REPORT 3 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-16)
Genome Editing and its Potential Clinical Use
(Reference Committee K)

EXECUTIVE SUMMARY

Objectives. The promise of gene therapy has increased substantially over the last decade due to rapid advancements in two technologies: DNA sequencing and genome engineering. Concurrently, techniques have been discovered that allow modification of the genome with a level of efficiency and precision that had not previously been achieved. One such technique, termed CRISPR-Cas9, has triggered a surge of research efforts to harness it for correcting mutations that are disease-causing, and to understand how it could be used as a therapeutic intervention in individuals with disease. Along with the scientific and medical advances in genome editing, ethical concerns also are evident, especially about the permanent editing of fertilized embryos. The Council on Science and Public Health has initiated this report to inform physicians and the House of Delegates about the remarkable advances in genome editing seen in recent years and its potential clinical applications in gene therapy, as well as concerns about it and proposals to ensure its responsible use.

Data Sources. Literature searches were conducted in the PubMed database for English-language articles published between 2006 and 2016 using the search terms “gene editing,” “genome editing,” and “CRISPR.” To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Genome editing information posted on the websites of the National Academies of Sciences, Engineering, and Medicine and the American Society of Human Genetics also was reviewed. Additional articles were identified by manual review of the references cited in these publications.

Results. Progress in gene therapy is likely to accelerate with the CRISPR-Cas9 genome editing techniques, which allows for precise and permanent modification of the genome without the complications that accompany other gene therapy techniques. The most immediate uses of genome editing have been in biomedical research settings. However, the relative ease of using CRISPR-Cas9 and other programmable nucleases has triggered the modeling of human disease and proof-of-concept studies in a number of species and in human cell lines. Early phase clinical trials are beginning to test genome editing as a therapeutic tool in select diseases. Translation of applications to the clinic will require the careful consideration of a number of factors, including the safety of the technology, its possible use in editing the germline, and high costs that could result in access problems and health disparities.

Conclusions. The last few years have seen unprecedented progress in the development of genome editing mechanisms and their potential applications for gene therapy. Much work remains to ensure the safety and effectiveness of genome editing, and questions remain about the appropriate use of germline editing. The Council supports continued research into the clinical applications of genome editing, but urges caution and thoughtful consideration before clinical germline editing is undertaken.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3-I-16

Subject: Genome Editing and its Potential Clinical Use

Presented by: Bobby Mukkamala, MD, Chair

Referred to: Reference Committee K
(Paul A. Friedrichs, MD, Chair)

BACKGROUND

The promise of gene therapy has increased substantially over the last decade due to rapid advancements in two technologies: DNA sequencing and genome engineering. Next-generation DNA sequencing techniques, reviewed by this Council in 2012, have allowed analysis of the genome and discovery of the genetic basis of disease with unprecedented speed and accuracy.[1,2] Concurrently, techniques have been discovered that allow modification of the genome with a level of efficiency and precision that had not previously been achieved.[3] One such technique, termed CRISPR-Cas9,[4] has triggered a surge of research efforts to harness it for correcting mutations that are disease-causing, and to understand how it could be used as a therapeutic intervention in individuals with disease.[5] Along with the scientific and medical advances in genome editing, ethical concerns also are evident, especially about the permanent editing of fertilized embryos, altering the genome of every differentiated cell that arises from that embryo and the offspring of that individual.[6]

The Council on Science and Public Health has initiated this report to inform physicians and the House of Delegates about the remarkable advances in genome editing seen in recent years and its potential clinical applications in gene therapy, as well as concerns about it and proposals to ensure its responsible use.

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2006 and 2016 using the search terms “gene editing,” “genome editing,” and “CRISPR.” To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Genome editing information posted on the websites of the National Academies of Sciences, Engineering, and Medicine and the American Society of Human Genetics also was reviewed. Additional articles were identified by manual review of the references cited in these publications.

GENE THERAPY

The concept of gene therapy, broadly defined as the use of genes or other genetic sequences to counteract or replace malfunctioning genes that cause disease, arose decades ago. Yet it has been slow in becoming a widespread therapeutic option, due in part to the complex mechanisms required

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Action of the AMA House of Delegates 2016 Interim Meeting: Council on Science and Public Health Report 2 Recommendations Adopted, and Remainder of Report Filed.

to deliver genetic material to the cell and drive appropriately timed therapeutic gene expression, while avoiding the disruption of endogenous cellular function.[7] The first successful attempt at gene therapy occurred in the early 1990s in two children with severe combined immune deficiency (SCID) caused by defects in the adenosine deaminase (ADA) gene. Normal copies of the *ADA* gene were inserted into their T-cells at repeated time points, resulting in sustained immune function.[8] Other gene therapy trials in the 1990s and 2000s were considered successful, but they were small, early-phase trials, and limited to only a few participants with very rare genetic diseases that were well characterized at the time. Challenges to using gene therapy more widely persisted, including the transient expression of genes inserted to the cell but not permanently into the cell's genomic DNA (called "transgenes"), requiring continual therapy; limitations in the ability of viral vectors to deliver functional genes to cells; insertional mutagenesis, the propensity of genetic sequences to randomly insert into genomic DNA, causing mutations and resultant disease; and immune responses to the introduced foreign DNA.[7,9]

Nevertheless, research to overcome gene therapy barriers continued, and important successes have been realized. In 2015, it was reported that gene therapy was successful in several patients with Wiskott-Aldrich syndrome (WAS), a severe primary immunodeficiency caused by mutations in the *WAS* gene.[10] The trial was one of the first to use an engineered viral vector that could limit insertional mutagenesis and reduce associated complications. Other gene therapy successes have included the use of modified T-cells to treat relapses in acute lymphoblastic leukemia;[11] restoration of vision in patients with Leber congenital amaurosis, an inherited abnormality of the retina that causes blindness;[12] and reduction of bleeding episodes in patients with severe hemophilia B.[13] Another milestone was achieved in 2012 with the approval by the European Medicines Agency (EMA) of the first gene therapy product available in Europe. Alipogene tiparvovec, marketed as Glybera, is designed for the treatment of the rare disease lipoprotein lipase deficiency.[14] This year, the EMA also approved Strimvelis, a gene therapy product for the treatment of ADA-caused SCID.[15,16] No human gene therapy products have been approved to date by the FDA, although development of products is underway in the biotechnology industry.[17]

Genome Editing

Progress in gene therapy is likely to accelerate with newly discovered techniques that allow for precise and permanent modification of the genome without the complications that accompany other gene therapy techniques. The risk for insertional mutagenesis is drastically reduced because the therapeutic genetic sequences used are engineered to insert into the cell's genomic DNA at precise locations.[7] Additionally, because the therapeutic sequence is inserted into the cell's genomic DNA rather than being expressed as a transgene, expression of it can be more tightly controlled.[7] Termed "genome editing" or "genome engineering," these techniques are being tested for gene therapy applications that could correct or inactivate disease-causing mutations, introduce protective mutations, insert functional genes, or disrupt foreign DNA (such as that present in viral or bacterial infections).[18]

HOW DOES GENOME EDITING WORK?

DNA Editing

The genome editing process is illustrated in the Figure (see page 14). It is dependent on an engineered DNA-cleaving enzyme (a nuclease) that is programmed to cut genomic DNA at specific locations. Four major classes of nucleases can be engineered for site-specific editing; of these four classes, the CRISPR-Cas9 class can be easily targeted to almost any location in the genome and carries out its nuclease activity most efficiently.[19] The Cas9 nuclease was first discovered in

bacterial adaptive immunity experiments. Bacterial genomes carry DNA sequences called "clustered regularly interspaced short palindromic repeats" (or "CRISPR"), which are located in close proximity to the coding sequence of a CRISPR-associated ("Cas") DNA-cleaving enzyme. In bacteria, the CRISPR sequences act as guides for Cas9's nuclease activity, providing a defense mechanism against phage infection.[19] Further studies demonstrated that Cas9 could be engineered to cleave the DNA of many organisms' cells, including humans', at specific locations by providing it with the correct guide.[19,20]

Once Cas9 is engineered to cleave genomic DNA at a specific location, it can be inserted into the cell to carry out its nuclease activity. It finds the location it has been engineered to recognize and cuts both strands of the DNA (Figure). When the DNA strand is cut, the cell uses its own DNA repair mechanisms to attempt to repair the cut. Two different repair mechanisms result in different outcomes. In one mechanism, called non-homologous end joining (NHEJ), the two ends of the DNA strand that have been cut are directly rejoined.[18] However, this process is often inaccurate and results in the insertion or deletion of a small number of nucleotides, disrupting normal gene function (Figure). This is the genome editing mechanism used to inactivate a gene. By cutting a gene in its coding region and forcing repair through NHEJ, the small insertions or deletions that occur in the coding region suppress gene function or inactivate the gene altogether.[18] An example of the way in which this type of genome editing could be used therapeutically is in sickle cell disease.[3] Sickle cell disease is caused by mutations in the *HBB* gene, which render γ-globin dysfunctional. Functional γ-globin can be restored by upregulating the expression of the *HBG* gene. However, *HBG* is suppressed by the gene *Bcl11A*. By using genome editing to inactivate *Bcl11A*, *HBG* gene function is activated and γ-globin expression can be restored.[3]

The other repair mechanism used by cells after the DNA strand has been cut is called homologous recombination (HR). In HR, the cell uses a DNA fragment that exactly matches the sequences surrounding the cut as a template to direct repair (Figure). Genome editing takes advantage of the use of these DNA fragments to direct repair; an exogenous DNA fragment containing a new gene or a corrected sequence of nucleotides, along with sequences that match those surrounding the site of the DNA cut, is inserted into the cell along with Cas9.[18] When Cas9 cuts the DNA in the location it has been engineered to recognize, the cell uses the exogenous DNA fragments as a template to repair the cut (Figure). This is the genome editing mechanism that is used to correct a mutation or insert a functional gene. The exogenous DNA repair fragment can be engineered to carry a correction to a mutation or a new functional gene that will be incorporated into the genome. In the example of sickle cell disease discussed above, this method could be used to either correct the mutation in the *HBB* gene, or insert a functional *HBB* gene in another location, restoring γ-globin expression.[3]

Delivery mechanisms

For genome editing to occur, the engineered nuclease has to be introduced into target cells. This can occur either *ex vivo* or *in vivo*. In *ex vivo* delivery, a portion of the cell population that is targeted for editing is removed from the body, undergoes genome editing, and then is returned to the host. In this mechanism, the engineered nuclease and DNA repair fragments (for HR editing) can be introduced into the cultured target cells through several methods, including electroporation, a pulse of electricity that briefly opens pores in the cell membrane to allow the nuclease and DNA repair fragments to enter; or non-pathogenic viruses that insert the nuclease and DNA repair fragments directly into the cell.[18] *Ex vivo* delivery results in high editing rates, and therefore is often used for gene therapy applications. However, because it is difficult for some target cell populations to survive manipulation outside of the body, *ex vivo* delivery is usually limited to

tissues with adult stem cell populations that are amenable to culture and manipulation, such as those from the hematopoietic system.[18]

In *in vivo* delivery, the engineered nuclease and DNA repair fragments are delivered to targeted cells in their native environment within the body. This has been achieved by using non-pathogenic viral vectors with affinity for the target tissue; the viruses are packaged with the nuclease and the DNA repair fragments (for HR editing), which are deposited directly into the cell when the virus "infects" it.[18] *In vivo* delivery is preferred when the target tissue is not amenable to culture or manipulation outside of the body. It can also be used to efficiently target multiple tissue types, allowing for its therapeutic use in a wider range of diseases.[18] However, the viruses that can be used as vectors are sometimes limited in their affinity for multiple tissue types, and while they are non-pathogenic, the amount of virus necessary for use in therapeutic genome editing may induce an immune response.[18]

CLINICAL APPLICATIONS OF GENOME EDITING

The most immediate uses of genome editing have been in biomedical research settings. The relative ease of using the CRISPR-Cas9 system, as well as other programmable nucleases, has triggered the modeling of human disease and proof-of-concept studies in a number of species and in human cell lines.[21] A few experimental uses have progressed to early clinical trial stages in humans. Selected examples that are most promising for gene therapy are discussed in this section.

Monogenic Disorders

Nearly 8,000 diseases are monogenic, i.e., caused by mutations in single genes.[3] Many of these diseases are candidates for gene editing because, simplistically speaking, the modification needed is only in one gene. At this time, successful genome editing for several monogenic diseases has been achieved in model organisms. For example, in a mouse model of Duchenne muscular dystrophy (DMD), which mimics the human form of DMD with a mutation in the *dystrophin* gene, a viral vector was used to deliver Cas9 *in vivo* to mouse muscle cells.[22-25] The Cas9 was engineered to cut the *dystrophin* gene in two places flanking the mutation, thereby removing the mutation from the cells' genomic DNA, then the cut ends of *dystrophin* were repaired by the NHEJ mechanism.[22-25] The technique only partially restored Dystrophin protein function, but it was enough to restore partial muscle function in the mice. Particularly exciting was the finding that gene editing occurred in satellite cells, stem cells that are present in muscle, implying that the satellite cells could populate the muscles with cells carrying the partially repaired *dystrophin* gene.[25]

Preclinical studies using genome editing to correct the mutations that cause cystic fibrosis have also been promising. Organoids are small amounts of functional tissue derived from human stem cells. In intestinal organoid tissue derived from patients carrying mutations in the *CFTR* gene, which causes cystic fibrosis, the CRISPR-Cas9 system was used to correct the mutations through the HR mechanism.[26] The corrected *CFTR* was fully functional and was able to "rescue" the cystic fibrosis phenotype in the organoids.[26] Together with other experiments showing that cultured intestinal organoids can be transplanted into and become functional in the colons of mice,[27] this provides a potential strategy for gene therapy in patients with cystic fibrosis.

Other studies demonstrated successful proof-of-concept results using genome editing for the treatment of many other monogenic diseases, including hemophilia B, hereditary tyrosinemia, ADA-caused SCID, sickle cell disease, and β-thalassemia.[3,18,19] The biotechnology company Editas has stated that it will begin a clinical trial in 2017 using CRISPR-Cas9 as a gene therapy mechanism to correct mutations causing Leber congenital amaurosis.[28]

Cancers

With more than 1.5 million cases of cancer diagnosed and half a million deaths from cancer each year,[29] the prospect of treating cancer using genome editing-based technologies is appealing. However, it is widely thought that direct repair of acquired or inherited mutations in cancer cells would not be effective.[18] Mutations in cancer cells give them a fitness advantage over non-cancerous cells, i.e., they divide quickly and do not respond to the cells' signals to halt growth or self-destruct. Even the most efficient genome editing could not repair every cancer cell present in a tissue or throughout the body, so cancer cells with repaired mutations would quickly be outcompeted by their non-repaired counterparts, rendering the therapy ineffective.[18]

Despite the inability to directly correct mutations in cancer cells, research has shown exciting results using engineered T-cells to harness the immune system's ability to fight cancer. T-cells are harvested from patients with certain types of cancer, engineered to express receptors that have specific and strong affinity for tumor antigens, and then infused back into patients, where they attack tumor cells.[30,31] This technique has been the most successful in trials for melanomas and leukemias and lymphomas of B-cell origin.[31]

Genome editing is now being explored as a technique to engineer T-cells that more stably and permanently express the receptors that target them to cancer cells. In June 2016, the National Institutes of Health approved a proposal to use the CRISPR-Cas9 system to edit T-cells from patients with one of three cancer types: multiple myeloma, sarcoma, or melanoma.[32] The genome editing will include inserting a gene that helps the T-cells better recognize cancer cells, inactivating a gene that interferes with the recognition process, and inactivating a gene that allows cancer cells to prevent T-cell attacks.[32] Recruitment could begin late in 2016, once FDA and institutional review board approval are granted.[33] Another trial using genome-edited T-cells is set to begin this year in China in patients who have metastatic non-small cell lung cancer and for whom chemotherapy, radiation therapy, and other treatments have failed. In that trial, CRISPR-Cas9 will be used to inactivate the gene that encodes PD-1, which normally acts as a check on the cell's capacity to launch an immune response.[34]

Non-Genetic Disorders

In addition to the use of genome editing to correct diseases caused by genetic mutations, it also is being investigated for use in treating infectious diseases and a variety of other health conditions. For example, the discovery that patients who carry mutations disabling the HIV receptor CCR5 are nearly completely resistant to HIV infection provided the basis for a genome editing-based clinical trial for treating HIV. A small, early-phase clinical trial removed T-cells from patients with HIV, used an engineered nuclease to mutate the *CCR5* gene, and then transplanted the edited T-cells back into the patients.[3,18,35] Preliminary results showed that in the majority of patients receiving the edited T-cells, HIV DNA levels in the blood decreased, and in one patient, HIV was undetectable.[35] Unlike the fitness disadvantage that directly edited cancer cells have when compared to their non-edited counterparts, T-cells with the edited *CCR5* gene have a fitness advantage over the non-edited T-cells; in the trial, the edited T-cell population had lower rates of cell death than did non-edited T-cells, suggesting that they are more stable.[35] Complete removal of the virus will be challenging, however, and will depend on extremely efficient delivery and editing strategies;[18] phase II trials are now ongoing to test such strategies. Similar genome editing mechanisms have also shown promising results in treating hepatitis B virus infection.[36,37]

Genome editing also is being explored as a therapy to reduce cardiovascular disease risk. The gene *PCSK9* was recently discovered as a modulator of LDL cholesterol function. People carrying dominant gain-of-function mutations in *PCSK9* have highly elevated LDL level and premature coronary heart disease, and those carrying homozygous loss-of-function mutations have a nearly 80 percent reduction in LDL level with no apparent adverse clinical consequences.[38,39] PCSK9-targeting monoclonal antibodies are currently being tested in clinical trials as LDL-lowering therapies.[40] Genome editing of *PCSK9* has been tested in the pre-clinical setting. A viral vector was used for *in vivo* delivery of Cas9, engineered to introduce mutations in the *PCSK9* gene using the NHEJ mechanism, to liver cells of mice.[41] Editing occurred in more than half of the liver cells, and resulted in a 35-40 percent reduction in total cholesterol and reduced LDL plasma fractions.[41] This study has contributed to the notion that the future of cholesterol management may first be a bi-weekly or monthly intervention using PCSK9-inhibitor antibody drugs, then eventually become a one-time intervention that permanently and selectively modifies the genome to inactivate *PCSK9* and thereby reduce cholesterol.[42]

CONSIDERATIONS BEFORE CLINICAL USE

The pace of exploration of genome editing as a potential tool for gene therapy has been rapid in recent years. However, translation of applications to the clinic will require the careful consideration of a number of factors, including the safety of the technology, its possible use in editing the germline, and high costs that could result in access problems and health disparities.

Safety

The specificity of engineered nucleases, i.e., their ability to cut DNA at precisely targeted positions and avoid cutting at non-targeted locations, will be a key factor in the translation of this mechanism of gene therapy into clinical practice. Genetic modifications resulting from genome editing are permanent, so off-target modifications could create cells with functional impairment or even oncogenic potential. CRISPR-Cas9 genome editing appears to result in only rare instances of off-target modification; one study estimated that one error in 300 trillion base pairs could occur, and given that the human genome is only 3 billion base pairs, that equates to one off-target modification per 100,000 cells.[43] However, more sophisticated methods are needed for evaluating the likelihood of off-target modification for each potential clinical use, and studies are ongoing to develop ways of preventing off-target modification.[44,45] Clinical use of genome modification would not be appropriate without mechanisms to ensure that off-target modifications are extremely rare and result in negligible clinical consequence.[18,46]

Another safety concern lies with using viral vectors as delivery mechanisms. Adeno-associated virus (AAV) vectors are approved for clinical use,[47] and have high delivery efficacy for a number of tissue types. But AAV vectors pose some challenges. In some cases, nucleases packaged within AAV vectors are constitutively active, increasing the chances of off-target modification.[18]Also, many people who have been naturally exposed to AAV have developed immunity to it, so it may not be an appropriate delivery mechanism for them.[18] Immunotoxicity also may occur upon exposure to certain engineered nucleases, including Cas9, since they are microbially derived.[48] Alternative delivery systems, including lipids and nanoparticles, are being explored to avoid the potential for immunotoxicity.[49,50]

Germline Editing

The most ethically-fraught conversations about genome editing center on the use of the technology to modify the genome of germline cells (eggs and sperm) or early-stage embryos. Such editing would result in permanent modifications to the individual arising from the germline cells or embryo, and would permanently change the gene pool since those modifications would be passed on to future generations. Conversations about these issues took on new urgency when researchers in China demonstrated that CRISPR-Cas9 could be successfully used to edit the genome of early-stage human embryos.[51] The embryos used in the study were genetically incapable of maturing into viable zygotes, and important limitations in the efficiency of CRISPR-Cas9 in human embryos were discovered, but the study nonetheless illustrated the application of genome editing to human embryos before ethical standards for its use have been widely promulgated. Further evidence that genome editing is close to being used in human embryos comes from a study that used CRISPR-Cas9 to induce genome modifications in one-cell stage embryos of cynomolgus monkeys, resulting in live births.[52] Cynomolgus monkeys are so genetically close to humans that they are often used to model human disease. The genome-edited animals are now being studied to determine the efficiency of the editing and potential health consequences stemming from it.[52]

Several organizations, including the National Academies of Sciences, Engineering, and Medicine (NASEM) and the American Society of Human Genetics (ASHG), have convened expert working groups to study the issue and define principles by which germline editing should or should not occur. Discussions center on the use of genome editing to treat or cure diseases for which no other equally effective therapy exists, and what types of disorders are sufficiently debilitating that extreme measures like genome editing are needed. The case for germline editing is most compelling when both parents are homozygous for a disease-related gene variant; however, that is a rare occurrence.[53] Another question that arises is whether genome editing has any value over preimplantation genetic diagnosis, which allows prospective parents who carry heritable disease-causing genes to select embryos lacking those genes.[54] Genome editing for complex polygenic diseases is likely not possible because those genes usually have very weak effects on their own and are often involved in a variety of physiological functions, some of which may be beneficial.[53,54] Discussions also focus on the potential for non-medical use of germline editing, such as for selecting desirable traits, and the autonomy of parents to make genetic modifications in their offspring, who themselves are not able to consent.[53]

NASEM, along with the Royal Academy and the Chinese Academy of Sciences, held a summit late in 2015 during which a committee of scientific and ethics experts discussed genome editing and developed conclusions about its use.[55] The consensus conclusions support preclinical research on genome editing, as well as its use in somatic gene therapy concordant with regulatory law. However, the committee does not support clinical use of germline editing until "(i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application."[55] The committee will complete a comprehensive study of the scientific underpinnings of human genome editing technologies, their potential use in biomedical research and medicine, including human germline editing, and the clinical, ethical, legal, and social implications of their use by late 2016.[56]

Similarly, ASHG has convened a Workgroup on the Implications of Genome Editing to craft policy on genome editing; in addition to ASHG, the Canadian Association of Genetic Counselors, International Genetic Epidemiology Society, National Society of Genetic Counselors, and Association of Genetic Nurses and Counselors (United Kingdom and Ireland) participated in the Workgroup.[57] It developed a draft policy outline that supports research into the use of germline editing as long is does not culminate in a human pregnancy, and believes that clinical application should not proceed unless, at a minimum, there is "a) a compelling medical rationale, b) an

evidence base that supports its clinical use, c) an ethical justification, and d) a transparent public process to solicit and incorporate stakeholder input."[57] ASHG has solicited member comments on the draft policy and will finalize it in the coming months.

The AMA Code of Medical Ethics contains similar sentiments regarding gene therapy and genetic engineering. Opinion 7.3.6, "Research in Gene Therapy & Genetic Engineering," states that genetic manipulation should be reserved for therapeutic purposes, and that efforts to enhance "desirable" characteristics are contrary to the ethical tradition of medicine. It sets out a number of conditions that should be met before physicians engage in research involving gene therapy or genetic engineering, including evidence that the intervention will be safe and effective, that no other suitable or effective therapies are available, and that it is restricted to somatic cells. The full opinion is in the Appendix. The Council believes that the principles set forth in Opinion 7.3.6 should guide AMA policy on genome editing.

Costs and Health Disparities

As is the case for many expensive therapies, access problems are likely to occur if genome editing-based gene therapies become viable clinical options. Use of the first gene therapy product approved by the EMA, Glybera, has been limited to only one patient because it carries a price tag of more than $1 million. It was covered by the patient's insurance company, but only after her physician worked intensely to obtain authorization.[16] It is not known what the cost of the newly EMA-approved gene therapy Strimvelis will be, but its manufacturer, GlaxoSmithKline, has stated that it will be "significantly less" than the $1 million mark.[16] According to the manufacturer of Glybera, UniQure, the high cost of gene therapy drugs is based on the substantial development costs, the fact that the market for the rare diseases they treat is exceptionally small, and in Glybera's case, that it is administered only once, rather than repeatedly over a period of time.[58] Compared to the $250,000 per year average cost of other orphan drugs that treat rare diseases, a one-time dose of a $1 million drug could be considered cost-saving. However, that cost is so high that it is unlikely patients who need the therapies could afford them, or that insurance companies would authorize payment. This undoubtedly would create health disparities issues, in which only the wealthiest patients, or those fortunate enough to have coverage through insurers who will approve the therapy, could have access to it. Although Glybera and Strimvelis are based on transgene expression rather than permanent genome modification, it is reasonable to assume that genome editing-based gene therapies would have similarly expensive development processes, leading to high costs for patients.

CONCLUSIONS

The last few years have seen unprecedented progress in the development of genome editing mechanisms and their potential applications for gene therapy. While most research is at the preclinical stages, a small number of clinical trials in humans have begun, with others planned for the near future. Much work remains to ensure the safety and effectiveness of genome editing, and questions remain about the appropriate use of germline editing. The Council supports continued research into the clinical applications of genome editing, but urges caution and thoughtful consideration before clinical germline editing is undertaken. The Council also urges continued work to develop international consensus standards for permissible therapeutic uses of germline editing.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report be filed.

1. That our American Medical Association (AMA) encourage continued research into the therapeutic use of genome editing. (New HOD Policy)

2. That our AMA urge continued development of consensus international principles, grounded in science and ethics, to determine permissible therapeutic applications of germline genome editing. (New HOD Policy)

Fiscal Note: Less than $1000

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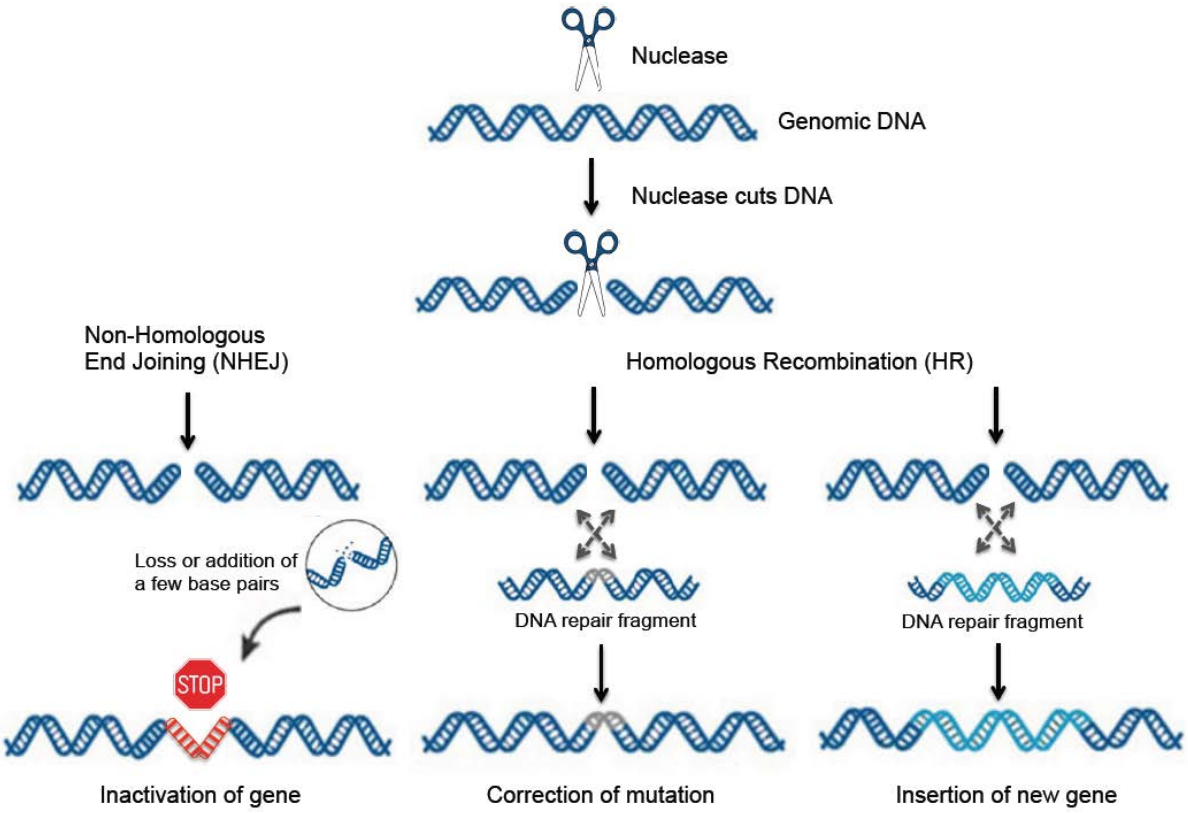
Figure. The genome editing process.



A nuclease engineered to cleave genomic DNA at a precise location is inserted into the cell. Once the DNA is cut, the cell uses either non-homologous end-joining (NHEJ) or homologous recombination (HR) to repair the cut. In NHEJ, the two ends of the DNA strand that have been cut are directly rejoined, but this process results in the insertion or deletion of a small number of nucleotides, disrupting normal gene function. In HR, an exogenous DNA fragment containing a new gene or a corrected sequence of nucleotides, along with sequences that match those surrounding the site of the DNA cut, is inserted into the cell. The cell uses the exogenous DNA fragment as a template to repair the cut, incorporating the sequence present into the genomic DNA, correcting a mutation or inserting a functional gene. (Figure adapted from http://www.calyxt.com/technology/targeted-genome-editing/.)

Appendix. AMA Code of Medical Ethics, 7.3.6, Research in Gene Therapy & Genetic Engineering

Gene therapy involves the replacement or modification of a genetic variant to restore or enhance cellular function or the improve response to nongenetic therapies. Genetic engineering involves the use of recombinant DNA techniques to introduce new characteristics or traits. In medicine, the goal of gene therapy and genetic engineering is to alleviate human suffering and disease. As with all therapies, this goal should be pursued only within the ethical traditions of the profession, which gives primacy to the welfare of the patient.

In general, genetic manipulation should be reserved for therapeutic purposes. Efforts to enhance "desirable" characteristics or to "improve" complex human traits are contrary to the ethical tradition of medicine. Because of the potential for abuse, genetic manipulation of nondisease traits or the eugenic development of offspring may never be justifiable.

Moreover, genetic manipulation can carry risks to both the individuals into whom modified genetic material is introduced and to future generations. Somatic cell gene therapy targets nongerm cells and thus does not carry risk to future generations. Germ-line therapy, in which a genetic modification is introduced into the genome of human gametes or their precursors, is intended to result in the expression of the modified gene in the recipient's offspring and subsequent generations. Germ-line therapy thus may be associated with increased risk and the possibility of unpredictable and irreversible results that adversely affect the welfare of subsequent generations.

Thus in addition to fundamental ethical requirements for the appropriate conduct of research with human participants, research in gene therapy or genetic engineering must put in place additional safeguards to vigorously protect the safety and well-being of participants and future generations.

Physicians should not engage in research involving gene therapy or genetic engineering with human participants unless the following conditions are met:

(a) Experience with animal studies is sufficient to assure that the experimental intervention will be safe and effective and its results predictable.

(b) No other suitable, effective therapies are available.

(c) Gene therapy is restricted to somatic cell interventions, in light of the far-reaching implications of germ-line interventions.

(d) Evaluation of the effectiveness of the intervention includes determination of the natural history of the disease or condition under study and follow-up examination of the participants' descendants.

(e) The research minimizes risks to participants, including those from any viral vectors used.

(f) Special attention is paid to the informed consent process to ensure that the prospective participant (or legally authorized representative) is fully informed about the distinctive risks of the research, including use of viral vectors to deliver the modified genetic material, possible implications for the participant's descendants, and the need for follow-up assessments.

Physicians should be aware that gene therapy or genetic engineering interventions may require additional scientific and ethical review, and regulatory oversight, before they are introduced into clinical practice.