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Application of genetic scissoring in the management of genetically related diseases

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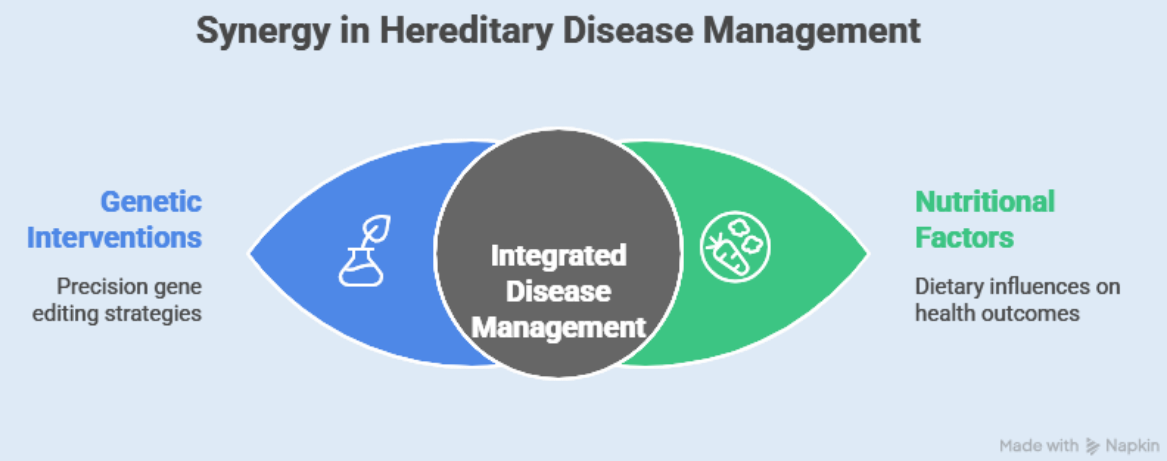
ABSTRACT: CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology has emerged as a groundbreaking tool for genome editing, revolutionizing the management of genetic diseases. Its precision, efficiency, and adaptability enable targeted modification of DNA sequences, offering therapeutic potential for a wide range of inherited disorders. This technology utilizes the Cas9 endonuclease, guided by RNA, to introduce site-specific cuts in the genome, facilitating the correction, disruption, or replacement of genes. Applications include addressing monogenic disorders such as cystic fibrosis, sickle cell anemia, and Duchenne muscular dystrophy, as well as polygenic conditions and diseases linked to somatic mutations, including certain cancers. Furthermore, CRISPR has opened avenues for ex vivo and in vivo gene therapies, including the use of stem cells and viral vectors for effective delivery. While significant ethical and technical challenges remain, such as the risk of unintended genetic modifications and equitable access to therapy, CRISPR represents a paradigm shift in the treatment of genetic diseases. These abstract highlights the current state, challenges, and prospects of CRISPR technology as a transformative tool in precision medicine.

Keywords: CRISPR; precision medicine; monogenic disorders; polygenic conditions,



Graphical Abstract: Application of genetic scissoring in the management of genetically related diseases

INTRODUCTION

Genetic scissoring, also known as CRISPR (an acronym for Clustered Regularly Interspaced Short Palindromic Repeats), is a method for identifying and modifying a specific segment of DNA within a single cell, utilizing a protein called Cas9 and a guide RNA [1]**.** Francisco Mojica was the first researcher to characterize what is termed the CRISPR Locus, reported in 1993. He worked with CRISPR throughout the 1990s, and in 2000, he observed that what had been reported repeatedly as disparate repeat sequences did share a standard set of features, now known as CRISPR sequences (he coined the term CRISPR through correspondence with Ruald Jansen, who first used the term in print in 2002) [2]. This finding led him to hypothesize, correctly, that CRISPR is an adaptive immune system.

The application of genetic scissoring, particularly through techniques like CRISPR-Cas9, has revolutionized the field of genetics, offering immense potential in the prevention and management of genetically related diseases [3-4]. This innovative technology opens up new avenues for treating conditions such as cystic fibrosis, sickle cell anemia, and certain types of cancer, offering hope for cures and preventive strategies that were previously unimaginable. As research advances, genetic scissoring stands at the forefront of personalized medicine, promising to transform healthcare by addressing the root causes of genetic disorders [5]. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has revolutionized molecular biology by enabling precise DNA modifications, transforming medicine, agriculture, and evolutionary science. Innovative variants—base editing and prime editing—introduced in 2019, allow single-letter changes and complex DNA edits without double-strand breaks [6-7]. Clinical trials have shown promising outcomes, including complete remission in some patients [8-9]. Figure 1 presents a schematic representation of the gene editing process.

In gene therapy, CRISPR has been used to modify both somatic and germ-line cells for treating genetic disorders and cancer [5,10]. In oncology, CRISPR enhances CAR-T therapy by increasing T-cell precision and reducing side

effects [11]. Engineered CAR-T cells have demonstrated persistent antitumor activity [12]. Gene drives, which use CRISPR to spread genetic traits through populations—like malaria-resistant mosquitoes—raise ecological concerns due to their potential irreversible impact [13-14]. CRISPR's precision in gene editing is rooted in stable RNA-DNA binding and Watson-Crick pairing rules [15-[16]. Guide RNAs direct nucleases to specific DNA targets, enabling sequence-specific genome modifications [17]

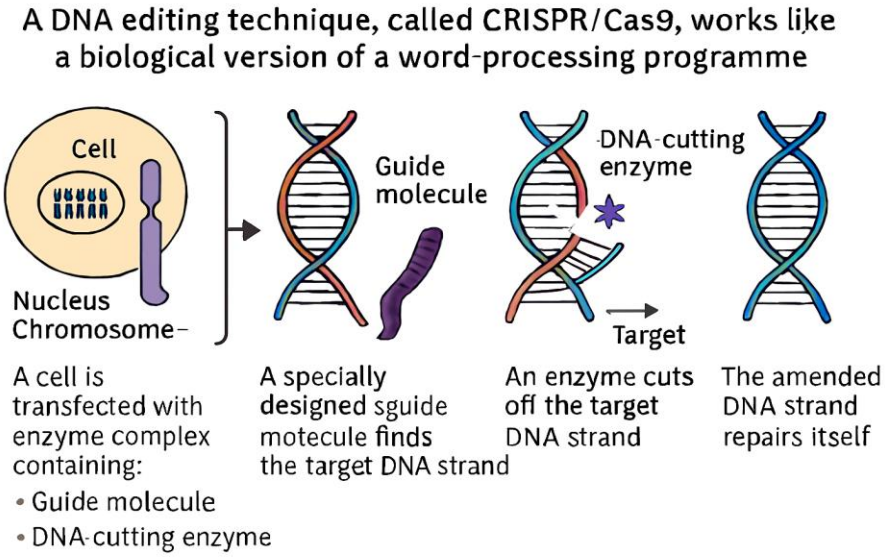


Figure 1: Schematic representation of the process of gene editing

MECHANISMS OF GENE THERAPY

Gene therapy employs key mechanisms to modify or regulate genes for therapeutic benefit. These include gene addition, in which a functional gene is introduced to correct a deficiency, such as CFTR restoration in cystic fibrosis [18]. Gene editing, using tools like CRISPR to directly correct mutations, is applicable in sickle cell disease and thalassemia [19]. Gene silencing, which uses RNAi and ASOs to inhibit harmful gene expression [20]. Additionally, gene replacement restores proper function by replacing defective genes [21]. Gene therapy is broadly classified into somatic and germline approaches. Somatic therapy modifies non-reproductive cells and isn't heritable. An example is Luxturna, which treats Leber's congenital amaurosis by delivering the RPE65 gene to retinal cells [22]. Germline therapy targets reproductive cells, with effects passed to offspring, but remains ethically contentious and banned in many countries [23]. Viral vectors—especially adeno-associated viruses (AAVs), lentiviruses, and retroviruses—are common due to their cell-targeting capabilities. AAVs have demonstrated success in therapies such as Zolgensma for SMA [24], while lentiviruses and retroviruses offer genome integration but vary in their cell-type applicability [25-26]. Non-viral methods like lipid nanoparticles and electroporation are safer but less efficient [25-26]. This multifaceted therapeutic field continues to evolve, promising targeted interventions for genetic disorders across diverse clinical landscapes. Figure 2 presents a Stepwise illustration of gene therapy in the management of diseases [27].

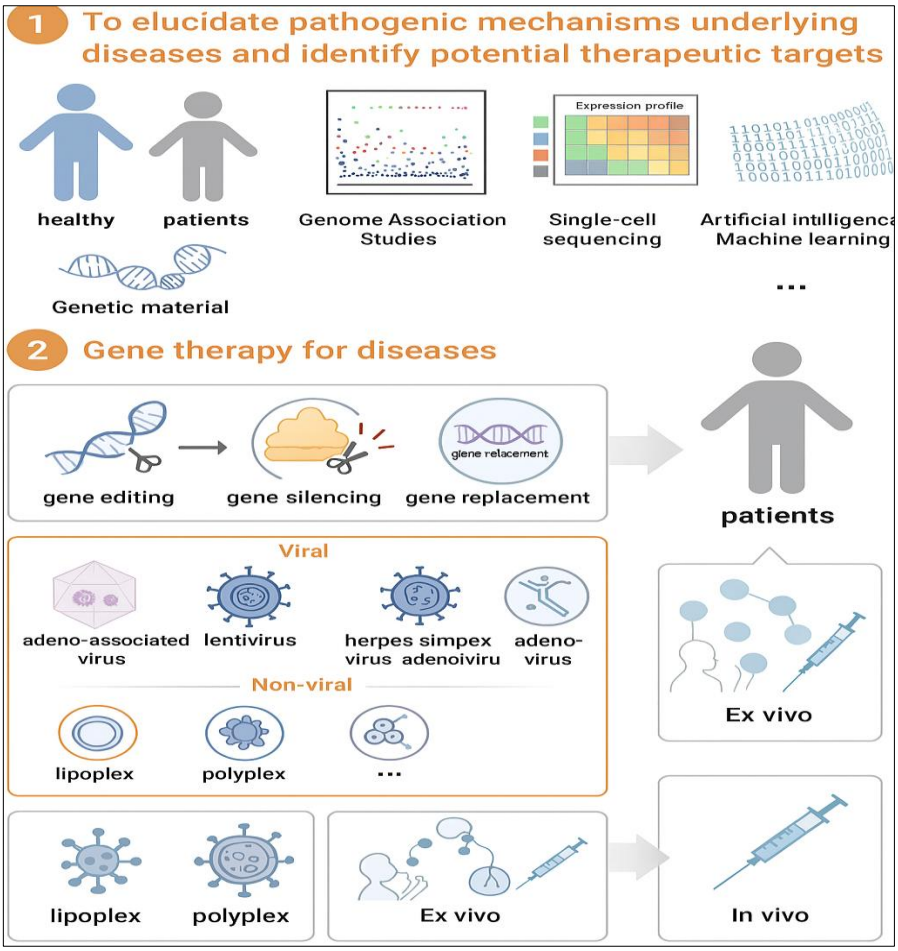


Figure 2: Stepwise illustration of gene therapy in the management of diseases, adapted from [27]

Crispr application in the management of some genetic disorders: CRISPR technology has revolutionized genetic medicine by enabling precise editing of monogenic disorder conditions caused by mutations in a particular gene [28-29]. The procedure for CRISPR application is presented in Figure 3. Sickle Cell Disease (SCD) is caused by a point mutation in the hemoglobin subunit beta (HBB) gene, resulting in the production of abnormal hemoglobin (HbS) that causes the sickling of red blood cells [30]. Ex vivo CRISPR-Cas9 editing of hematopoietic stem cells (HSCs) has yielded promising clinical results [31]. Disrupting BCL11A boosts fetal hemoglobin (HbF), which reduces sickling [32]. Future methods may include in utero editing to prevent disease onset [33]. Cystic Fibrosis (CF) results from mutations in the CFTR gene, notably the ΔF508 mutation, which causes thick mucus and organ damage [34]. CRISPR in vivo editing targets lung cells using viral vectors or lipid nanoparticles [35]. Ex vivo approaches edit airway epithelial cells for reintroduction [36]. Prenatal interventions may prevent CF but pose ethical challenges. Duchenne Muscular Dystrophy (DMD) results from mutations in the DMD gene, which eliminates dystrophin and destabilizes muscles [37]. CRISPR enables exon skipping [38] or direct gene correction using AAVs [39]. Germline editing could block inheritance [40]. Huntington's Disease (HD) is driven by CAG repeat expansion in the HTT gene, producing a toxic protein [41]. CRISPR can silence or edit only the mutant allele to halt progression [42-43]. Embryonic editing might prevent transmission [44].

CRISPR technology offers transformative solutions for managing both monogenic and polygenic disorders.

Leber Congenital Amaurosis (LCA) is caused by mutations in CEP290 and RPE65, leading to early-onset blindness [45]. In vivo CRISPR trials corrected retinal mutations [46], with AAVs used to deliver components [47]. Future prevention could involve embryonic editing [48]. Beta-Thalassemia, due to HBB gene mutations, causes anemia [49]. CRISPR-corrected stem cells have restored red blood cell production [50] and increased fetal hemoglobin (HbF) offers symptom relief [51]. Germline editing may prevent inheritance [52]. Polygenic Disorders involve multiple genes and environmental triggers [52]. For Cardiovascular Disease, CRISPR has been used to knock out PCSK9, lowering cholesterol [53], and is also validating risk alleles [54]. In Type 2 Diabetes, gene editing enhanced insulin secretion via SLC30A8 [55]. In Alzheimer's Disease, CRISPR converted harmful APOE4 into protective APOE2 [56], and gene screens revealed new targets [57]. For Schizophrenia, GRIN2A knockouts clarified synaptic roles [58-59]. In Obesity, editing FTO improved metabolism [60], while MC4R editing showed therapeutic potential [61].

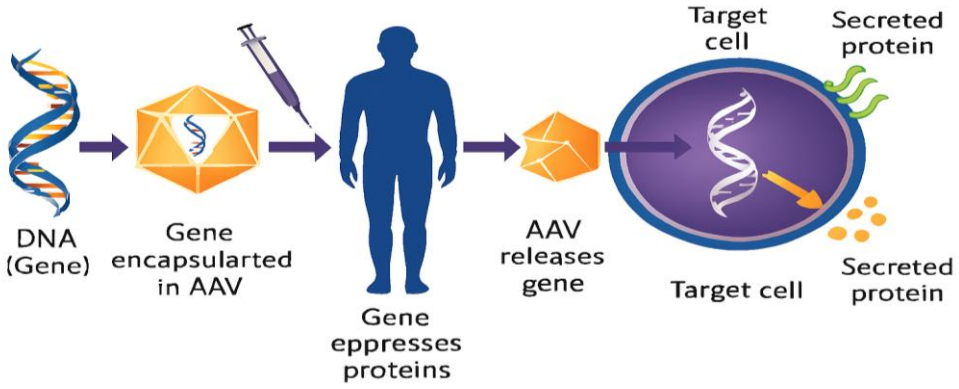


Figure 3: The procedures of CRISPR's application in the treatment of polygenic disorders, adapted from [62]

Application of CRISPR in the management of chromosomal disorders: Chromosomal disorders arise from structural or numerical abnormalities in chromosomes, leading to developmental, intellectual, and physical impairments. Common examples include Down syndrome, Turner syndrome, Klinefelter syndrome, and Cri-du-chat syndrome. CRISPR-Cas9 has created new possibilities for dealing with these complex conditions. Down Syndrome (Trisomy 21) results from an extra chromosome 21 [63]. CRISPR has been used to silence this copy via XIST activation [64], and to target the APP gene—linked to Alzheimer's risk—in trisomic cells [65]. Turner Syndrome (Monosomy X) affects females with a single X chromosome [66]. Researchers are developing CRISPR strategies to boost expression on the remaining X [67] and correct heart-related defects [68]. Klinefelter Syndrome (XXY) involves an extra X chromosome in males, causing infertility and cognitive issues [69]. CRISPR has been used to reduce X-linked gene overexpression [70] and enhance spermatogenesis via SRY gene editing in mouse models [71]. Cri-du-chat Syndrome (5p deletion) causes cognitive and developmental challenges, named for a cat-like infant cry [72]. CRISPR has been shown to upregulate genes on the homologous chromosome [73], while neural progenitor cell editing elucidates its effects on brain development [74]. CRISPR applications offer targeted approaches for managing these complex chromosomal disorders.

Chromosomal translocations and rearrangements, which involve abnormal reattachment of chromosome segments, can cause cancers like chronic myelogenous leukemia (CML) and developmental disorders such as

Jacobsen syndrome [75]. CRISPR technology offers targeted therapeutic strategies; in CML, CRISPR has successfully disrupted the BCR-ABL1 fusion gene resulting from a chromosome 9–22 translocation [76]. CRISPR's precision has enabled somatic cell editing for sickle cell anemia, allowing blood cells to produce healthy hemoglobin [77], and for treating Leber congenital amaurosis, a genetic form of blindness [78]. However, human germline editing raises ethical issues, as seen in He Jiankui's controversial embryo modification for HIV resistance [79]. Concerns include the rise of "designer babies" and societal inequities [80]. Equity remains a challenge—CRISPR therapies are expensive, limiting access for low-income populations [81-82]. Philosophical debates also linger over the distinction between enhancement and treatment, echoing past eugenic practices [79]. Regulatory frameworks vary globally, with some nations lacking oversight, which can lead to the risk of misuse [83]. Coordinated international governance is crucial to ensure the safe and ethical use of gene-editing technologies in treating genetic diseases.

The role of nutrition in gene-editing outcomes: Genetic editing, particularly using CRISPR-Cas9, has significantly altered the treatment of genetically linked disorders such as sickle cell anaemia, cystic fibrosis, and certain types of cancer. However, nutritional status is crucial in regulating gene expression, cellular repair processes, and immunological responses that support the effectiveness of gene editing, so the success of these interventions depends on more than just molecular tools [84]. While nutrigenomics studies how nutrients affect gene expression, nutrigenetics examines how genetic variants influence an individual's response to nutrients. Folate and vitamin B12, for instance, are necessary for DNA methylation, which might change chromatin accessibility and affect the results of gene editing [85]. Cellular repair processes, including homology-directed repair (HDR) and non-homologous end joining (NHEJ), are essential to gene editing. Zinc, magnesium, and vitamin D are essential cofactors for enzymes that repair DNA. Reduced editing efficiency or off-target effects could result from deficiencies in several nutrients, which could also affect repair fidelity [86].

Furthermore, dietary components can modify the immune responses that are produced by gene-editing vectors (such as viral delivery systems). The anti-inflammatory properties of polyphenols and omega-3 fatty acids may improve vector absorption and lessen immunological rejection [87]. Dietary factors can impact gene accessibility through epigenetic changes, including DNA methylation and histone acetylation [88]. For example, by altering chromatin structure, resveratrol and curcumin are known to modify histone acetylation, which may improve the accuracy of CRISPR targeting [89]. Gene editing provides a treatment option for monogenic illnesses such as phenylketonuria (PKU) [90]. Dietary control is still necessary both before and after editing, though, to maintain metabolic pathways. Antioxidant-rich diets may also lessen oxidative stress in sickle cell disease, enhancing the cellular environment for gene correction [91]. There are still obstacles despite encouraging intersections. A significant amount of nutritional data is self-reported, which can lead to inaccuracies. Furthermore, interdisciplinary cooperation and a robust bioinformatics infrastructure are essential for integrating genetic and nutritional data into therapeutic procedures [92]. Creating databases of nutrient-gene interactions, standardizing nutritional guidelines for gene-editing candidates, and investigating the impact of microbiota on gene-editing results should be the main goals of future studies. In genetic scissoring, nutrition is more than just a background variable; it is a dynamic modulator that can enhance accuracy, reduce risks, and improve treatment outcomes [93]. Personalized diet will be crucial to maximizing the

promise of gene-editing technologies in the treatment of genetically associated disorders as they develop.

CONCLUSION

Gene scissoring represents a paradigm shift in the treatment of genetic diseases, offering unprecedented precision and the possibility of permanent cures. While significant advances have been made, particularly in the treatment of monogenic diseases and cancers, ongoing research and technological improvements are essential to overcome the existing challenges. With further refinement of gene-editing tools, increased accessibility, and a thoughtful approach to ethical considerations, gene scissoring holds the potential to become a cornerstone of modern medicine, profoundly altering the landscape of disease treatment in the coming decades.

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