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Review Article

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CRISPR-Cas9 in human Gene Therapy: Clinical Progress, Ethical Dilemmas, and Regulatory Responses

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Abstract

The CRISPR-Cas9 technology is a powerful tool for targeted modifications of DNA sequences with unprecedented precision. In enabling researchers with the ability to fix certain lethal and non-lethal mutations that cause diseases like Duchenne muscular dystrophy, sickle cell anaemia, and beta-thalassemia, this powerful technology has shown promise in treatment of these genetic conditions. Several ethical questions have been raised about using CRISPR-Cas9, the most concerning being the editing of human embryos, particularly those pertaining to germline modifications that can alter genes in subsequent generations. Furthermore, the creation of so-called "designer babies" raises ethical questions about consent, autonomy, and potential damage from unintended off-target effects. The possibility that CRISPR-Cas9 may be used for purposes other than medicine, such as altering physical characteristics and intellect, is another concern. The main aim of this review is to curate updated literature on CRISPR-Cas9 technology, its potential for use in genetic therapies, and the ethical and legal issues associated with it. The review also discusses the need for robust ethical framing and regulatory oversight, assuring that gene-editing technologies will be responsible and equitable, with consideration of human dignity and diversity.

Keywords: CRISPR-Cas9, Gene editing, Human embryo editing, Designer babies, Genome editing regulations

1. Introduction

Over the past two decades, developing reliable and inexpensive techniques for making accurate specific changes to the genome has been a critical goal for scientists. Genome editing techniques, involving precise alterations using programmable sequence-specific nucleases (SSN) to create double stranded breaks at specific genomic loci and then utilizing microhomology-mediated end joining (MMEJ), homology-directed repair (HDR), or non-homologous end joining (NHEJ) mechanisms serve as powerful tools to alter disease causing genes [1, 2]. However, with Clustered regularly interspaced short palindromic repeats or CRISPR-Cas9 technology, the gene editing process became highly accurate, making it a gamechanger for gene-editing process.

CRISPR was discovered in the DNA of *Escherichia coli* bacteria by Ishino and his team at Osaka University in Japan who sequenced these difficult DNA fragments to know their origin and role or role in the cell. However, finding comparable structures in the archaeal genome of *Haloferax mediterranei* by scientists marked a major advancement in deciphering the biological role of CRISPR loci.

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas (CRISPR associated) is an RNA-based immune system developed by archaea and bacteria to defend against viral and plasmid invasions. These defense mechanisms are designed

in a way that uses RNA to combat plasmid attacks and identifies and suppresses foreign genetic material in a sequence-specific manner. Cas genes are organized in operons, along with a CRISPR array that contains unique genome-targeting sequences. These sequences are called spacers, interspersed with identical repeats [3–5]. CRISPR-Cas systems consist of six different types, with types IV–VI being newly discovered. On the other hand, types I and III share characteristics for processing pre-crRNAs by specific Cas endonucleases. The pre-crRNAs, once matured, are assembled into large multi-Cas protein complexes. These complexes can cleave and recognize nucleic acids that are complementary to crRNA. In comparison, type II systems use a transactivating crRNA (tracrRNA) that matches repeat sequences in pre-crRNA to aid processing by RNase III alongside the Cas9 protein. The genes for Cas9, Cas1, Cas2, and, in the case of subtype II-B, Cas4 are present in subtypes of the type II system. Cas9 has become a popular choice for gene therapy due to its relative simplicity and efficiency [6].

Since then, considerable advancements in the field of CRISPR including identification of nuclease Cas9 and directional cutting of foreign DNA known as "genetic scissors," gained further objective direction. In addition to this, an essential component of the CRISPR–Cas9 system-a short RNA molecule, known as tracrRNA, that directs prokaryotic immune system proteins to foreign molecules containing genetic information, further strengthened this technique putting a functional CRISPR–Cas9 system in use. On the other hand, refining of this technique with joining of two RNA molecules, crRNA and tracrRNA, to form a single chimeric molecule (sgRNA, or single guide RNA) significantly aided practical implementation of CRISPR–Cas9 in various applications [1].

Due to its use of safe viral (Adeno-Associated Virus AAV), and non-viral vectors such as Cas9-sgRNA ribonucleoproteins (RNPs), CRISPR-Cas9 technology has been labelled as safe and effective [1]. However, reports of CRISPR techniques being susceptible to errors, such as off-target effects or unintended on-target events have been documented. In addition, in some report's activation of immune response against the bacteria used to generate Cas-9 proteins has also been documented [1].

Several studies have documented the utility of CRISPR-Cas9 as gene editing tool for gene therapy in genetic disorders such as Duchenne muscular dystrophy (DMD), cystic fibrosis (CF), Wolfram syndrome or Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness (DIDMOAD), Huntington's disease, Leber congenital amaurosis, β-thalassemia, sickle-cell disease, and human immunodeficiency virus (HIV) [7–9]. For example, in an X-linked neuromuscular disorder, Duchenne muscular dystrophy, in which a lack of functioning dystrophin protein leads to progressive muscle degeneration, loss of mobility, and early mortality from cardiac issues, the role of CRISPR-Cas9 gene editing of the dysfunctional gene leading to synthesis of functioning dystrophin protein has life altering consequences for people suffering from this disorder [10–12].

On the other hand, various unethical uses of CRIPR-Cas technique for gene editing have also been reported. In 2018, twin girls born in China from In Vitro Fertilization (IVF), with their embryos edited to disable HIV replication genes, with the help of CRISPR genome-editing technique, exposed the unprincipled relevance and approach of this technique. In fact, the sheer audaciousness of directly editing and altering the genes embryonically, without knowing the on/off-target effects and in turn making the gene-edited babies vulnerable to unknown after-effects was an eye-opening realization for the scientific community [13].

Keeping both the pros, especially in gene therapy for rare disorders and cons, such as unethical utility of CRISPR-Cas9 for embryonic gene editing in perspective, this review article aims to provide updated information on CRISPR-Cas9 technology and its significance in gene editing.

2. Methodology

All retrieved articles relevant to CRISPR-Cas9 gene editing were included in this review. Articles were considered relevant if they contained information regarding CRISPR-Cas9 technology, including its mechanisms, clinical applications, advantages, limitations, and ethical considerations. All articles were retrieved from indexed databases including PubMed and Google Scholar.

Articles included in this review were filtered based on publication year. The literature used in this manuscript ranges from 1989 to 2023. Foundational earlier studies were included to provide historical context, while more recent publications were selected to reflect current developments in CRISPR-Cas9 research and its ethical implications. No specific weightage was given to articles. All articles were weighed similar without any discrimination.

The search keywords included "CRISPR-Cas9", "gene editing", "clinical uses of CRISPR-Cas9", "ethics of gene editing", and "ethical concerns of CRISPR-Cas9". Only articles published in English were included. Ethical perspectives were additionally retrieved from developed countries including Germany, the United Kingdom, the United States of America, and China. Preprints were not included in this review; all cited sources consist of peer-reviewed journal articles, institutional reports, or official policy documents.

3. Discussion

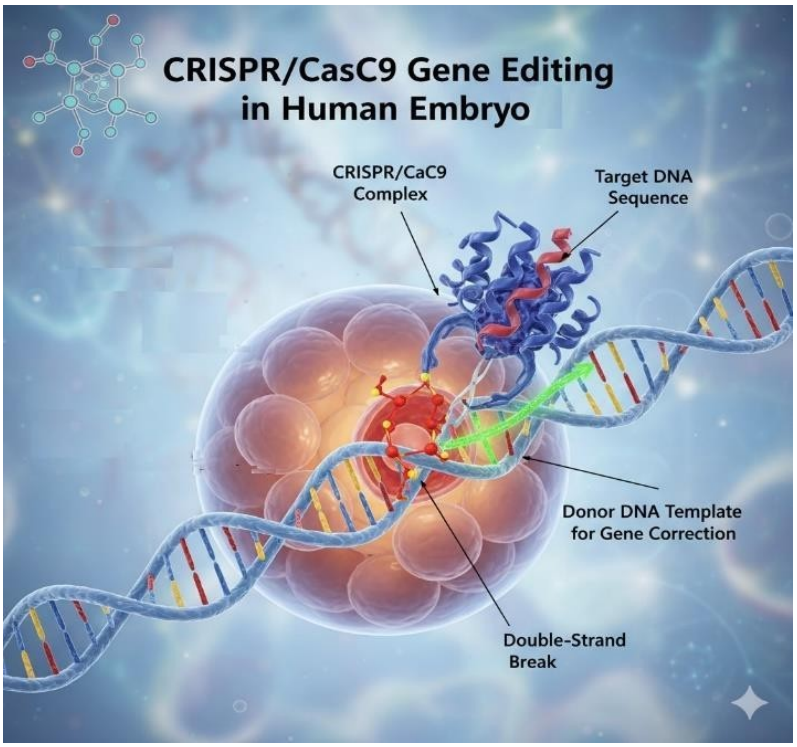

Figure 1: Mechanism of CRISPR-Cas9 Gene Editing in a Human Embryo. This schematic illustration depicts the CRISPR-Cas9 genome editing process within a human embryonic cell. The CRISPR-Cas9 complex, composed of the Cas9 endonuclease protein bound to a single guide RNA (sgRNA), is directed toward a specific target DNA sequence through complementary base pairing between the sgRNA and the genomic DNA. Upon recognition of the protospacer adjacent motif (PAM) sequence, Cas9 induces a precise double-stranded break (DSB) at the target locus. Following cleavage, the cell's endogenous DNA repair mechanisms are activated. In the presence of a donor DNA template, homology-directed repair (HDR) enables precise gene correction or insertion. In the absence of a donor template, non-homologous end joining (NHEJ) may occur, potentially introducing insertions or deletions (indels) that disrupt gene function. This mechanism underlies the therapeutic potential of CRISPR-Cas9 for correcting pathogenic mutations but also raises concerns regarding off-target effects and unintended genomic alterations.

3.1. Benefits, Risks, and Ethical Implications of CRISPR-Cas9 in embryonic editing

CRISPR-Cas9 works in a systematic manner system via RNA molecule that directs Cas9 to function as an endonuclease, allowing double-strand breaks (DSBs) [14, 15]. With respect to human embryonic editing, Adenoviral vectors (AAV) have been used to alter genes with studies in transgenic animal models reporting that utero transfer of modified embryos can result in offsprings exhibiting the predicted gain-of-function or loss-of-function traits. Furthermore, the development of new base editors has enabled precise single-base changes in animal disease models, representing a major advancement in both accuracy and safety of embryo editing [14, 15].

In mammalian germline genome editing, nucleases are usually microinjected directly into zygotes that is comparable to intracytoplasmic sperm injection (ICSI), a popular ART method [16, 17]. The Cas9 enzyme, guided by a strand of CRISPR RNA, can find a specific gene in the genome and cut both strands of DNA at that location. This cut starts a natural repair process in the cell, usually resulting in a mutation through deletion of DNA at the site. If a "donor" DNA template is provided, then the cell can incorporate this new DNA to repair the break. This technique enabled scientists to introduce desired sequences into a cell, allowing a paradigm shift in genome editing to either correct mutated genes or insert functioning genes as a treatment tool/prevention of genetic diseases in future generations [15]. *Liang et al.* reported the first-ever use of CRISPR-Cas9 gene editing in human embryos by using a nonviable tripronuclear (3PN) human zygote. The team checked the correction efficiency of mutated *haemoglobin subunit beta (HBB)* gene (responsible for blood disorder) by introducing targeted DNA breaks [18]. The landmark study was followed up with animal studies. For example, rodent viable foetuses were obtained after loss-of-function or gain-of-function editing, while rabbit models using ABE7.10 and BE3 systems achieved single-base edits with efficiencies of 44%–100% and no off-target effects. These in vivo studies demonstrated the potential of embryonic editing for the treatment of fatal conditions such as hemoglobinopathies or muscular dystrophies.

In 2018, a controversy regarding the CRISPR-Cas9 editing was reported. The C-C chemokine receptor 5 (CCR5) gene in viable human embryos was done by a scientist, to make the embryos and the subsequent offspring HIV-resistant. Twins with the altered embryos were born with HIV negative phenotype. Though the results were promising, the experimental design

involving alteration of genes by CRISPR-Cas9, using a viable human embryo sparked a global ethical debate. The scientific community raised alarms on the experimental design, ethical dilemmas, limited animal models data before experimenting on humans, no plan of action to address the long-term effects of the experiment and possibility of accidental mutations/on-off target effects. This case served as hallmark case regarding the monitoring and long-term surveillance requirements for CRISPR-Cas9 editing of human heritable genes [19]. In the next section, the pros and cons of CRISPR-Cas9 gene editing of human heritable genes are given.

3.2. Utility of CRISPR/Cas9 for treating genetic disorders:

CRISPR editing for human heritable genes was FDA approved in 2023. Since then, many studies have showed promising results. For example, CRISPR-Cas9 has been documented to be highly effective in treating sickle cell disease and beta-thalassemia patients, by precise targeting and deactivation of *BCL11A* gene and disrupting a regulatory element that normally turns off the gene for Fetal haemoglobin (HbF) after birth in these patients. In a clinical trial on sickle cell anaemia and beta-thalassemia patients, 29/30 patients (sickle cell anaemia) and 39/42 (beta-thalassemia patients) were successfully treated and healthy Fetal haemoglobin production was restored leading to alleviation of symptoms and lifetime cure [20, 21]. The ability of CRISPR-based therapeutics to provide long-lasting, one-time cures as opposed to recurring treatments is another strong benefit [20].

Similarly, another study on the utility of CRISPR-Cas9 editing in human embryos for correcting *MYBPC3* mutation linked to heart diseases showed promising results. Using the maternal wild-type allele, researchers reported effective HDR repair and a 97.1% embryo survival rate, resulting in a considerable number of embryos homozygous for the repaired allele [22]. This breakthrough results highlights the promise of CRISPR-Cas9 in addressing inherited genetic disorders. On the other hand, technological advancements have enhanced the technique addressing any issues associated with it. For example, the addition of base editors and high-fidelity Cas9 variations such as dead Cas9 (dCas9) effectors and single-base substitution tools like cytosine base editors (CBEs), adenine base editors (ABEs), and prime editors (PEs) have helped to reduce off-target effects, enhancing the CRISPR-Cas9 system's dependability and safety. Furthermore, the use of novel strategies such as ribonucleoprotein complexes and modified viral vectors have increased the overall safety and efficiency [22].

Despite the successful treatment of genetic disorders using CRISPR, addressing ethical concerns including issues of informed consent and autonomy, justice, and accessibility to the risk of abuse in designer babies in wealthy individuals must be considered. The next sections give an insight on the ethical concerns with CRISPR-Cas9 editing.

3.3. Autonomy and Consent

According to the Nuffield Council on Bioethics, heritable genome editing may be morally permissible provided it promotes the well-being of individuals, and such interventions does not lead to social exclusion, prejudice, or division [23]. However, since future generations are unable to give their consent to actions that might significantly impact their health and well-being, germline alterations that are passed down to descendants pose ethical questions. In 2017, the National Academies of Sciences, Engineering, and Medicine explicitly stated that heritable genome editing is currently impermissible. Off-target errors using CRISPR-Cas9 might result in new features, and such alterations could have unforeseen evolutionary effects that future generations would not want to happen [24].

3.4. Potential for Misuse and "Designer Babies"

"Designer babies" includes DNA alteration of an embryo to enhance or change certain phenotypic traits using genetic engineering or genetic modification [25, 26]. The slippery slope argument states that if we start genetically modifying embryos to choose particular qualities, it will be difficult to establish limits and halt the pursuit of extreme or socially manufactured ideals of perfection. The concern is that the original objectives of improving health or curing genetic abnormalities would ultimately lead to a culture that is fixated on creating genetically superior or "ideal" individuals. The slippery slope argument advises exercising caution and carefully examining the possible consequences of persistently pushing the boundaries of genetic manipulation [27, 28].

Germline gene editing, mostly using CRISPR-Cas9, has recently gained attention as a viable method for correcting germline mutations and a way to avoid the need for embryo selection. By increasing the number of embryos accessible for transfer, this might increase overall success rates; nevertheless, at this time, germline editing is not yet suitable for clinical usage due to ethical and technological concerns [15].

3.5. Justice and Accessibility

Editing human embryos could result in future challenges such as selecting embryos for characteristics like IQ, physical attractiveness, or athletic ability. A society divided between those who can afford such modifications and those who cannot. It would worsen socioeconomic inequality. Furthermore, it tends to violate fundamental aspects of equality by raising doubts

about the significance of natural variation and how it permits discrimination against those who are seen to be "naturally" inferior [26]. This might further exacerbate unfavourable biases and prejudices by causing discrimination against individuals in society based on whether they have the genetic alteration. Such prejudice can diminish the principles of inclusion and equality and eventually have an impact on social connections, mental health, and self-esteem. There is a significant chance that parents will base their chosen parenting choices on broad social preconceptions or prejudices if they had the ability to choose certain features for their kids. As a result, prejudices will become much more ingrained and cultural standards of brilliance, attractiveness, and other traits will become even more tangible. Individual autonomy, self-identity, and personal expression may thus be lost because of pressure to live up to these standards. Additionally, it might promote disrespect for human uniqueness and natural diversity [26–28].

Other scholars argue from the standpoint of health economics that correcting a mutation within a family is more cost-effective in the long run than paying for a patient's and their descendants' lifelong medical treatment. For nations having a national healthcare system, this factor becomes essential. One example of how genome editing technology could be included in the future is the UK's launch of mitochondrial replacement therapy. Preventing the transfer of incurable mitochondrial illnesses from mother to kid was the goal of the development of MRTs. This is accomplished by a procedure called nuclear transfer, in which the defective mitochondria are removed from a donor egg by taking nuclear DNA from an oocyte or zygote of a mother with a mitochondrial mutation. The nuclear DNA is then transferred to a cell with healthy mitochondria, thereby avoiding the source of the disorder [29, 30].

Experts, religious organizations, patients, and the public all participated in a lengthy consultation process in the UK to express their opinions. As a result, the Human Fertilization and Embryology (Mitochondrial Donation) Regulations 2015 were drafted and debated via Parliament. This offered a thorough licensing procedure that was independently monitored to guarantee that clinics followed stringent safety, ethical, and scientific guidelines. Additionally, it committed to continue follow-up investigations for a long time and noted the appropriate consent that should be obtained from the patients [13].

3.6. Public Perception and Existing Regulations and Guidelines

A survey conducted by the Royal Society in the United Kingdom highlighted some of the cultural nuances in public opinion. While the majority (60%) opposed editing to increase and improve IQ, 83% of individuals favoured adopting germline genome editing to cure incurable illnesses. This demonstrates how society is concerned about the moral limits of genome editing [31].

Currently, different nations have different laws and regulations pertaining to the altering of germline and embryonic genes. China, the US, and the UK are among the eleven nations that have taken a more lenient stance toward embryonic gene editing for non-reproductive purposes. Conversely, at least nineteen countries have officially prohibited gene editing research involving human embryos, including Belarus, Canada, Sweden, and Switzerland. Russia is one of the nations that maintains a neutral stance on this matter [32].

The Embryo Protection Act [33] and the Genetic Diagnosis Act are the two main statutes that govern genetic testing, reproductive technology, and most of the associated ethical concerns [34]. The Embryo Protection Act specifically addresses genetic information tampering and reproductive technology. It forbids creating embryos in any way other than for reproduction, and it also bans using techniques that change an embryo's genetic makeup unless necessary for medical reasons. With an emphasis on a person's physical, emotional, and overall well-being, the Genetic Diagnosis Act supports genetic testing [34].

In the US, there are no specific federal laws governing designer babies [35]. In any case, the FDA has control over assisted reproductive technologies and requests that specific ethical and safety standards must be followed in such clinics. Similarly, gene editing for specific medical objectives is currently up for dispute, whereas human embryo editing using technologies like CRISPR is outlawed for non-medical purposes [36].

3.7. Research involving embryo editing.

In cases when Preimplantation Genetic Diagnosis (PGD) is not an option, such germline genome editing research may be able to help high-risk couples to have genetically related children that are disease free [37]. Additionally, it can save IVF embryos with disease-promoting variations, increasing the procedure's effectiveness [38, 39]. If the technique is safe, efficient, and widely used, broader applications may reduce the prevalence of genetic diseases in communities, with possible long-term health and economic advantages [40].

However, Germline Genome Editing (GGE) also raises significant ethical concerns related to the creation and destruction of embryos for scientific purposes, the moral status of embryos, and broader societal implications such as commercialization of reproduction and the potential emergence of consumer-driven eugenics [15, 41–44].

Federal funds cannot be used for research that creates or destroys embryos, according to federal laws. Similarly, the NIH no longer funds any research involving gene editing in human embryos. Many bioethical and research groups agree that gene editing in embryos has substantial scientific value, even though the NIH does not currently finance such research. If it is not now utilized for reproduction, it can still provide important answers about human biology [24, 45]. Research on genome editing in nonviable embryos—those that cannot produce a live birth—has been permitted in certain countries while research techniques involving viable embryos have been authorized by others [46, 47]. Typically, embryos used in research are either

generated especially for the study or remain following IVF treatments, each of which presents unique ethical issues.

4. Conclusion

Indeed, CRISPR-Cas9 has enormous promise for gene therapy and disease prevention, particularly for hereditary illnesses. Through precise DNA sequence alterations, this technology has in fact been extremely successful in curing genetic illnesses like sickle cell disease, Duchenne muscular dystrophy, and beta-thalassemia. In particular, the potential to rectify out-of-frame mutations in the dystrophin gene offers fresh hope for the management of Duchenne muscular dystrophy, a crippling and deadly condition. However, germline modifications with capability of passing genetic modifications to human generations hold a profound set of ethical questions considering consent, autonomy, potential for misuse, and even the social implications of creating individuals with genetically modified characteristics. The "designer baby" dilemma has raised debates on choosing characteristics unrelated to diseases, like intelligence or physical traits, which result in divided society into genetic enhancements. Justice and accessibility issues then surface because, in the main, it may be only the rich or rich nations can be granted access to these powerful technologies, thus further increasing disparities. Despite the phenomenal medical successes achieved through gene therapies applied to genetic diseases, ethical and regulatory frameworks will have to evolve in a balancing act of innovation with responsible use in ensuring that CRISPR technology applies for the greater good of humanity.

From a global perspective, CRISPR-Cas9 should not be viewed merely as a scientific breakthrough but as a responsibility shared by the international community. Clear global governance, strict ethical oversight, and equitable access policies must be established to prevent misuse and ensure fairness across nations. Moving forward, international collaboration among scientists, policymakers, and bioethicists is essential to develop unified standards that safeguard human dignity while allowing scientific progress. Ultimately, the future of CRISPR-Cas9 technology depends not only on what we can edit, but on what we choose to edit and why.

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Author Contributions

KS and HN: Conceptualization, Investigation, Writing – original draft, Writing – review & editing; ZH: Illustrations and editing; AR: Writing – review & editing.

Ethics Approval and Consent to Participate

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Conflicts of Interest

No conflict of interest to declare.

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AI declaration:

During the preparation of the manuscript, authors used ChatGPT for language editing, clarity, and preparation of graphic. After using the tool, authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

6. Abbreviations

The following abbreviations are used in this manuscript:

MMEJ	Microhomology-mediated end joining
HDR	Homology-directed repair
NHEJ	Non-homologous end joining
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
tracrRNA	Transactivating crRNA
sgRNA	Single guide RNA
AAV	Adeno-Associated Virus
RNPs	Ribonucleoproteins
DMD	Duchenne muscular dystrophy
CF	Cystic Fibrosis
DIDMOAD	Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness
HIV	Human Immunodeficiency Virus
IVF	In Vitro Fertilization
DSBs	Double-strand breaks
ICSI	Intracytoplasmic Sperm Injection
dCas9	Dead Cas9
CBEs	Cytosine Base Editors
ABEs	Adenine Base Editors
PEs	Prime Editors
PGD	Preimplantation Genetic Diagnosis
GGE	Germline Genome Editing

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