacteria. To insert or make corrections in the DNA, a new template DNA must be added to the therapy along with the nuclease. All genome editing systems must also be delivered into the body as DNA or RNA in order to function.

Zinc Finger and TALEN platforms rely on modular proteins, in addition to the nuclease, to recognize a target sequence of DNA (*e.g.*, a gene). Modification of the Zinc Finger or TALE proteins allows for a variety of DNA sequences to be targeted for editing. Due to the optimization process of the binding proteins, these platforms allow for high on-target efficiency.

The CRISPR genome editing system utilizes specifically designed guide RNA that can find and bind to a specific DNA sequence. The CRISPR nuclease then edits or removes the targeted DNA that is the root cause of a disease. Different guide RNAs can be created to target different DNA sequences enabling multiple sites within a genome to be targeted in a single procedure. This provides for the versatility to address complex diseases at the genetic level.

## **SOMATIC CELL GENOME EDITING IN HUMANS TO TREAT DISEASE**

### What are the potential applications and benefits of human genome editing technologies to treat or cure disease?

Genome editing technologies hold tremendous promise to treat genetically-defined diseases. Using genome editing, scientists and clinicians may not only treat the symptoms of a disease, but address its underlying root cause at the genetic level. Genome editing has the potential to someday mitigate, prevent, or cure genetically defined diseases. Depending on the disease and treatment in question, researchers expect that some genome editing treatments might need to be repeated, whereas others may only need to be given once. In some cases, genome editing may be used to create healthy edited cells that divide, crowd out, and replace their unhealthy counterparts. It is hoped that these last cases lead to a permanent benefit.

Research is currently underway on clinical applications of genome editing technologies to treat genetic disorders like sickle cell disease, cystic fibrosis, congenital blindness, hemophilia, amyloidosis, and lysosomal storage disorders. In

addition, significant progress in therapeutic genome editing has been demonstrated in cancer and infectious diseases, such as HIV and Hepatitis B. (See [page 5](#) for examples of human genome editing to treat/cure disease.)

### How do current genome editing technologies differ from other genomic medicines (e.g., gene therapy)?

Genomic medicine is a broad term that describes any medical intervention that uses knowledge of genetics to guide the care of patients and the development of new therapies. The goal of genome editing is to target and alter disease-affiliated genes at the DNA level to cure, mitigate, or potentially prevent disease. It can be contrasted with a second major type of genomic medicine: gene therapy.

**Gene therapy** refers to a method that introduces one or more new copies of a gene into the patient's genome to restore cell function despite the continued presence of the mutated gene. In order to have a durable effect, the new genes must be expressed for a prolonged period of time (ideally, the entire life of the patient).

**Genome editing**, by contrast, corrects or removes a defect in the natural context of that gene. Once changed, the correction will persist throughout the life span of the cells, or be faithfully passed to all decedents of the originally edited cell in an individual patient. From a dosing perspective, it is anticipated that a cell in a patient would only need to be exposed to genome editing therapy for a short duration of time in order to achieve the desired genetic change.

### How does somatic cell genome editing work in patients?

Somatic cell genome editing can happen **outside the body (*ex vivo*)** or inside the body (***in vivo***). Each method has benefits and limitations, and preference of method depends on the disease being treated.

In ***ex vivo* genome editing**, the target cells—for example, blood cells—are first removed from the patient. The cells are then isolated and sustained in a laboratory before undergoing genome editing treatment to target and edit (or fix) the damaged gene. Upon successful editing, the 'fixed' normally functioning cells are returned back to the patient.

*Ex vivo* editing allows researchers to examine the accuracy of the editing in the laboratory before the cells are returned to the patient, but *ex vivo* editing can only be performed in cells that can be safely removed from that patient, kept alive in a laboratory, and then given back to the patient in exactly the right location in the body. This is why *ex vivo* genome editing is being tested mainly for blood and immune disorders, both of which involve cells from the bloodstream or bone marrow that can be collected, grown, and edited outside the body, and then returned to the patient.

***In vivo* genome editing** occurs inside a human body and therefore can potentially address many more diseases than the *ex vivo* process. During *in vivo* genome editing, the editing therapeutics are delivered directly to the target site by using a vector. The delivery vector can either be a virus that is naturally benign or altered so that it is rendered completely harmless to a patient, or a chemical-based, non-viral cargo that carries the editing therapy. Other non-viral vectors are also being explored. The vector travels through the body to find and enter the target cells where it can deliver the editing therapy.

In some cases, genome editing can be used to create healthy cells with corrected or edited genes that will divide and reproduce inside the body until they crowd out and replace the unhealthy cells containing the unedited (flawed) gene, thus

leading to a permanent benefit. Depending on the type of cell involved in the treatment and the lifespan of these cells in the body, researchers expect that some genome editing treatments might need to be repeated to achieve therapeutic benefits, whereas others might only need to be given once.

### How does a patient get treated with somatic cell genome-editing medicines?

The actual items that patients will be treated with will depend on whether genome editing needs to be performed *in vivo* or *ex vivo* (see above). Hypothetically, after cells are edited *ex vivo* a patient would need to have their own edited cells re-administered to them by a procedure like intravenous infusion. To perform *in vivo* editing a patient needs genome editing therapy delivered to the target tissue, so an *in vivo* genome editing medicine may look like a direct injection or an inhalation.

### Are genome editing technologies currently being studied in human clinical trials?

Yes. The first zinc finger based somatic cell genome editing treatment to enter U.S. clinical trials in human targets was completed and published in early 2014. This 12-patient study used *ex vivo* genome editing to knockout (or disrupt) a gene in immune cells of patients with HIV enabling them to fight off infection. As of 2017 a number of other human clinical trials were expected to begin in the U.S.. Genome editing trials using CRISPR technology have also begun in China studying an *ex vivo* gene disruption approach to treat lung cancer. (See [page 5](#) for examples of human genome editing to treat/cure disease)

### How far away are we from having an approved human genome editing medicine?

We are still some years away from having genome editing medicines approved by the FDA. At present, there are currently a number of clinical trials under way involving human genome editing technologies, which are designed to assess the safety and effectiveness of these therapeutic approaches. (See [page 5](#) for examples of human genome editing to treat/cure disease.)

### What is the current state of the science in genome editing in humans to treat or cure disease?

There is a tremendous amount of basic research currently underway with genome editing tools. Genome editing technologies have allowed for the rapid development of cell and animal models of disease. The specificity of these platforms, allows scientists to uncover the roles certain genes play in disease. The drop in DNA sequencing costs, synthesis costs, and the development of DNA delivery methods have expedited the development of the first therapeutics.

All preclinical and clinical testing by BIO member companies using genome editing for the treatment of disease are being delivered into somatic cells, either *in vivo* or *ex vivo*. Preclinical animal research using genome editing therapies has been underway since 2008, when the first *ex vivo* Zinc Finger Nuclease (ZFN) experiment was completed. The first somatic cell *in vivo* preclinical studies were reported in 2011. Scientists have made advances in the translation of these preclinical efforts into potential human therapies.

Human clinical trial research efforts for somatic cell human genome editing technologies (*ex vivo* and *in vivo*) were scheduled to begin in early 2017. These editing techniques offer the potential to provide lifelong or curative treatments

for human diseases. In addition to increasing the percentage of correctly edited target cells for each therapy, these early trials aim to minimize ‘off-target’ edits and possible immune responses. Researchers advancing the science of *in vivo* approaches are also working to address potential complications associated with delivery, i.e. making sure the genome editing occurs only on the specified target and does not cause a harmful immune response or other undesirable effects on the patient.

It is critical to understand that there are regulatory frameworks that carefully evaluate human genome editing in clinical trials before they start and while they are underway. (See [page 7](#) on regulatory oversight for more information.)

Because of these projects, the scientific community’s understanding of genome editing technologies is evolving daily. And as the scientific community’s knowledge advances, the potential benefits to patients increases and the risks to patients decreases.

### Examples of human genome editing to treat/cure disease in human clinical trials or being researched

Research is underway on clinical applications of genome editing technologies to treat various diseases including HIV, leukemia, hemophilia, leber congenital amaurosis 10, mucopolysaccharidosis, sickle cell disease, amyloidosis of the transthyretin, and cystic fibrosis.

## **SOMATIC CELL HUMAN GENOME EDITING MEDICINES - OVERSIGHT AND REGULATORY FRAMEWORKS FOR APPROVAL**

What oversight and regulatory frameworks currently govern approval of human genome editing medicines in the U.S.?

Over the past 40 years, the United States has continuously added to a biomedical R&D framework of laws, regulations, and guidelines to keep pace with advances in genomics. Today, research in genomic medicines is principally governed by the U.S. Department of Health and Human Services (HHS) and two of its constituent agencies: The Food and Drug Administration (FDA) and the National Institutes of Health (NIH).

Current regulatory language in the United States covers genome editing through its references to “genetic therapies” or “genetic manipulations.” The intention of gene therapy and genome editing clinical applications in somatic cells is so analogous that the policies in place effectively govern both.

Dr. Robert Califf, former FDA commissioner, clarified on January 18, 2017, that “*Human medical products* that apply gene editing to exert their therapeutic effect are regulated under our existing framework for biological products, which include gene therapy products,” and that “FDA’s Center for Biologics Evaluation and Research (CBER) has a well-established program and policies in place to evaluate gene therapy products.” Similarly, a 2017 U.S. National Academies of Science (NAS) report on human genome editing concluded that “clinical trials of genome editing in somatic cells for the treatment or prevention of disease or disability should continue, subject to the ethical norms and regulatory frameworks that have been developed for existing somatic gene therapy research.” This view is shared by the American Society of Gene and Cell Therapies (ASGCT).

The rules and regulations applicable to somatic cell genome editing in the United States are as follows:

1. Any genome editing research conducted with federal funding or that occurs at an institution that accepts federal funds is overseen by the NIH and is generally reviewed by its recombinant DNA advisory committee (**RAC**).
2. Any research that aims to use or create medical products is regulated by the FDA. All genetic manipulations done on human cells outside of the body (i.e., *ex vivo*) are considered medical products and are regulated by the FDA,
3. including genome editing on reproductive cells or embryos. This covers all *ex vivo* editing of human cells for clinical aims. In addition, any human cell genome editing that would occur *in vivo* requires the administration of a genome editing drug, which falls under FDA's regulatory jurisdiction.
4. Any research that requires human volunteers as research subjects is required to be regulated by safety and ethics review committees at the local institutions conducting such research. These local review committees are managed by the HHS Office of Human Research Protections (**OHRP**).

The established U.S. regulatory frameworks covering genetic therapies have been used to review the initiation of genome editing clinical trials. Zinc Finger Nuclease clinical trials were reviewed and initiated back in 2011. More recently, CRISPR clinical trials have been reviewed. FDA Commissioner Robert Califf commented in early 2017, "The RAC [the NIH's Recombinant DNA Advisory Committee] recently discussed (and did not find any objections to) the first clinical protocol to use CRISPR/Cas9-mediated gene editing".

### What oversight and regulatory frameworks currently govern approval of human genome editing medicines internationally?

Each country maintains its own regulatory frameworks governing the application of human genome editing technologies and other genetic manipulations in their own countries. In Europe, the European Medicines Agency utilizes a **Committee for Advanced Therapies** to assess quality, safety, and efficacy of new technologies for biologic medicines.

See below for additional information on international regulation of germline editing.

## **GERMLINE HUMAN GENOME EDITING - REGULATORY OVERSIGHT & CONSENSUS ON ETHICAL STANDARDS**

### How is germline human genome editing regulated in the U.S.?

FDA considers the use of *ex vivo* genome editing tools on cells to be regulated medical products, including reproductive cells and *in vitro* fertilization (IVF) embryos. A 2016 federal funding bill – Section 749 of the Consolidated Appropriations Act of 2016 – states that the FDA cannot review research or clinical applications that modify gametes, embryos, or germline cells to cause heritable genetic modifications. Known as the Aderholt Amendment, this language effectively precludes the possibility of any germline clinical research applications in the United States, both *ex vivo* and *in vivo*.

**With respect to non-clinical research, NIH does not fund germline genome editing research in human materials.** Appendix M of the *NIH Guidelines* explicitly states that the recombinant DNA advisory committee (RAC) will not accept clinical research protocols involving germline modification or in utero gene transfer. In addition, the Dickey-Wicker Amendment (DWA), passed in 1996, added a set of specific restrictions on HHS's ability to support embryo research. The DWA forbade the HHS, and thus also NIH, from using federal funds to create embryos for research purposes, or to fund research in

which embryos are destroyed, discarded, or damaged. The DWA is still in force today and prevents federal research funding from being used to study human embryo genome editing.

### How is germline human genome editing regulated internationally?

A 2014 review of international policies on germline alterations found that, of 39 countries surveyed, 29 of these had bans in place to prevent germline editing. Twenty-five of these countries had bans based in legislation (including Canada, Mexico, Brazil, EU, Israel, Australia, New Zealand), while four countries' bans were based in research guidelines (China, Japan, India, Ireland). Since 2018, Chinese authorities have clarified that germline editing for clinical application is illegal under its 2003 regulations governing such research. The remaining countries did not have clear policies in place (including Russia, Iceland, South Africa, Peru, and Chile).<sup>1</sup>

One additional note regarding the EU: the general EU agreement in opposition to germline editing was first solicited by the **Oviedo Convention** Agreement of 1997, which unequivocally opposes human germline modification and permits human somatic alterations only for preventative, diagnostic, or therapeutic reasons. Though many member states have signed the agreement, not all signing states have ratified its measures, leaving non-ratifying nations to design their own regulations on human germline editing.

<sup>1</sup> Araki, M., & Ishii, T. (2014, November 24). International regulatory landscape and integration of corrective genome editing into in vitro fertilization. *Reprod Biol Endocrinol Reproductive Biology and Endocrinology*, 12(1), 108. doi:10.1186/1477-7827-12-10