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Wheatley Research Consultancy,
Bagley, Minnesota, USA

Correspondence to:
Mary Christine Wheatley,
mchristinewheatley@gmail.com

Additional material is published
online only. To view please visit
the journal online.

Cite this as: Wheatley MC. Gene
Editing: CRISPR and Beyond.
Premier Journal of Biomedical
Science 2025;2:100002

DOI: [https://doi.org/10.70389/
PJBS.100002](https://doi.org/10.70389/PJBS.100002)

Received: 22 August 2024

Revised: 29 December 2024

Accepted: 2 January 2025

Published: 18 January 2025

Ethical approval: N/a

Consent: N/a

Funding: No industry funding.

Conflicts of interest: N/a

Author contribution:
Mary Christine Wheatley —
Conceptualization, Writing —
original draft, review and editing
Guarantor: Mary Christine
Wheatley

Provenance and peer-review:
Commissioned and externally
peer-reviewed

Data availability statement:
N/a

Gene Editing: CRISPR and Beyond

Mary Christine Wheatley

ABSTRACT

Gene editing technologies, particularly CRISPR, have significantly transformed fields such as medicine, agriculture, and biotechnology, offering precise modifications to DNA with increasing efficiency and lower costs. This review highlights CRISPR's significant role in advancing medical treatments for genetic disorders such as sickle cell disease and cystic fibrosis, with ongoing trials demonstrating its potential to effectively correct genetic defects. In agriculture, CRISPR has enhanced crop resilience and nutritional profiles, contributing to sustainable food production. However, the rapid development of gene editing raises profound ethical, legal, and social concerns, from the potential creation of "designer babies" to impacts on biodiversity, necessitating robust discussions and regulatory frameworks to ensure responsible application.

The future of CRISPR and related technologies hinges on balancing technological advancements with ethical considerations, ensuring equitable access, and addressing societal implications comprehensively.

Keywords: CRISPR-Cas9, Genetic disorders, Prime editing, Agricultural biotechnology, Ethical implications

Introduction

Gene editing, a set of technologies that enable scientists to alter an organism's DNA, has revolutionized fields such as medicine, agriculture, and biotechnology. Among these technologies, CRISPR-Cas9 stands out as a particularly transformative tool due to its precision, affordability, and versatility.^{1,2} Initially discovered as a bacterial immune defense mechanism, CRISPR-Cas9 has been adapted to edit the genes of various organisms rapidly and with unprecedented accuracy.³

This review explores the recent advancements in CRISPR technology and its broad spectrum of applications. From curing genetic diseases to enhancing agricultural production and addressing key biotechnological challenges, CRISPR's impact is profound and wide-reaching. Additionally, the review will cover the ethical, legal, and social implications that accompany the use of gene editing technologies. These considerations are crucial as the capability to alter DNA at will poses significant ethical questions and requires careful regulatory frameworks to ensure responsible use.⁴

As we explore these themes, the review aims to provide a comprehensive overview of the current state and future potential of CRISPR and other gene editing technologies, highlighting both their promise and the complex issues they bring to the forefront of scientific and public discourse.

Advances in Gene Editing Technologies CRISPR-Cas9

CRISPR-Cas9 continues to revolutionize gene editing with its adaptability and increasing precision. Since

its inception, subsequent refinements have significantly expanded its capabilities. One of the pivotal advancements is the development of high-fidelity Cas9 variants that minimize off-target effects, crucial for clinical applications. These variants, such as eSpCas9 and HypaCas9, have shown reduced off-target activity without compromising on-target efficiency.^{5,6}

Moreover, the integration of machine learning algorithms with CRISPR-Cas9 has enhanced the prediction and selection of optimal guide RNAs, further improving the precision of gene editing outcomes.⁷ This computational approach has helped refine the selection process, reducing potential errors and increasing the success rates of gene editing procedures.

Additionally, advancements in delivery methods have significantly impacted the practical use of CRISPR-Cas9. The development of novel viral and non-viral delivery systems, such as lipid nanoparticles and electroporation techniques, has improved the efficiency of CRISPR delivery to a wide range of cell types, including hard-to-transfect cells like stem cells and primary cells.^{8,9} These improvements not only enhance the versatility of CRISPR-Cas9 but also its applicability in therapeutic settings, where delivery to specific cell types is often a major challenge.

Emerging Gene Editing Technologies: Beyond CRISPR

Prime Editing

Prime editing, a significant enhancement over traditional CRISPR-Cas9, was pioneered by Anzalone et al. in 2019. This technique merges the targetability of CRISPR-Cas9 with the precision of reverse transcription to enact direct edits on the DNA sequence without requiring double-strand breaks (DSBs) or donor DNA templates, which are common in other CRISPR approaches.¹⁰ Prime editing allows for all 12 types of base-to-base conversions, as well as small insertions and deletions, reducing the risk of unintended indels and enhancing the potential for correcting genetic disorders with minimal error rates.¹¹

Base Editing

Developed earlier by Komor et al. in 2016, base editing represents a foundational shift in gene editing technology by enabling direct, irreversible conversion of one DNA base into another without the use of DSBs.¹² This method utilizes a disabled Cas9 protein fused to a base deaminase enzyme, capable of converting cytosine to thymine or adenine to guanine within a narrow editing window, significantly increasing the precision of gene editing. The precision of base editing has been particularly noted for its potential in therapeutic contexts, especially in correcting point mutations that underlie many hereditary diseases, thereby expanding

the scope of treatable genetic conditions with high accuracy.¹³

These technologies represent transformative advances in gene editing, enhancing both the scope and applicability of genetic modifications. The development of prime and base editing technologies underscores a pivotal shift toward more targeted and less invasive approaches in genetic research and therapy, potentially reducing the risks associated with earlier gene editing methods and improving patient safety in clinical applications.¹⁴

Efficiency, Precision, and Accessibility of Emerging Gene Editing Technologies

As gene editing technologies evolve, assessing their efficiency, precision, and accessibility becomes crucial. The advent of CRISPR-Cas9 revolutionized genomic research with its simplicity and efficiency, but newer technologies such as prime editing and base editing offer refined approaches with potentially greater precision and fewer off-target effects.^{10,15}

Prime editing, a “search-and-replace” technique for DNA, is designed to achieve accurate gene editing without DSBs, reducing the risk of unintended mutations commonly associated with traditional CRISPR-Cas9 methods. This makes prime editing particularly valuable in clinical settings, where precision is paramount.^{14,16} Studies have demonstrated prime editing’s ability to correct up to 89% of known pathogenic human genetic variants, showcasing its broad applicability and precision. This was highlighted in a 2019 study by Anzalone et al., which exemplified the versatility and efficiency of this genome editing method across various genetic targets.¹⁰

Base editing, another CRISPR-derived technology, facilitates the conversion of one DNA base pair into another, directly and without introducing DSBs. This method enhances editing efficiency and offers a substantial reduction in unintended edits, which is critical for therapeutic applications. Recent advancements have expanded the editable genome sites by overcoming the previous limitations of base editing tools.^{17,18}

Accessibility of these technologies, however, varies significantly across different regions and institutions, often influenced by resource availability. While CRISPR technologies are relatively economical and have proliferated globally, the more advanced prime and base editing tools require specialized equipment and deeper technical expertise, limiting their widespread adoption.¹⁹ Efforts are underway to simplify these technologies and reduce costs, which could democratize advanced gene editing tools, making them accessible to a broader range of researchers and clinicians worldwide.⁵

These developments not only enhance the capabilities of gene editing technologies but also promise to expand their use from basic research to more clinical settings. The therapeutic potential of gene editing is immense, with applications ranging from treating genetic disorders to engineering disease-

resistant crops. For instance, recent clinical trials using CRISPR technologies have shown promising results in treating conditions like sickle cell disease (SCD) and beta-thalassemia. A 2021 clinical trial by Esrick et al. focused on SCD, employing posttranscriptional genetic silencing of BCL11A to induce robust and stable fetal hemoglobin (HbF) production. This approach reduced clinical manifestations of the disease and demonstrated a favorable risk–benefit profile.²⁰ A 2018 clinical trial by Thompson et al. investigated gene therapy for beta-thalassemia using the LentiGlobin BB305 vector. This therapy significantly reduced or eliminated the need for long-term red-cell transfusions in patients with transfusion-dependent beta-thalassemia, improving hemoglobin levels and alleviating transfusion requirements.²¹

Moreover, the ethical, legal, and social implications of these technologies are being intensively discussed in the scientific community, aiming to establish a framework that ensures safe and equitable access to gene editing advancements.²² As regulatory pathways evolve, the accessibility of these technologies in clinical settings may see significant changes, potentially allowing for broader application in medicine and agriculture.²³

In conclusion, while the efficiency and precision of gene editing technologies like prime editing and base editing are advancing rapidly, their accessibility remains a critical challenge.

Overcoming this barrier requires not only technological innovation but also collaborative efforts to ensure ethical considerations are met and resources are equitably distributed.²⁴

CRISPR Applications in Genetic Diseases

CRISPR’s Role in Treating Genetic Disorders

CRISPR-Cas9 technology has revolutionized the field of genetics by providing a powerful tool for directly modifying the DNA of various organisms, including humans. This technology has particularly significant implications for the treatment of genetic disorders, which are typically caused by specific and often well-characterized mutations in the DNA. By targeting these mutations, CRISPR has the potential to correct or alleviate the underlying genetic defects responsible for diseases.¹⁵

One of the most notable applications of CRISPR technology in medicine is its use in treating hereditary blood disorders such as SCD and β -thalassemia. These diseases are caused by mutations that affect hemoglobin, a protein in red blood cells that carries oxygen. Recent advances in gene therapy have demonstrated the potential of CRISPR-Cas9 to modify hematopoietic stem and progenitor cells, offering promising strategies for treating monogenic disorders such as beta-thalassemia and other blood-related diseases.^{25,26}

Furthermore, CRISPR is being explored for its potential to treat cystic fibrosis (CF), a genetic disorder that results in severe damage to the respiratory and digestive systems. Researchers are investigating the use of CRISPR to correct the mutation in the CFTR gene, which is known to cause CF. Early-stage

research and preclinical trials have shown promising results, suggesting that gene editing could eventually become a viable therapeutic option for this challenging condition. In a 2018 study, Davies et al. evaluated a triple-combination therapy, VX-659–tezacaftor–ivacaftor, designed to restore the function of Phe508del CFTR protein in CF patients. The clinical trial demonstrated significant improvements in lung function, as measured by the percentage of predicted forced expiratory volume in 1 second (FEV1), with increases of up to 13.3 points in patients with Phe508del–MF genotypes. These results underscore the potential of targeted treatments to address the underlying cause of CF in approximately 90% of patients.²⁷

In addition to these diseases, CRISPR technology is being applied to a wide range of other genetic disorders, including muscular dystrophy, Huntington's disease, and some forms of inherited blindness. Each of these applications involves targeting and modifying specific genetic mutations to either restore normal function or prevent the progression of the disease.^{28,29}

The ongoing development and refinement of CRISPR technology continue to improve its accuracy, efficiency, and safety, which are crucial for its application in clinical settings.

Enhancements in delivery methods, such as the use of nanoparticles and viral vectors, are also expanding the potential of CRISPR-based therapies to treat a broader range of genetic disorders.^{30,31}

Case Studies of Significant Breakthroughs:

SCD and CF

Sickle Cell Disease

SCD has been a prime target for CRISPR gene editing due to its well-defined genetic cause—a single-nucleotide mutation in the HBB gene that leads to the production of abnormal hemoglobin. This mutation causes red blood cells to assume a rigid, sickle shape, leading to severe pain, organ damage, and shortened lifespan.³²

In a groundbreaking 2016 preclinical study, researchers employed CRISPR-Cas9 technology to target and correct the HBB gene mutation in hematopoietic stem cells derived from patients with SCD. These modified cells demonstrated restored function in lab models, indicating the potential for developing effective gene therapies. The study's success highlights the precise and efficient editing capabilities of CRISPR-Cas9, which allowed for the specific targeting and correction of the HBB gene without off-target effects that could potentially lead to other health complications. This precision underscores CRISPR's potential for not only treating SCD but also addressing other single-gene disorders, such as β -thalassemia.³³

Moreover, the study emphasized the importance of developing safe and effective delivery mechanisms for CRISPR components, an area of ongoing research that includes both viral and non-viral delivery systems. Ensuring the long-term efficacy and safety of gene-edited cells remains a priority to transition such treatments from the laboratory to the clinic.³⁴ This case not only

demonstrates the transformative potential of CRISPR for gene therapy but also emphasizes the collaborative efforts between genetic engineers, clinicians, and regulatory bodies to ensure that these innovative therapies are both effective and safe for widespread clinical use.

Cystic Fibrosis

CF, a debilitating genetic disorder, arises from mutations in the CFTR gene that impairs the protein responsible for regulating ions and water transport in the cells, affecting the lungs, digestive system, and other organs.³⁵ Researchers have harnessed CRISPR technology to target and correct these mutations in the CFTR gene with the goal of restoring normal function to the CFTR protein. In a 2021 study, Maule et al. provided a comprehensive review of the latest advancements in gene editing strategies specifically aimed at the CFTR gene, which is responsible for CF. They delve into how CRISPR technology has been employed not just for correcting the mutations within the CFTR gene, but also for enhancing the expression of the CFTR protein to restore its normal function.³⁶

One of the significant challenges in treating CF with gene editing is the delivery of CRISPR components to the lungs, where thick, sticky mucus often prevents effective treatment. Despite these hurdles, recent studies have made notable progress. For example, in a 2022 study, researchers successfully applied CRISPR to edit the CFTR gene in cultured human stem cells, and these cells reportedly showed restored function in laboratory models.³⁷ This suggests a potential pathway for developing effective therapies that could alleviate the symptoms and complications associated with CF.

Further advancements in CRISPR technology have involved refining the delivery mechanisms. For example, a 2022 study used lipid nanoparticles and adeno-associated viruses designed specifically to penetrate the mucus barriers in the lungs.³⁸ Additionally, ongoing research is focusing on enhancing the precision and efficiency of CRISPR editing to ensure that the corrected genes perform their functions without unintended effects.

These developments offer a glimpse into the potential of gene editing as a transformative treatment for CF, highlighting the critical need for continued research and innovation to overcome the remaining barriers. This case exemplifies the broader implications of CRISPR technology in treating not just CF but potentially other genetic disorders as well.

Analysis of Ongoing Clinical Trials and Their Preliminary Results

The exploration of CRISPR technology in clinical settings has accelerated, with several trials underway to assess its efficacy and safety in treating genetic disorders. Notably, clinical trials employing CRISPR for SCD and beta-thalassemia have shown promising early results. A 2021 trial conducted by Frangoul et al. demonstrated successful CRISPR-mediated editing of the HBB gene, which led to significant improvements in disease symptoms and patient outcomes.³⁹ These results

indicate not only the potential of CRISPR in treating hemoglobinopathies but also its adaptability to other genetic conditions.

While much of the focus is on clinical applications, foundational preclinical studies continue to inform and guide clinical strategies. For example, a pivotal preclinical 2016 study by Mendell and Rodino-Klapac utilized CRISPR/Cas9 to target Duchenne muscular dystrophy (DMD) in a mouse model.⁴⁰ Their findings, suggesting that CRISPR can safely make targeted cuts in DNA sequences responsible for DMD, underscore the potential for future therapeutic interventions in muscular dystrophies. This study highlights the critical role of precise and targeted gene editing in achieving therapeutic outcomes in preclinical settings, emphasizing the importance of ongoing improvements in CRISPR delivery methods.

Furthermore, clinical trials and preclinical studies focusing on hereditary blindness have utilized CRISPR to edit genes directly within the body, marking a significant advancement in *in vivo* gene editing. For example, a 2019 preclinical study by Maeder et al. developed EDIT-101, a CRISPR-based therapeutic aimed at correcting the CEP290 gene mutation responsible for Leber congenital amaurosis type 10.⁴¹ This therapeutic intervention demonstrated successful gene editing in humanized mouse models and non-human primates, confirming the feasibility and potential efficacy of CRISPR/Cas9 for direct *in vivo* application in somatic cells. These results support the continued development of CRISPR-based treatments for inherited retinal disorders and potentially other genetic diseases.

The ongoing trials underscore the transformative potential of CRISPR technology in clinical applications. However, they also highlight the challenges that remain, such as ensuring long-term safety, minimizing off-target effects, and improving delivery mechanisms. As these trials progress, they will provide valuable insights into the practical limitations and capabilities of CRISPR as a tool for genetic therapy. While clinical trials have demonstrated the promise of CRISPR in treating genetic disorders, the economic scalability of these treatments remains a key consideration. Scaling up CRISPR-based therapies will depend on several factors, including technology costs, infrastructure, and market demand.⁴² Although CRISPR treatments are currently expensive, they are expected to become more affordable as technology advances and economies of scale come into play.⁴²

CRISPR in Agriculture and Biotechnology

Exploration of CRISPR's Impact on Agricultural Practices

CRISPR technology has revolutionized agricultural science by enabling precise modifications to crop genomes, thereby enhancing resistance to diseases, pests, and environmental stresses. For instance, CRISPR has been employed to develop rice varieties with improved resistance to devastating diseases like bacterial blight and fungal infections, significantly boosting crop yields.⁴³ Researchers have also utilized

CRISPR to enhance the drought resistance of maize, an advancement that promises to increase sustainability in arid regions. For example, in their 2017 study, Shi et al. demonstrated how CRISPR-Cas9 was used to create variants of the ARGOS8 gene, which significantly enhanced maize yields under drought conditions. By editing the native ARGOS8 locus to achieve elevated expression levels across various tissues, these variants led to a five bushels per acre increase in grain yield under flowering stress conditions, without affecting yield under well-watered conditions.⁴⁴

Moreover, CRISPR's applications extend to improving the nutritional profiles of crops. Biofortification of staple crops like wheat and potatoes has been achieved by increasing their content of essential nutrients such as vitamins and minerals, making these crops more beneficial for regions facing nutritional deficiencies.⁴⁵ Such modifications not only enhance the health benefits of these crops but also add value to agricultural produce, potentially opening new markets for farmers.

Additionally, CRISPR has enabled the reduction of antinutritional factors in crops like soybeans, enhancing their safety and digestibility.⁴⁶ This application is particularly impactful as it addresses both human health concerns and increases the commercial viability of crops by meeting stringent regulatory standards.

The versatility of CRISPR in agriculture is further demonstrated through its use in modifying crop attributes such as size, growth rate, and tolerance to various climatic conditions, which are crucial for adapting to the challenges posed by climate change.⁴⁷ These innovations not only enhance food security but also contribute to the sustainability of agricultural practices globally.

Examples of CRISPR-Modified Organisms in Agriculture

CRISPR technology has facilitated the creation of various genetically edited organisms with improved traits that are significant for agricultural advancement. One notable example is the development of non-browning mushrooms, where CRISPR has been used to reduce the expression of genes responsible for browning in mushrooms, extending their shelf life and reducing food waste.⁴⁸

In tomatoes, researchers have employed CRISPR to increase the concentration of gamma-aminobutyric acid (GABA), an amino acid that helps lower blood pressure in humans.

This modification not only enhances the nutritional value of tomatoes but also addresses health concerns associated with hypertension. A 2017 study by Nonaka et al. demonstrated that targeted mutagenesis of SIGAD2 and SIGAD3 genes via CRISPR/Cas9 could significantly elevate GABA content in tomato fruits, promising an effective natural approach to managing high blood pressure.⁴⁹

Another breakthrough involves CRISPR-modified cassava resistant to viruses, particularly the cassava brown streak disease, which has been devastating crops across East Africa. By targeting and modifying

specific sequences within the cassava genome, scientists have developed strains that show enhanced resistance to these viruses, promising a significant boost to food security in affected regions.⁵⁰

Additionally, CRISPR has been used to modify the fatty acid composition in soybeans, increasing the oleic acid content which is better for heart health and provides a longer shelf life for soybean oil. This modification not only improves the health properties of soybean oil but also increases its industrial applicability, replacing less healthy oils in food production.⁵¹

These examples underscore the diverse applications of CRISPR in agriculture, enabling the production of crops with desired traits that meet specific consumer needs, environmental challenges, and health benefits. As CRISPR technology is increasingly employed in agriculture to modify crops for improved yields and disease resistance, there is growing potential for the economic scalability of these innovations.⁵² While the costs of gene editing remain high, they are expected to decrease over time with larger production, enhanced techniques, and increased adoption.⁵² This could lead to more affordable solutions for farmers, benefiting global food security.

CRISPR's Role in Biotechnological Applications: Biofuel Production and Industrial Bioprocessing

CRISPR technology has significantly advanced biotechnological applications, especially in the fields of biofuel production and industrial bioprocessing. This gene-editing tool has enabled precise alterations in microbial genomes to enhance the production of biofuels and other valuable chemicals.⁵³ For instance, CRISPR has been utilized to engineer yeast and algae strains to increase lipid production, a key component in biodiesel, making biofuel production more efficient and cost-effective.⁵⁴

In the realm of industrial bioprocessing, CRISPR has facilitated the development of microbial strains with enhanced capabilities to break down complex carbohydrates into bioethanol, a renewable energy source. This is particularly important in the production of cellulosic ethanol, where CRISPR has helped overcome some of the enzymatic barriers to efficient biomass conversion.⁵⁵

Moreover, CRISPR has been employed to increase the tolerance of these bioengineered microbes to harsh processing conditions, such as high temperatures and acidic environments, which are common in industrial settings. This not only improves the viability of microbial strains but also enhances their productivity and stability, leading to more robust bioprocessing workflows.⁵⁶

These applications of CRISPR in biotechnology not only underscore its versatility but also highlight its potential to revolutionize industrial processes by making them more sustainable and less dependent on fossil fuels. The ongoing advancements in CRISPR technology promise further improvements in biofuel production and industrial bioprocessing, paving the way for more environmentally friendly and economically viable alternatives to traditional

methods. The biotechnological applications of CRISPR, including biofuel production and industrial bioprocessing, also stand to benefit from scaling up. As research and adoption grow, the costs associated with gene editing in these industries are expected to decrease. Larger-scale production and improved techniques will make CRISPR-based solutions more economically viable, potentially transforming biofuel production and other industrial processes.⁵⁷

Ethical, Legal, and Social Implications

Ethical Debates Surrounding Gene Editing

The ethical discussions surrounding gene editing, particularly with CRISPR technology, have intensified as the potential for creating “designer babies” and impacting biodiversity looms large.⁵⁸ The concept of “designer babies” involves selecting genetic traits such as intelligence, physical appearance, or disease resistance, raising significant ethical concerns about inequality, eugenics, and human diversity.⁵⁹ Critics argue that such practices might lead to societal divisions where genetically enhanced individuals could have unfair advantages or could lead to new forms of discrimination.⁶⁰

On the biodiversity front, gene editing offers tools such as gene drives, which could potentially eradicate vectors carrying diseases like malaria. However, the ecological consequences of removing an entire species are unpredictable and could lead to ecological imbalances.⁶¹ This brings forth ethical considerations about human rights to alter ecosystems and the long-term impacts on biodiversity.⁴

These ethical issues underscore the need for a cautious approach, emphasizing that the power to edit genes comes with the responsibility to consider the far-reaching implications of such actions on human society and the natural world.⁶²

Overview of the Legal Landscape: International Regulations and Country-Specific Laws

The regulatory framework governing gene editing is as diverse as the technology itself, reflecting varied international perspectives on its ethical and safety implications. Internationally, the World Health Organization (WHO) has issued guidelines emphasizing a responsible approach to human genome editing, calling for transparency, inclusive public engagement, and a clear regulatory pathway before clinical applications are considered.⁶³ These guidelines serve as a reference for countries developing their own regulations but do not enforce legal compliance.

In the United States, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) play critical roles in overseeing gene editing activities, focusing particularly on the safety and ethical implications of genetic research and therapy.⁶⁴ The US regulatory approach is characterized by rigorous review processes that aim to balance innovation with public health safety.

Europe presents a more complex legal picture. The European Union's highest court ruled in 2018 that

organisms obtained by gene editing are genetically modified organisms (GMOs) and should be regulated under the strict GMO directive, contrary to the more lenient stance taken on older genetic modification techniques.⁶⁵ This has implications for both research and the commercial use of CRISPR and other gene editing technologies, potentially stifling innovation within EU borders.

Meanwhile, countries like China have been at the forefront of gene editing clinical trials, particularly in oncology and genetic disorders. However, following international controversy, China has tightened its regulations, implementing stricter approval processes for genetic research to ensure ethical compliance and scientific integrity.⁶⁶

This varied legal landscape illustrates the challenges and complexities of governing a rapidly evolving scientific field. Each country's legal framework reflects its cultural, ethical, and social priorities, which can either foster rapid development and deployment of gene editing technologies or impose significant constraints that might slow progress.

Social Implications: Public Perception, Accessibility, and Potential Inequalities

The social dimensions of CRISPR and other gene editing technologies are as profound as their scientific possibilities. Public perception of gene editing varies widely, influenced by ethical concerns, media portrayal, and cultural values.⁶⁷ Surveys have shown that while there is cautious optimism about the potential health benefits of gene editing, there is also significant apprehension about its ethical and safety implications, particularly regarding changes to human embryos and the potential for creating "designer babies."⁶⁸

Accessibility is another critical issue, as CRISPR technologies are not equally accessible across different regions of the world. Developed countries, possessing more advanced research infrastructures and funding, are more likely to benefit from these technologies sooner than developing countries.⁶⁹ This discrepancy raises concerns about widening the global inequality gap in health outcomes and medical advancements.

Moreover, the cost of gene editing treatments poses potential barriers, potentially limiting access to affluent individuals and nations.⁷⁰ Without strategies to make these therapies affordable, widespread adoption may be slow, and the promise of gene editing could exacerbate existing health disparities rather than alleviate them.

Finally, the dialogue around CRISPR in society also touches on potential impacts on biodiversity. The ability to genetically modify organisms quickly and efficiently has raised concerns about unforeseen ecological consequences, such as gene drives designed to eradicate pests or alter ecosystems, which could have irreversible effects on biodiversity.⁷¹

These social implications underscore the need for inclusive policymaking that considers the broad spectrum of socioeconomic, cultural, and ethical dimensions. Engaging diverse communities in the dialogue

about gene editing technologies will be crucial in navigating the complex landscape of opportunities and challenges they present.

Conclusion

The exploration of CRISPR and related gene editing technologies throughout this review has highlighted significant advancements and illuminated the complex interplay of scientific innovation with ethical, legal, and social concerns. From enhancing agricultural practices to treating genetic diseases and understanding the intricate legal frameworks that govern these technologies, the breadth of CRISPR's impact is immense.

CRISPR's evolution from a niche scientific tool to a mainstream technological marvel shows its potential to revolutionize multiple sectors. In agriculture, CRISPR promises crops with improved yields, resistance, and nutritional values, potentially transforming food security dynamics globally. In the medical field, CRISPR has opened doors to potentially curative treatments for diseases such as sickle cell and CF, showcasing its capacity to alter human health profoundly.

However, the journey of CRISPR from labs to real-world applications is fraught with challenges. The ongoing debates surrounding the ethical implications of gene editing, particularly concerns about "designer babies" and irreversible ecological impacts, underscore the need for cautious and responsible development. Legal landscapes vary significantly across the globe, reflecting diverse societal values and raising questions about accessibility and inequality in the benefits of gene editing technologies.

Looking ahead, the economic scalability of CRISPR technology will be a key driver in its widespread adoption across medicine, agriculture, and biotechnology. While the costs associated with CRISPR are currently high, advancements in technology, improved infrastructure, and market demand are expected to bring down costs, making it economically feasible for large-scale applications and potentially revolutionizing industries worldwide.

As we stand on the brink of possibly reshaping the genetic foundations of life, the future of CRISPR and gene editing technologies hinges on balancing innovation with responsibility. It is imperative that the development and implementation of these technologies are guided by robust ethical frameworks and inclusive policies that ensure equitable benefits. Moving forward, the dialogue between scientists, policymakers, and the public will be crucial in steering the responsible evolution of gene editing technologies, making the extraordinary promise of CRISPR accessible and beneficial for all.

References

- 1 Doudna JA, Charpentier E. Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science*. 2014;346(6213):1258096.
- 2 Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science*. 2012;337(6096):816–21.

- 3 Hsu PD, Lander ES, Zhang F. Development and applications of CRISPR-Cas9 for genome engineering. *Cell*. 2014;157(6):1262–78.
- 4 Oye KA, Esvelt K, Appleton E, Catteruccia F, Church G, Kuiken T, et al. Regulating gene drives. *Science*. 2014;345(6197):626–8.
- 5 Kleinstiver BP, Pattanayak V, Prew MS, Tsai SQ, Nguyen NT, Zheng Z, et al. High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects. *Nature*. 2016;529(7587):490–5.
- 6 Chen JS, Dagdas YS, Kleinstiver BP, Welch MM, Sousa AA, Harrington LB, et al. Enhanced proofreading governs CRISPR-Cas9 targeting accuracy. *Nature*. 2017;550(7676):407–10.
- 7 Hsu PD, Scott DA, Weinstein JA, Ran FA, Konermann S, Agarwala V, et al. DNA targeting specificity of RNA-guided Cas9 nucleases. *Nat Biotechnol*. 2013;31(9):827–32.
- 8 Lino CA, Harper JC, Carney JP, Timlin JA. Delivering CRISPR: A review of the challenges and approaches. *Drug Delivery*. 2018;25(1):1234–57.
- 9 Mout R, Ray M, Lee YW, Scaletti F, Rotello VM. In vivo delivery of CRISPR/Cas9 for therapeutic gene editing: Progress and challenges. *Bioconjug Chem*. 2017;28(4):880–4.
- 10 Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature*. 2019;576(7785):149–57.
- 11 Lin Q, Zong Y, Xue C, Wang S, Jin S, Zhu Z, et al. Prime genome editing in rice and wheat. *Nat Biotechnol*. 2020;38(5):582–5. doi:10.1038/s41587-020-0455-x.
- 12 Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*. 2016;533(7603):420–4. doi:10.1038/nature17946.
- 13 Rees HA, Liu DR. Base editing: Precision chemistry on the genome and transcriptome of living cells. *Nat Rev Genet*. 2018;19(12):770–88. doi:10.1038/s41576-018-0059-1.
- 14 Cox DBT, Platt RJ, Zhang F. Therapeutic genome editing: Prospects and challenges. *Nat Med*. 2015;21(2):121–31. doi:10.1038/nm.3793.
- 15 Schwank G, Koo BK, Sasselli V, Dekkers JF, Heo I, Demircan T, et al. Functional repair of CFTR by CRISPR/Cas9 in intestinal stem cell organoids of cystic fibrosis patients. *Cell Stem Cell*. 2013;13(6):653–8.
- 16 Gaudelli NM, Komor AC, Rees HA, Packer MS, Badran AH, Bryson DI, et al. Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage. *Nature*. 2017;551(7681):464–71.
- 17 Richardson CD, Ray GJ, DeWitt MA, Curie GL, Corn JE. Enhancing homology-directed genome editing by catalytically active and inactive CRISPR-Cas9 using asymmetric donor DNA. *Nat Biotechnol*. 2016;34(3):339–44.
- 18 Lin S, Staahl BT, Alla RK, Doudna JA. Enhanced homology-directed human genome engineering by controlled timing of CRISPR/Cas9 delivery. *Elife*. 2014;3.
- 19 Slaymaker IM, Gao L, Zetsche B, Scott DA, Yan WX, Zhang F. Rationally engineered Cas9 nucleases with improved specificity. *Science*. 2016;351(6268):84–8.
- 20 Esrick EB, Lehmann LE, Biffi A, Achebe M, Brendel C, Ciuculescu MF, et al. Post-transcriptional genetic silencing of BCL11A to treat sickle cell disease. *N Engl J Med*. 2021;384(3):205–15.
- 21 Thompson AA, Walters MC, Kwiatkowski J, Rasko JEJ, Ribeil JA, Hongeng S, et al. Gene therapy in patients with transfusion-dependent β -thalassemia. *N Engl J Med*. 2018;378(16):1479–93.
- 22 Moore JD. The impact of CRISPR–Cas9 on target identification and validation. *Drug Discov Today*. 2015;20(4):450–7.
- 23 National Academies of Sciences, Engineering, and Medicine. Human Genome Editing: Science, Ethics, and Governance. The National Academies Press; 2017.
- 24 Macnaghten P, Shah E, Ludwig D. Making dialogue work: Responsible innovation and gene editing. In *The Politics of Knowledge in Inclusive Development and Innovation 2021*; (pp. 243–55). Routledge.
- 25 Song B, Fan Y, He W, Zhu D, Niu X, Wang D, et al. Improved hematopoietic differentiation efficiency of gene-corrected β -thalassemia induced pluripotent stem cells by CRISPR/Cas9 system. *Stem Cells Dev*. 2015;24(9):1053–65.
- 26 Ferrari G, Thrasher AJ, Aiuti A. Gene therapy using haematopoietic stem and progenitor cells. *Nat Rev Genet*. 2021;22(4):216–34.
- 27 Davies JC, Moskowitz SM, Brown C, Horsley A, Mall MA, McKone EF, et al. VX-659-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. *N Engl J Med*. 2018;379(17):1599–611.
- 28 Nelson CE, Hakim CH, Ousterout DG, Thakore PI, Moreb EA, Rivera RMC, et al. In vivo genome editing improves muscle function in a mouse model of Duchenne muscular dystrophy. *Science*. 2016;351(6271):403–7.
- 29 Bakondi B, Lv W, Lu B, Jones MK, Tsai Y, Kim KJ, et al. In vivo CRISPR/Cas9 gene editing corrects retinal dystrophy in the S334ter-3 rat model of autosomal dominant retinitis pigmentosa. *Mol Ther*. 2016;24(3):556–63.
- 30 Yin H, Song CQ, Suresh S, Wu Q, Walsh S, Rhym LH, et al. Structure-guided chemical modification of guide RNA enables potent non-viral in vivo genome editing. *Nat Biotechnol*. 2017;35(12):1179–87.
- 31 Wang M, Glass ZA, Xu Q. Non-viral delivery of genome-editing nucleases for gene therapy. *Gene Ther*. 2017;24(3):144–50.
- 32 Park SH, Bao G. CRISPR/Cas9 gene editing for curing sickle cell disease. *Transfus Apher Sci*. 2021;60(1):103060.
- 33 Dever DP, Bak RO, Reinisch A, Camarena J, Washington G, Nicolas CE, et al. CRISPR/Cas9 β -globin gene targeting in human haematopoietic stem cells. *Nature*. 2016;539(7629):384–9.
- 34 Zeng S, Lei S, Qu C, Wang Y, Teng S, Huang P. CRISPR/Cas-based gene editing in therapeutic strategies for beta-thalassemia. *Hum Genet*. 2023;142(12):1677–703.
- 35 Xu X, Wan T, Xin H, Li D, Pan H, Wu J, et al. Delivery of CRISPR/Cas9 for therapeutic genome editing. *J Gene Med*. 2019;21(7):e3107.
- 36 Zhang L, et al. Targeted gene editing in human cells using CRISPR/Cas9 technology. *Cell Res*. 2023;33(1):150–64.
- 37 Maule G, Ensinn M, Bulcaen M, Carlon MS. Rewriting CFTR to cure cystic fibrosis. *Prog Mol Biol Transl Sci*. 2021;182:185–224.
- 38 Vaidyanathan S, Baik R, Chen L, Bravo DT, Suarez CJ, Abazari SM, et al. Targeted replacement of full-length CFTR in human airway stem cells by CRISPR-Cas9 for pan-mutation correction in the endogenous locus. *Mol Ther*. 2022;30(1):223–37.
- 39 Zhang H. Development of non-viral systems for pulmonary nucleic acid delivery and gene editing (Doctoral dissertation, The University of Texas at Austin). 2019.
- 40 Frangoul H, Altshuler D, Cappellini MD, Chen YS, Domm J, Eustace BK, et al. CRISPR-Cas9 gene editing for sickle cell disease and β -thalassemia. *N Engl J Med*. 2021;384(3):252–60.
- 41 Mendell JR, Rodino-Klapac LR. Duchenne muscular dystrophy: CRISPR/Cas9 treatment. *Cell Res*. 2016;26(5):513–4.
- 42 Kliegman M, Zaghlula M, Abrahamson S, Esensten JH, Wilson RC, Urnov FD, et al. A roadmap for affordable genetic medicines. *Nature*. 2024;1–8.
- 43 Maeder ML, Stefanidakis M, Wilson CJ, Baral R, Barrera LA, Bounoutas GS, et al. Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10. *Nat Med*. 2019;25(2):229–33.
- 44 Ye Z, Zhang Y, He S, Li S, Luo L, Zhou Y, et al. Efficient genome editing in rice with miniature Cas12f variants. *ABIOTECH*. 2024;1–5.
- 45 Shi J, Gao H, Wang H, Lafitte HR, Archibald RL, Yang M, et al. ARGOS 8 variants generated by CRISPR-Cas9 improve maize grain yield under field drought stress conditions. *Plant Biotechnol J*. 2017;15(2):207–16.
- 46 Jones HD. Future of breeding by genome editing is in the hands of regulators. *GM Crops Food*. 2015;6(4):223–232.
- 47 Liao W, Guo R, Li J, Liu N, Jiang L, Whelan J, et al. CRISPR/Cas9-mediated mutagenesis of seed fatty acid reducer genes significantly increased seed oil content in soybean. *Plant Cell Physiol*. 2024;pcae148. <https://doi.org/10.1038/nm.3793>
- 48 Noman A, Aqeel M, He S. CRISPR-Cas9: Tool for qualitative and quantitative plant genome editing. *Front Plant Sci*. 2016;7:1740.
- 49 Waltz E. Gene-edited CRISPR mushroom escapes US regulation. *Nature*. 2016;532:293.
- 50 Nonaka S, Arai C, Takayama M, Matsukura C, Ezura H. Efficient increase of γ -aminobutyric acid (GABA) content in tomato fruits by targeted mutagenesis. *Sci Rep*. 2017;7(1):7057.
- 51 Odipio J, Alicai T, Ingelbrecht I, Nusinow DA, Bart R, Taylor NJ. Efficient CRISPR/Cas9 genome editing of *Phytoene desaturase* in cassava. *Front Plant Sci*. 2017;8:1780.
- 52 Ahmad S, Wei X, Sheng Z, Hu P, Tang S. CRISPR/Cas9 for development of disease resistance in plants: Recent progress, limitations and future prospects. *Brief Funct Genomics*. 2020;19(1):26–39.
- 53 Haun W, Coffman A, Clasen BM, Demorest ZL, Lowy A, Ray E, et al. Improved soybean oil quality by targeted mutagenesis of the fatty acid desaturase 2 gene family. *Plant Biotechnol J*. 2014;12:934–40.

- 54 Marella ER, Holkenbrink C, Siewers V, Borodina I. Engineering microbial fatty acid metabolism for biofuels and biochemicals. *Curr Opin Biotechnol.* 2018;50:39–46.
- 55 Jakočiūnas T, Jensen MK, Keasling JD. CRISPR/Cas9 advances engineering of microbial cell factories. *Metab Eng.* 2016;34:44–59.
- 56 Wagner JM, Alper HS. Synthetic biology and molecular genetics in non-conventional yeasts: Current tools and future advances. *Fungal Genet Biol.* 2016;89:126–36.
- 57 Shah K, Kaur A, Saxena S, Arora S. CRISPR-based approach: A way forward to sustainable development goals (SDGs). In *Gene Editing in Plants: CRISPR-Cas and Its Applications 2024*; (pp. 709–33). Springer Nature Singapore.
- 58 Kaczmarzyk D, Fulda M. Fatty acid activation in cyanobacteria mediated by acyl-ACP synthetase enables fatty acid recycling. *Plant Physiol.* 2010;152:1598–610.
- 59 Greely H. CRISPR'd babies: Human germline genome editing in the 'He Jiankui affair'. *J Law Biosci.* 2019;6(1):111–83.
- 60 Gyngell C, Douglas T, Savulescu J. The ethics of germline gene editing. *J Appl Philos.* 2017;34(4):498–513.
- 61 Conley JM, Cadigan RJ, Davis AM, Juengst ET, Kuczyński K, Major R, et al. The promise and reality of public engagement in the governance of human genome editing research. *Am J Bioethics.* 2023;23(7):9–16.
- 62 Caplan AL, Parent B, Shen M, Plunkett C. No time to waste—The ethical challenges created by CRISPR. *EMBO Rep.* 2015;16(11):1421–6.
- 63 Lewis MS. Is germline gene editing exceptional?. *Seton Hall L Rev.* 2020;51:735.
- 64 World Health Organization. Human Genome Editing: Recommendations. WHO; 2021. <https://www.who.int/publications/i/item/9789240030381>
- 65 National Institutes of Health. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). NIH; 2024. https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf
- 66 Court of Justice of the European Union. Judgment in Case C-528/16. CJEU; 2018. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A62016CA0528>
- 67 Zhang D, Lie RK. Ethical issues in human germline gene editing: A perspective from China. *Monash Bioeth Rev.* 2018;36:23–35.
- 68 Funk C, Hefferon M. Public views of gene editing for babies depend on how it would be used. *Pew Res Center.* 2018. <https://www.pewresearch.org/science/2018/07/26/public-views-of-gene-editing-for-babies-depend-on-how-it-would-be-used/>
- 69 Scheufele DA, Xenos MA, Howell EL, Rose KM, Brossard D, Hardy BW. U.S. attitudes on human genome editing. *Science.* 2017;357(6351):553–4.
- 70 Juma C. *Innovation and Its Enemies: Why People Resist New Technologies.* Oxford University Press; 2016.
- 71 Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015;372(9):793–5.