AMERICAN SOCIETY of GENE & CELL THERAPY

THERAPEUTIC GENE **EDITING:**

AN AMERICAN SOCIETY OF GENE & CELL THERAPY WHITE PAPER

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EXECUTIVE SUMMARY

Gene editing* is a process that repairs or changes a **gene**. Medical researchers are exploring ways to use gene editing to treat or prevent human diseases. According to a recent public opinion survey, Americans are both excited and concerned about this.[1] Given the complexity of gene editing and the rapid pace at which the science is progressing, it is no wonder that the public is both intrigued and perhaps uneasy.

Today, even though no gene editing treatments are commercially available to patients anywhere in the world, a Google News search for "gene editing" links to more than 95,000 media stories. These stories often talk about gene editing as if it were something out of science fiction, with the power to "remake the world" or "rewrite human beings." In fact, researchers are looking less into changing the world and more into treating individuals—one at a time—to alleviate human disease and suffering.

This report provides a foundation for understanding the science of gene editing, its potential therapeutic applications and its current U.S. regulatory framework. It was prepared by a taskforce of the American Society of Gene & Cell Therapy (ASGCT). ASGCT is a nonprofit medical and professional membership organization of 2,300+ scientists, physicians and patient advocates working in academia, industry and the government. ASGCT is dedicated to advancing the knowledge, awareness and education of gene and cell therapies, including gene editing, to alleviate human disease.

Human Applications of Gene Editing

The roots of today's gene editing can be traced back to the start of the biotechnology revolution and the first targeted edit made in a yeast cell in the 1980s. Many of the major breakthroughs facilitating therapeutic gene editing have occurred only in the past decade. Today, gene editing is a rapidly developing field of twenty-first–century medicine that holds promise for providing new medical treatments.

Genetic Diseases Have Significant Unmet Medical Needs

Researchers, physicians and patients believe gene editing can greatly improve the outlook for currently incurable genetic diseases, such as muscular dystrophy, sickle cell disease (SCD), cystic fibrosis, hemophilia, adrenoleukodystrophy (ALD) and others caused by **mutations** in genes. These genetic diseases are among the 7,000 rare diseases that affect 30 million Americans—or 1 in 10 of us, two-thirds of whom are children—and millions more around the world, according to the National Organization for Rare Disorders.[2] There are no effective therapies for more than 95 percent of these patients.[3]

* Bold-faced words and phrases are defined in the glossary, page 11.

TIMELINE OF GENE EDITING TECHNOLOGY DEVELOPMENT

1980s: First targeted gene editing, performed on yeast cells in several laboratories

1987: First report of clustered repeats in bacteria (knowledge required for later CRISPR editing development)

1991: First insights into how zinc finger proteins recognize specific DNA sequences

1994: Discovery that DNA breaks induced by a nuclease can be efficiently repaired by homologous recombination, a key foundation of today's gene editing technology

2002: First targeted gene edit made in a living organism

2002: Clustered repeats that were discovered in 1987 are renamed "clustered regularly interspaced short palindromic repeats" or CRISPR

2009: Discovery of a simple code explaining how transcription activator-like effectors (TALE) can recognize specific DNA sequences, an important foundation for the first description of TALENs a year later

2009: First U.S. clinical trials of gene editing in humans begins in patients with HIV

2012: First report of engineered CRISPR Cas 9 systems that cut specific DNA sequences

2013: First reports using engineered CRISPR Cas 9 systems to modify genes in human cells

2014: Report published in the New England Journal of Medicine on the first human clinical trial using ZFNs to target and destroy the CCR5 gene in T-cells of 12 people with HIV

2015: The National Academy of Sciences and the National Academy of Medicine's Human Genome-Editing Initiative co-hosts a summit in Washington, DC to gather international experts to discuss scientific, ethical and governance issues associated with human gene editing research

2016: The first AIDS patient receives ZFN-edited blood stem cells

2016: First cancer patient receives CRISPR edited immune cells in China

The few drug treatments approved for genetic diseases may manage or modify symptoms but they do not address the underlying genetic cause of the disease and most must continue to be administered for life. By contrast, the successful development of effective treatments based on gene editing could shift today's approach from a lifetime of symptom management for **hereditary diseases** to tomorrow's ideal of making a one-time curative repair or change to an individual's affected gene. The goal is a long lasting, perhaps life-long effect that minimizes or even eliminates disease. Three examples of current gene editing approaches to treat serious human diseases are included in this report, namely HIV/AIDS, sickle cell disease, and hemophilia. These research directions are among those further along the developmental pipeline, yet represent just a few of the myriad possible applications of gene editing technologies to improve human health.

Improving Cancer Treatments and Personalized Medicine

Gene editing also holds great promise as an approach for treating cancer patients. For example, scientists are already using gene editing to create improved and more efficacious versions of immune cells that show great promise to fight certain cancers. Because these approaches are focused on individualized treatements, they also answer the call for more precision, or personalized care, medicine that moves away from the "one-size-fits-all" approach to cancer therapy.

Biomedical Research, Regenerative Medicine and Gene Editing

The uses of gene editing extend beyond individual patients and into the larger area of **biomedical research**, which is the scientific study of the human body, health and diseases. For example, researchers are using gene editing to modify and compare different versions of genes in cells and whole organisms. These side-by-side comparisons help them to better understand how diseases start, how they progress and how to treat them better. Scientists and drug companies are also using gene editing in the process of drug identification and development. These types of laboratory research are at the heart of scientific discovery that leads to better patient care at the bedside.

As the genetic basis for many organ-related diseases becomes better known (e.g., for bone loss, heart failure or memory loss), the field of regenerative medicine will also be enhanced by gene editing. Regenerative medicine aims to regenerate healthy human cells to replace or repair a defective organ. With gene editing, researchers believe they may be able to correct a defective gene in tissue derived from a given patient and then use the corrected cells for regenerative medicine therapy.

Improvements in gene editing technologies are driving these and other exciting advances. In the laboratory, the gene editing process is becoming faster, easier, less expensive and more precise. But there is much more to do in order to move from where we are today to having a broad range of approved gene editing medical treatments for diseases like HIV/AIDS, Alzheimer's, heart disease, diabetes, emerging infectious diseases such as Zika and the thousands of genetic diseases that our children are born with every year.

This process of translating exciting science into real medicines for patients on a broad scale remains time-consuming, expensive and prone to failure. It is essential that research continue to ensure discovery, development and comprehensive testing of effective and safe human treatments.

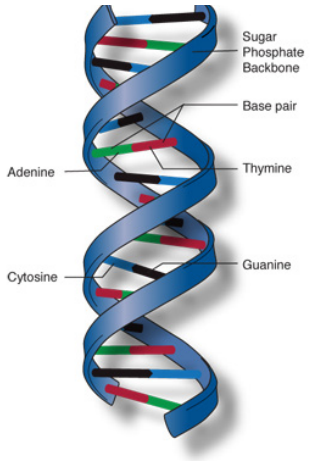
The goal of gene editing as a medical intervention is to target and edit disease-causing sequences of DNA to improve patient health.

The U.S. Has Robust Regulatory Oversight of Gene Editing

All of these medical benefits rely upon an existing, robust U.S. regulatory system centered on the U.S. Food and Drug Administration (FDA) and the National Institute of Health's (NIH) Recombinant DNA Advisory Committee (RAC), which provide stringent, complementary and (in the case of the RAC) public reviews of proposed human research and potential new gene editing therapeutic products. This system, built on decades of experience, has already reviewed pioneering gene editing clinical trial proposals. Although no gene editing therapeutic products have yet been approved by the FDA, the expectation is that many therapies currently in or soon to enter clinical trials will come up for approval in the coming years.

THE STRUCTURE AND FUNCTION OF GENES

Genes are the individual segments of **DNA** (deoxyribonucleic acid) that make us who we are. Genes are the instructions that guide the production of all of the **proteins** that serve as building blocks as well the machines that run all the processes in our body. Proteins do everything from fighting infections, carrying oxygen, clotting our blood after injury and controlling muscle movements. Some proteins carry the signals in our brains that process what we see and store how our memories, while others regulate and influence our mood and behaviors.



Each gene is in charge of making a different protein. For example, the INS gene makes the protein insulin, a hormone that helps control the body's blood sugar level. The HBB gene makes part of hemoglobin, a complex of proteins that carries oxygen to the body's organs and tissues.

Humans have approximately 24,000 genes and each one is unique. Every gene is made up of a string of **nucleotides**—the four basic building blocks of DNA—**adenine, guanine, cytosine** and **thymine**, which are referred to by the letters A, G, C and T. Each gene can be made up of a few hundred or even a few million individual nucleotides. The exact composition and order of nucleotides in genes serve as precise directions for producing that gene's protein.

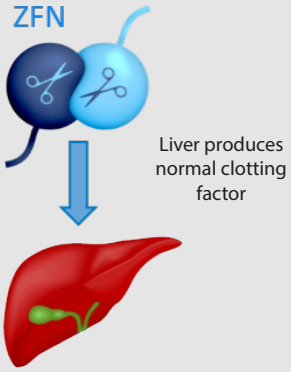
Just one single "mistake" or mutation in a gene's normal sequence of DNA, with a substitution of one nucleotide for another (e.g., replacing a G with an A), can prevent it from doing its job. An altered gene may produce too much of its protein, too little, a damaged version or no protein at all. These mutations can lead to diseases or complicate their treatment. **The goal of gene editing as a medical intervention is to target and edit disease-causing sequences of DNA to improve patient health.**

All of our genes together make up our **genome**—the total recipe that makes us who we are. Genes are made of two bonded strands of DNA shaped like a "double helix." The human genome exists on 23 pairs of **chromosomes,** which look like long threads and function to keep our DNA organized.

Genes, DNA and chromosomes are not unique to humans; they exist in virtually all living organisms, plants, animals and bacteria. While gene editing in humans is the main focus of this report, gene editing can also be used successfully in animals and plants, particularly those that are part of our food supply.

A RETURN TO NORMAL FOR HEMOPHILIACS?

About 1 in 5,000 male babies in the United States are born with hemophilia every year; it is very rare in females.[4] Hemophilia is caused by a mutation in a gene that leads to too little or no clotting factor VIII or factor IX, two proteins in the blood absolutely critical for preventing or stopping bleeding. Without sufficient clotting factors, patients bleed into their joints, brain, skin, stomach and intestines and mouth.



Depending on the severity of the disease, patients receive either on-demand or regular preventive intravenous administration of the missing clotting factor. On demand clotting factors cost $200,000-300,000 each year and ongoing preventive use costs $500,000-900,000 each year. Additionally, clotting factor given during surgery or treatment of major trauma can cost $150,000.

Scientists have developed a method for gene editing using a system that delivers a ZFN and then inserts the corrected clotting factor gene to the liver of patients with hemophlia. If successful, this single treatment could correct the disease. No patient has been treated yet, but trial enrollment is currently active and the first patients will be treated at City of Hope in California in the very near future.

The Target of Gene Editing: Somatic Cells

The entire human genome—23 chromosomes holding about 24,000 genes—is duplicated and housed in virtually every **cell** in the human body. Cells are the basic structural unit of all living things. They fall into two main categories: **germline** and **somatic cells**. Germline cells—ova and sperm—are hereditary; their genetic content is passed down from parent to child. Somatic cells are not hereditary and their genetic content cannot be passed down. Somatic cells are the main target of gene editing in humans.

Somatic cells are further identified based on the kind of tissue they make, such as bone, nerve, muscle and blood cells, or by their function: immune cells help fight infections, secretory cells secrete substances such as insulin or saliva and conductive cells carry electrical signals from one part of the body to another.

While each type of cell holds the entire set of human genes, each type of cell "reads" only the instructions contained in the gene or genes it needs to produce the proteins necessary for the cell to do its job. For example, certain cells in the pancreas read the genes they need to create insulin, while nerve cells read the genes they need to make chemical transmitters to control brain functions such as movement or memory.

Gene editing seeks to correct or change specific genes only in cells in which the alteration is expected to have therapeutic benefit. So, for example, if the goal is to treat muscular dystrophy, the gene edits will be targeted to muscle cells; if HIV/AIDS is being treated, the gene edits will be targeted to immune cells, which are killed by the virus. Currently, medical research aims only to make gene edits in somatic cells, so they cannot be passed down from parent to child. Members of future generations can then make their own choices about whether a gene editing treatment is right for them.

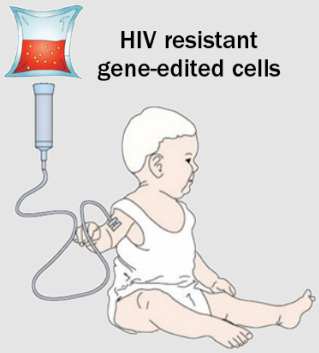
THE GENE EDITING PROCESS

Nucleases are naturally occurring proteins that can cut specific sequences of DNA inside living cells. These cuts can then be repaired by normal processes that exist in most organisms (including humans) to repair DNA damage. Researchers are using these nucleases and their knowledge of how cells repair DNA to create breaks in certain genes and to generate specific desired edits of interest.

Although the comparison is somewhat simplistic, the gene editing process is similar to the "search and delete" or "search and replace" features in word processing. In the case of delete, the typist locates and removes a word or the researcher locates and removes a gene. This is the easiest type of gene editing, and is called a "knockout." In the case of replace, the typist fixes one or more letters in a misspelled word or the researcher corrects or alters one or more of the mutated **AGCT**s in a gene before the ends of the DNA are joined back together.

CLOSING THE DOOR ON HIV BY MIMICKING NATURAL RESISTANCE

Human immunodeficiency virus (HIV) does harm by finding its way into immune cells in the blood and in lymph nodes, where it disrupts the cells' ability to fight infections. A gene editing treatment was designed that prevents HIV from ever entering immune cells. The treatment knocks out a gene called CCR5, which creates a protein on immune cells that HIV latches onto in order to enter and then harm them. Very rare individuals are born without CCR5 on their immune cells, and are naturally completely resistant to infection with HIV.



This gene editing approach begins with collection of an HIV patient's T cells, the very important immune cell that HIV normally infects and harms. Zinc finger nucleases can be used in the laboratory to delete the CCR5 gene in these T-cells. The edited cells are then infused back into the patient. These cells continue to multiply in the patient, and because they cannot be infected by HIV, they eventually crowd out HIV-infected T cells and result in less HIV virus being produced and harming other cells.

This is the first gene editing treatment to be studied in humans in the world and the results are promising.[5] Early clinical trials (Phase 1 and 2) conducted in a small number of HIV patients found that editing immune cells to delete the CCR5 gene was safe, and also resulted in a drop in the amount of HIV in the patient's blood, even when anti-HIV drugs were stopped. Another approach being studied edits blood stem cells, which then develop into T cells.

Ex Vivo and *In Vivo* Gene Editing

Gene editing can happen outside the body (***ex vivo***) or inside the body (***in vivo***). Each method has benefits and limitations.

In *ex vivo* gene editing, the target cells—for example, blood cells—are isolated and removed from the patient. The target gene inside the blood cells is edited while the cells are grown in a laboratory, and then the cells are returned back to the patient, often simply by infusing them into a vein.

The tools scientists use today to find and cut targeted genes are remarkably precise; still, one advantage of *ex vivo* editing is that researchers can examine the accuracy of the editing in the laboratory before the cells are returned to the patient. The main limitation of ex *vivo* editing is that it can only be performed in cells that can be removed from a patient, kept alive in a laboratory during the editing process, and then given back to the patient in such a way that they return to and function in exactly the right location in the body. This is why *ex vivo* gene editing is being tested mainly for blood and immune disorders, both of which involve cells from the bloodstream or bone marrow that are easy to collect, grow and edit outside the body, and then return to the patient.

In vivo gene editing occurs inside the human body and therefore can potentially address many more diseases than the *ex vivo* process. The nuclease that cuts genes is delivered by a **vector**. The vector is most often a virus that is naturally benign or that has been altered so that its dangerous components have been permanently removed. The vector travels through the body, and then finds and enters the target cells where it can deliver the nuclease so it can do its job. For example, to treat hemophilia, a vector would target liver tissue. The vector might be given into a vein, but then travel via the blood to the liver, where it enters liver cells and completes the gene editing process, correcting the mutation in a gene producing a blood clotting factor.

In some cases, gene 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 gene editing treatments might need to be repeated to achieve therapeutic benefits whereas others might only need to be given once.

CRISPR and Other Gene Editing Technologies

CRISPR (pronounced "crisper") is one of several kinds of nucleases that scientists are using to make targeted DNA cuts and gene edits. CRISPR represents a significant advance in gene editing because of its speed and low cost. Like other nucleases, it appears to work on any type of DNA—for example, human, animal or plant. Reflecting excitement about its potential impacts for biomedical research and treatment of disease, CRISPR was named "Breakthrough of the Year" for 2015 by Science magazine.[6]

CRISPR stands for **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats. Scientists first noticed these unusual genetic sequences in the DNA of bacteria nearly 30 years ago. Research eventually revealed that sequences found in the DNA of certain viruses, which are a natural enemy of bacteria, were also copied within the CRISPR sequences in bacteria. Scientists came to understand that the bacteria had incorporated these sequences into their own DNA as a defense mechanism—a kind of mug shot—to help them remember the invading virus.

But the bacteria do not stop at simply identifying the invading virus—they actually attack it. The CRISPR enzymes zero in on the identified DNA sequences and cut into them—disabling the virus and stopping it from attacking.

Scientists have adopted and modified this elegant system as a laboratory technique to make targeted cuts in genes. Instead of identifying sequences in viruses, scientists are using CRISPR systems to identify and cut sequences in human DNA—that is, specific stretches of A, G, C and T found within an individual gene. These systems can be exquisitely targeted to any gene in the human genome.

CRISPR is just one of several effective gene editing technologies in use today. Others include zinc finger nucleases (**ZFNs**), transcription activator-like effector nucleases (**TALENs**) and **meganucleases**. Although each works slightly differently, all of them can bind to target genes and make cuts that lead to editing.

The first nuclease-mediated gene editing treatment to enter U.S. **clinical trials** in humans targets the CCR5 gene, which makes a protein that HIV needs to get into human cells. In this trial, zinc finger nucleases were designed to target the CCR5 gene, and then used *ex vivo* to knockout the CCR5 gene in immune cells of patients collected from patients with HIV. Cells in which the CCR5 gene is knocked out are then expected to be completely resistant to infection by HIV. These cells are then able to function normally to fight infections, in contrast to cells infected with HIV. Gene editing trials for patients with Cancer have recently begun in China, and a number of other trials will begin in 2017 in the US.

CURRENT RESEARCH AND FUTURE DIRECTIONS

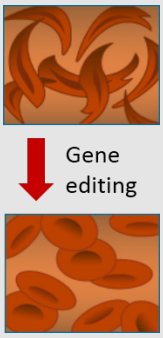
There are many potential uses for gene editing, from treating and preventing human disease to ensuring a more robust and reliable food supply. Although the early human studies and laboratory advances showcased in this report hold great promise, medical research is a long, expensive and meticulous process. Every promising application of gene editing, like all medical treatments, must undergo rigorous clinical trials following well established regulations to protect patient safety before it is available for routine use. This process typically takes years and is monitored closely by global regulators, including the FDA and their counterparts in the European Medicines Agency (EMA).

Beyond its potential to treat specific diseases, gene editing is also giving researchers the unique capability to manipulate genes within cells in their laboratories. This type of research, which scientists call "basic," is anything but basic. It improves our scientific understanding of how cells produce proteins and how genes are involved in the development of diseases. Basic research is the foundation of virtually all major medical advances, including the discovery of CRISPR.

Recent breakthroughs in gene editing are also allowing researchers to edit genes in more animal species than ever before, with broadened potential implications for human health. For example, gene editing may help scientists to remove certain immune antigens or virus sequences from some animals, greatly increasing the supply of kidneys and other organs to patients currently spending years on dialysis waiting for a matched organ.

FIXING THE RED BLOOD CELLS IN SICKLE CELL DISEASE

Sickle cell disease is among the most common genetic disorders in the world. The disease causes red blood cells to lose their normal round shape and become sickle shaped. These stiff, abnormally-shaped red blood cells get stuck in small blood vessels and prevent normal oxygen delivery to muscles and other organs and tissues resulting in severe pain, serious organ damage, many hospitalizations per year, and a shortening of the life span by several decades.



Researchers at many universities and companies are working on using gene editing to correct the mutation in the gene that controls the protein hemoglobin, which carries oxygen in red blood cells. This approach is working in cells from sickle cell patients studied in the laboratory, and in animals. For a clinical trial to treat sickle cell anemia, stem cells would be removed from a patient's bone marrow, CRISPR or another nuclease would be used to edit the hemoglobin genes and the edited cells would be returned back into the patient. These stem cells return to the marrow, where they can produce normal red blood cells for the rest of the patient's life.

Unlike many other genetic diseases that are caused by a variety of gene mutations, sickle cell disease is associated with one specific mutation. This means that finding a way to make that single letter change in the AGCT sequence on the target gene, called the hemoglobin-Beta gene, has the potential to help every single patient living with sickle cell disease.

Gene editing in animals can also be used to address issues that affect their safety and our food supply. Farmers remove the horns from Holstein and Jersey dairy cows so they do not harm each other or farm workers. Using gene editing, scientists have replaced the horn gene in these breeds with the corresponding gene from Angus cattle, which are naturally hornless. Veterinarians say this is a win for all concerned, including the cows, who will be born without horns versus having them surgically removed at a young age, a painful process for these animals.

Broadly speaking, gene editing in food crops is a very old concept. Plant breeding of specific desirable DNA changes has been practiced for centuries as a way to improve food quality and increase crop yield to feed a growing population. It used to take years or even decades of breeding and cross-pollination to develop better crops to slowly favor certain gene sequences. Gene editing breakthroughs have enabled researchers to make targeted changes that greatly reduce the time to choose and then pass on a desired trait. The end result is similar, though—a change in a plant gene that improves crop yields and leads to improved **food security** here and around the world.

U.S. REGULATORY FRAMEWORK OF GENE EDITING

Our regulatory system is a robust, pro-patient and pro-innovation model that other countries to follow for best practices in monitoring advances and research into gene editing in human somatic cells. Today, the FDA has more than 30 years of experience reviewing gene therapy-related research that will be of direct relevance to gene editing. The regulatory mechanisms at FDA and NIH are both experienced and substantively well prepared for evaluating ongoing advances in technology and for the testing of gene editing products for treatment of human diseases.

APPLICATIONS FOR GENE EDITING

Reprinted with permission.
Hsu PD, Lander ES, Zhang F. Cell. 2014; 157(6):1262-1278.

The RAC, in existence for 40 years, directly advises the NIH Director about all research that alters DNA, including individual genes.[7] The committee includes 15 expert physicians, researchers and ethicists from across the country. The RAC was established specifically to "allow for an in-depth examination" of "scientific, medical, ethical and social considerations worthy of special attention and public discussion" which arise when "techniques being used are relatively new."

As part of its Federal charter, the RAC reviews all novel protocols and proposals to investigate gene editing products in humans. Most importantly, the RAC's review—unlike FDA's—is a public and highly transparent process that affords unprecedented access to information that might otherwise be protected as confidential when submitted to the FDA.

As with all medical research, gene editing is also under the supervision of institutional or facility-specific review boards that assess both the scientific goals and ethical aspects of research. They include local institutional review boards (IRBs) to protect patient rights and safety, and institutional bio-safety committees to protect the public and the workforce. IRBs play a critical role in overseeing clinical research, determining the adequacy of protections for patients enrolling in clinical trials, and approving informed consent forms that explain the risks and benefits of each specific new treatment to patients considering participating in a clinical trial. All entities receiving federal research funding must, by law, have IRBs review all human research as a condition of that funding.[8]

Finally, FDA has legal authority in the U.S. to regulate human cell and gene therapy products as biological products or drugs, which must be demonstrated to be safe and effective for their intended uses before marketing. The FDA oversees every step in the process between the first administration of a new therapy and the final approval of a therapy required for marketing of a product in the U.S. The FDA reviews clinical trial proposals under its Investigational New Drug (IND) authority, ensuring that preclinical data from the laboratory and animal studies predict that a new treatment, such as gene editing, is likely to be safe and effective before proceeding to human administration. The FDA has the power to suspend or terminate clinical trials in the event of unanticipated problems impacting on patient safety. The FDA has not yet approved any human gene editing product for sale. All gene editing therapeutic products will almost certainly be regulated by FDA as biological products and human drugs.

The FDA is also proactively seeking scientific interchange and staff training on the topic of gene editing through its collaborations and dialogue with leading academic researchers and its peer global regulatory authorities. When sponsor companies begin to submit gene editing Biological License Applications (BLAs) to the FDA for premarket review and approval, potentially under expedited approval pathways and for the treatment of rare genetic diseases, the FDA will have unprecedented experience and scientific competencies to assess and scrutinize the candidate therapies for their safety and effectiveness.

Where somatic cell editing is expected to be regulated much like traditional medicines (through the framework described above), additional restrictions exist in the U.S. and abroad to deter research and clinical use of in human germline editing. In the U.S., Federal research funding cannot be used to create human embryos for research purposes or for research in which human embryos are destroyed; measures that apply to any relevant gene editing research.[9] The FDA is also prohibited from considering or approving an IND for any clinical trial in which a human embryo is intentionally created or modified to include a heritable genetic modification—a measure that prevents such proposals from proceeding under FDA's jurisdiction.[10] Lastly, the international research community has reached a consensus through the National Academies of Science, Engineering and Medicine that germline editing clinical applications should not proceed until a democratic stakeholder consensus determines otherwise.

While the U.S. model is one means of regulating this space, other models are also worth mentioning. For example, the United Kingdom (UK) and the European Union (EU) both regulate gene editing medical research under a legal framework for Advanced Therapy Medicinal Products, or ATMPs. The UK also has a national regulating body, the Human Fertilisation and Embryology Authority (HFEA), that is responsible for issuing licenses to allow and control gene editing research in human embryos outside the body. A key limitation in the UK is that the use of embryos is limited to 14 consecutive days following fertilization in a dish, and cannot be used to establish a pregnancy.

LOOKING FORWARD: PAVING THE WAY FOR GENE EDITING TREATMENTS

Gene editing science is moving forward steadily, but human therapies are just beginning to be tested. Medical research is a labor and time-intensive process that requires repeat testing to assure the safety and effectiveness of treatments. Ongoing and thorough research is needed to take gene editing from bench to bedside.

Success will require maintaining rigorous but flexible regulations that not only monitor, but adapt to this constantly evolving field. It will also require stable ongoing Federal biomedical research and development funding. Gene editing advances will benefit from policies that continue to encourage and support robust, pro-patient and pro-innovation models to monitor advances and research into somatic cell gene editing.

It is essential to continue support of basic research as well as research that is closer to human application. Basic science is the backbone of scientific breakthroughs, even though it happens years earlier than the eventual approval of medicines for patients. It was basic science research in bacteria and viruses, after all, that led to the discovery of CRISPR and the dramatic recent advances in gene editing.

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GLOSSARY OF TERMS

Adenine: One of the four kinds of DNA molecules, or nucleotides, that make up all genes. The others are cytosine, guanine and thymine.

AGCT Adenine, guanine, cytosine and thymine; the four building blocks of all genes. Changes in a normal sequence can stop a gene from functioning properly.

Biomedical research: Scientific research concerned with the human body, health and diseases.

Cell: Basic structural unit in living organisms. Each human cell has a complete copy of the individual's DNA on 23 pairs of chromosomes.

Chromosome: Threadlike structures that encompass human DNA.

Clinical trial: A study in human volunteers designed to answer questions about new therapies, including gene-editing therapies. Clinical trials are conducted in four carefully designed phases to test first for safety and tolerability of a treatment and then for its effectiveness.

CRISPR: Clustered regularly interspaced short palindromic repeats; one of several nuclease platforms used to make targeted DNA breaks and edits in genes.

Cytosine: One of the four kinds of DNA molecules, or nucleotides, that make up all genes. The others are adenine, guanine and thymine.

DNA: Deoxyribonucleic acid. There are four kinds of DNA building blocks that are referred to as nucleotides: adenine, cytosine, guanine and thymine. Sequences of these molecules encode all of a living organism's genes.

***Ex vivo*:** Outside the body. With *ex vivo* gene editing, target cells are removed from a patient, edited in a laboratory and then reinfused into the patient.

Food security: The ability to provide reliable access to enough affordable, nutritious food for a population.

Gene: A segment of DNA that is responsible for creating a single protein. Every gene includes a unique nucleotide sequence (composed of A,G,C and T).

Gene editing: A process of modifying genes in living cells. For example, a flawed gene sequence can be removed or replaced with one that has the correct DNA sequence.

Genome: The complete set of genes that together make up a living entity.

Germline cell: Reproductive cells; egg and sperm in humans. Changes in germ cells can be passed down to future generations (children).

Guanine: One of the four kinds of DNA molecules, or nucleotides, that make up all genes. The others are adenine, cytosine and thymine.

Hereditary disease: When a child is born with an illness that is a result of defective genes that came from one or both parents, who can in some cases be silent carriers.

***In vivo*:** Inside the body. With *in vivo* gene editing, a vector is used to deliver gene editing materials to cells inside the body.

Meganucleases: One of several nuclease platforms used to make targeted DNA breaks and edits in genes.

Mutation: An alteration in the normal DNA sequence of a gene.

Nucleases: Naturally occurring enzymes that organisms use to make cuts in DNA; they have been harnessed by science to make targeted cuts in genes.

Nucleotides: Four basic building blocks that make up genes; see also ACGT.

Protein: A compound made by genes that controls or manages a function in the body.

Somatic cell: A cell whose genetic material is not inherited by the next generation. Somatic cells are the target of current gene editing research.

TALENs: Transcription activator-like effector nucleases; one of several nuclease platforms used to make targeted DNA breaks and edits in genes.

Thymine: One of the four kinds of DNA molecules, or nucleotides, that make up all genes. The others are adenine, cytosine and guanine.

Vector: A carrier that is used to deliver material into cells. Vectors are chosen because they are naturally benign or can be made benign and they can deliver material into specific target cells.

ZFNs: Zinc finger nucleases; one of several nuclease platforms used to make targeted DNA breaks and edits in genes.

RESOURCES

The **American Society of Gene & Cell Therapy** website includes a section for the general public (http://www.asgct.org/general-public) with educational and media resources that answer FAQs, define common terms, provide a guide to ongoing clinical trials and much more.

The National Academy of Sciences and the National Academy of Medicine provide online information about their human gene-editing initiative (http://www.nationalacademies.org/gene-editing/index.htm). The goal of the initiative is to "provide researchers, clinicians, policymakers, and societies around the world with an understanding of human gene editing to help inform decision making about this research and its application."

The National Institutes of Health Office of Science Policy posts proceedings of Recombinant DNA Advisory Committee meetings (http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/rac), as well as reports for the public.

TASKFORCE MEMBERS

The following members of the ASGCT Taskforce led development and drafting of this document.

Rachel Salzman, DVM, Taskforce Chair
Chief Science Officer
The STOP ALD (Adrenoleukodystrophy) Foundation
Houston, Texas

Kenneth I. Berns, MD, PhD
Distinguished Professor
Department of Molecular Genetics and Microbiology
University of Florida College of Medicine
Gainseville, Florida

Cynthia E. Dunbar, MD
President, American Society of Gene & Cell Therapy
Head, Molecular Hematopoiesis Section
Hematology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Timothy D. Hunt, JD
Senior Vice President
Corporate Affairs
Editas Medicine, Inc.
Cambridge, Massachusetts

J. Keith Joung, MD, PhD
Professor of Pathology
Harvard Medical School
Associate Chief of Pathology for Research
Pathologist
The Jim and Ann Orr Research Scholar
Massachusetts General Hospital
Boston, Massachusetts

Donald B. Kohn, MD
Professor of Microbiology, Immunology and Molecular Genetics, and Pediatrics
Director, Human Gene Medicine Program
David Geffen School of Medicine
Los Angeles, California

Philip R. Reilly, MD, JD
Venture Partner
Third Rock Ventures
Boston, Massachusetts
Trustee Emeritus
Cornell Medical College
New York, New York

John A. Zaia, MD
Director, Center for Gene Therapy
Hematological Malignancy and Stem Cell Transplantation Institute
City of Hope
Duarte, California

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ASGCT EXECUTIVE OFFICE

555 East Wells Street, Suite 1100
Milwaukee, WI 53202
Phone: 414.278.1341
Fax: 414.276.3349
Email: info@asgct.org
Website: www.asgct.org

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