

The Genetic Programming Leap

Genes are not destiny, they are possibilities.

- Siddhartha Mukherjee, The Gene



About the Centre for Trustworthy Technology



CTT

Centre for Trustworthy Technology



Our vision

Our vision is to empower all through the responsible integration and use of innovative and potentially disruptive technologies.



Our mission

Our mission is to guide organizations in understanding, preparing for, and leveraging transformative and trustworthy technologies, thereby promoting a future where technological innovation benefits all.



Our core values

Our core values include Collaboration, Global inclusivity, Human-Centered outcomes, Being Action-Oriented, Passionate and Committed to Learning and Education.

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Foreword

The field of gene editing represents an extraordinary fusion of healthcare and emerging technology, paving the way for treatments that once seemed to be in the domain of science fiction. Technologies like CRISPR have ushered in an era of precision medicine, offering the capability to edit the human genome with astounding accuracy. Now, advancements such as base editing allow scientists to target specific genes with even greater precision, marking an evolution in the treatment of genetic disorders, cancers, and other chronic diseases. These tools offer not only new hope for patients but also the prospect of fundamentally reshaping healthcare by tackling conditions at their genetic origins, rather than merely managing symptoms.

As emerging technologies reshape every facet of healthcare, the promise of gene editing extends well beyond treating individual diseases. Imagine a future where medical interventions begin in the genome, reducing or even eliminating the risk of inherited conditions like cystic fibrosis or sickle cell disease from birth. The integration of gene editing with other advanced technologies—such as artificial intelligence, predictive analytics, and bioinformatics—could accelerate the development of targeted therapies, tailor interventions to individuals' unique genetic profiles, and dramatically reduce the healthcare burden associated with genetic diseases. This convergence of technology and healthcare marks the beginning of an era where medical care is not just reactive but also profoundly preventative and personalized.

However, the potential of these technologies brings challenges that must be addressed. The power to alter the genome raises important questions around consent, equity, and access. For gene editing to become a trusted pillar of healthcare, we must

focus on establishing robust ethical guidelines and ensuring equitable access to its benefits. Trust is paramount: the public needs assurance that gene editing will be regulated responsibly, applied safely, and equitably accessible. Trends in the adoption of generative AI within healthcare applications demonstrate that a lack of trust can significantly reduce consumer engagement, thereby limiting the full potential of these technological advancements. Building societal trust will be fundamental to gene editing's adoption and success as this technology moves from research labs into hospitals and clinics.

Healthcare innovation also calls for a shift in our approach to regulation and public policy. Industry leaders, healthcare providers, and policymakers need to collaboratively define frameworks that address the dual imperatives of fostering innovation and safeguarding public welfare. Regulatory bodies must be agile enough to adapt to new discoveries while maintaining rigorous standards for safety and ethics. Furthermore, industry incentives must align not only with commercial interests but also with the long-term goal of making gene editing trustworthy.

The following paper examines these emerging technologies within a framework of trustworthiness and ethical responsibility. It underscores the importance of fostering a culture of transparency, inclusion, and global collaboration in gene editing. Together, by harnessing this technology wisely, we can unlock an era of unprecedented health advances. This vision for healthcare's future—a future where gene editing serves as a transformative, trusted, and inclusive force—is within reach. Let us work to ensure that the benefits of these groundbreaking technologies are felt across all borders and generations, fostering a healthier world shaped by responsible innovation.

Bill Fera, MD,
Principal,
Deloitte

Executive Summary

Deoxyribonucleic Acid (DNA) builds the codebase for living organisms. These tiny but resourceful molecules contain the necessary data to inform and direct biological processes, including their genomics and the genetic expression of inherited diseases. The data is stored in the nucleotide bases that comprise each DNA polymer, **and now, it can be edited.** *Genetic Editing* is a reductive phrase to describe a movement that starts with editing genomic sequences but extends to the debugging and optimization of the most ambitious programming project: the code of life itself.

If successful, humans will have proven their ability to transcend the limitations of nature by altering the fundamental rules - the immutable genetics - that regulate their own existence. Changing these rules means rewriting the belief that had governed medicine for centuries - of which chronic, especially hereditary, conditions were inescapable.

The World Economic Forum's flagship report featuring the Top 10 Emerging Technologies of 2024 highlighted Clustered Regularly Interspaced Short

Palindromic Repeats (CRISPR) technology-enabled pig organ transplants in human patients.¹ CRISPR technologies replaced the pig genes with human genes to prepare for the transplant, demonstrating genetic editing developments as having immense potential to alleviate human suffering and extending lifespan. The report also advocated for further interdisciplinary discussions surrounding the ethics of the technology and its applications.

This paper serves as a primer to explore the use of genetic editing in expanding the availability and diversity of medical interventions to treat chronic diseases. The paper will focus on the emerging applications of gene editing medicine, including its use, development, investment, and ethics, while presenting a **Trustworthy Framework** to conceptualize the field's future direction. The Trustworthy Framework will draw from the insights articulated throughout the paper to propose a set of guidelines aiming to align innovation and market incentives with the technology's ethical and responsible development.



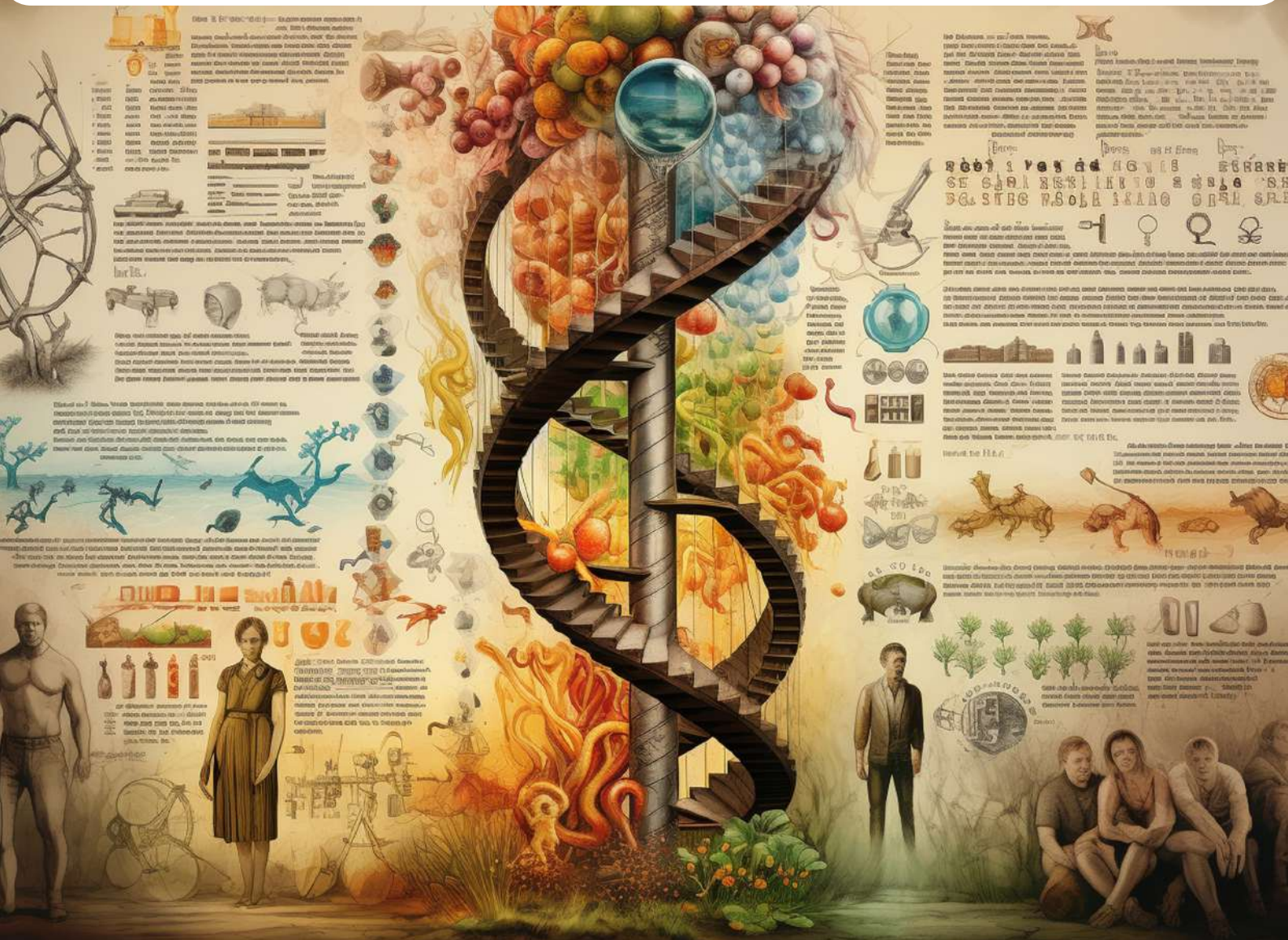
Insights

- » **Advancements in Gene Editing:** Gene editing-enabled transplants have captured significant attention, named in the top 10 emerging technologies of 2024 by the World Economic Forum. At the forefront, is the groundbreaking CRISPR-Cas9 technology which enables precise genome modifications enhancing the efficiency and versatility of genetic editing. This technology not only paves the way for innovative therapies and treatments but also holds promise for addressing genetic disorders.
- » **Market Growth:** The gene editing industry is poised for significant growth, driven partially by cutting-edge advancements in CRISPR-based technologies. CRISPR-generated revenue is expected to grow with a compounded annual growth rate (CAGR) of 15.6% from 2023 to 2028, pushing the USD 3.4 billion revenue in 2023 to reach \$7.1 billion by 2028.
- » **Ethical and Societal Implications:** Gene editing raises critical ethical questions, particularly around distinguishing therapeutic interventions from genetic enhancements. This challenge is amplified by concerns over unintended edits, exacerbation of societal inequalities, and the sanctity of human biology. These issues demand inclusive global dialogue, where diverse cultural, ethical, and religious perspectives are acknowledged and integrated into regulatory frameworks. Only through such broad and open discussions can we establish boundaries that safeguard humanity's core values while embracing the promise of gene-editing technologies.
- » **Building Trust in Gene Editing:** Trust is fundamental to the future of gene editing. Public confidence can only be cultivated through a steadfast commitment to transparency, patient autonomy, and informed consent. By proactively addressing potential risks, ensuring equitable access, and engaging diverse societal perspectives, we can create a foundation of trust. This trust will be key in gaining public support and facilitating the responsible adoption of these transformative technologies.
- » **Market and Technological Growth:** The commercialization of gene editing must proceed with a deep commitment to ethical considerations. Growth must not come at the expense of safety or long-term societal well-being. A balanced approach is needed, where technological progress is accompanied by ethical stewardship to ensure gene-editing innovations contribute positively to human welfare.
- » **Global Governance and Coordination:** The absence of consistent national regulations and binding international agreements presents significant challenges to the responsible development of gene-editing technologies. These gaps create the risk of 'regulatory havens,' where unethical practices may thrive. To prevent unauthorized applications and promote global equity, international cooperation is vital with clear, harmonized guidelines to define permissible and prohibited uses of gene editing, ensuring that all nations share a common commitment to responsible governance of these powerful technologies.
- » **Aligning Market Incentives with Ethical Development:** Market-driven incentives—such as targeted funding, tax benefits, and streamlined patent regulations—can align commercial interests with the responsible development of gene-editing technologies. By encouraging companies to prioritize safety, accessibility, and ethical practices, these economic measures can drive innovation while safeguarding public interests. Such incentives can support long-term research, improve patient outcomes, and foster trust in gene-editing advancements.
- » **Equitable Access to Gene Editing:** While the cost of genome sequencing has decreased, accessibility to gene-editing therapies remains a significant challenge for many populations. Without deliberate efforts to address these disparities, advanced medical treatments will remain out of reach for much of the global population, particularly in low- and middle-income countries. Ensuring that technological advancements benefit patients across socioeconomic boundaries is imperative. By restructuring healthcare systems and reducing the costs of research and development, we can make gene-editing therapies accessible to all, not just the privileged few.

Background and History

The study of genes dates to Charles Darwin's Theory of Genetic Evolution through Natural Selection, which acknowledged the variety of traits that underscore human individuality.ⁱⁱ This theory brought forth the inclination that humans with preferable genetics, passed through generations of selective reproduction, were naturally designated to survive. Taking this hypothesis a step further, Darwin also concluded that this 'natural selection' was healthy, preferable even, due to the limitation of resources and desire for evolutionary human advancement.ⁱⁱⁱ Darwin's theory laid the foundation for the idea that human genes, or rather, distinguishable traits, existed as a basis of human individuality. This theory became the cornerstone of the genetic studies conducted in the 20th century and beyond.^{iv}

Researchers first achieved successful genetic transfer across organisms in 1973 with the insertion of an antibiotic resistance gene into bacteria.^v The initial excitement was fueled by the expanding understanding of the biological phenomenon of homologous recombination, which is the process of repairing DNA damage by exchanging genetic material between two similar DNA molecules.^{vi} However, these early genetic editing tools were imprecise relative to modern methods and frequently led to unintended and, sometimes, dangerous genetic edits.^{vii} Fortunately, the early scientific efforts paved the way for more precise editing tools.^{viii}



CRISPR: The Molecular Scissors

The Rise of CRISPR-Cas9

Genome modification in the modern era has been traditionally synonymous with CRISPR-based techniques, which originated from the 1987 discovery of repeated sequences in *E. coli* genomes while studying the *iap* gene.^{ix} In 1993, Jan Van Embden, a researcher in the Netherlands, noted similar sequences in *Mycobacterium tuberculosis* and subsequent studies demonstrated similar sequences in other bacteria and archaea.^x These sequences, which protect microbes from viruses, became widely known as 'CRISPR' in the early 2000s.^{xi}

In the early 2000s, scientists hypothesized that CRISPR may be a component within bacterial immune systems^{xii} and in 2008, researchers found that CRISPR could be useful in building immunity in bacteria against viruses.^{xiii} In 2012, Jennifer Doudna and Emmanuelle Charpentier worked together to demonstrate CRISPR-Cas9 as a programmable gene editing tool, and soon scientists realized that these CRISPR-based editing tools were simpler and more efficient than using the previously used genetic editing tools like meganucleases or transcription activator effector nucleases (TALENs).^{xiv}

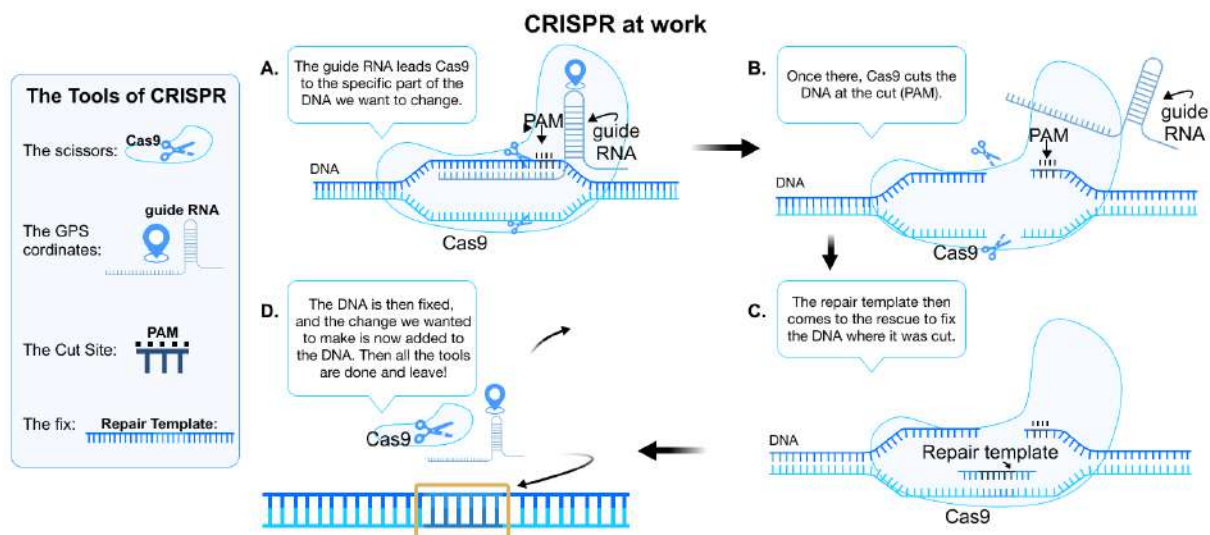
The Versatility of Double-Stranded Breaks (DSBs)

In the CRISPR Cas-9 system, Cas9 refers to the molecular 'scissors' that create DSBs, comprising a guide RNA (gRNA) that is complementary to the target DNA sequence, and the Cas9 endonuclease.^{xv} The gRNA guides the Cas9 protein to the specific DNA sequence of interest. The Cas9 protein creates the DSB.^{xvi} Finally, the cell's natural repair mechanisms repair the sequence to reflect the intended genetic changes.^{xvii} These repairs can be non-homologous end joining (NHEJ) small insertions, deletions, or homology-directed repair (HDR), which are used to insert specific genetic sequences.^{xviii}

NHEJ insertions are quicker repairs of DNA whereas HDR repairs follow more specific instructions.^{xix} As CRISPR Cas9 systems can leverage both NHEJ and HDR repair pathways, they are equipped to support a wider variety of gene modifications, allowing scientists to adapt the system to various cell types, precise edits, and therapeutic approaches.^{xx} Figure 1 illustrates the CRISPR Cas9 editing process, starting with the gRNA directing Cas9 to the specific location of the sequence, then the insertion of a repair template, and the alteration of the target DNA.^{xxi}



Figure 1: The CRISPR Cas9 Editing Template.



Source: Delivery and therapeutic applications of gene editing technologies.^{xxii}

The variety of genetic modifications available renders CRISPR Cas9 a far more versatile tool than its predecessors like zinc finger nucleases (ZFNs) and TALENs. For example, while CRISPR is best known for direct DNA editing, modifications of the system can also be adapted to control gene expressions without altering the underlying DNA sequence.^{xxiii}

Proteins needed to be re-engineered for new targets under ZFNs and TALENs to ensure effective binding at the target site. In contrast, the standardized Cas 9 protein used in CRISPR is suitable across various targets and therefore does not require re-engineering for new targets.^{xxiv} Adapting CRISPR Cas9 to new targets only requires slight changes to the gRNA.^{xxv} These gRNAs can be quickly synthesized using common molecular biology techniques, allowing scientists to develop multiple gRNAs at once, each designed to target a specific gene.^{xxvi} Multiple gRNA types can also be introduced using a single introduction of genetic material, reducing the need for more cell manipulations, and thus, decreasing the risks of unintended effects.^{xxvii}

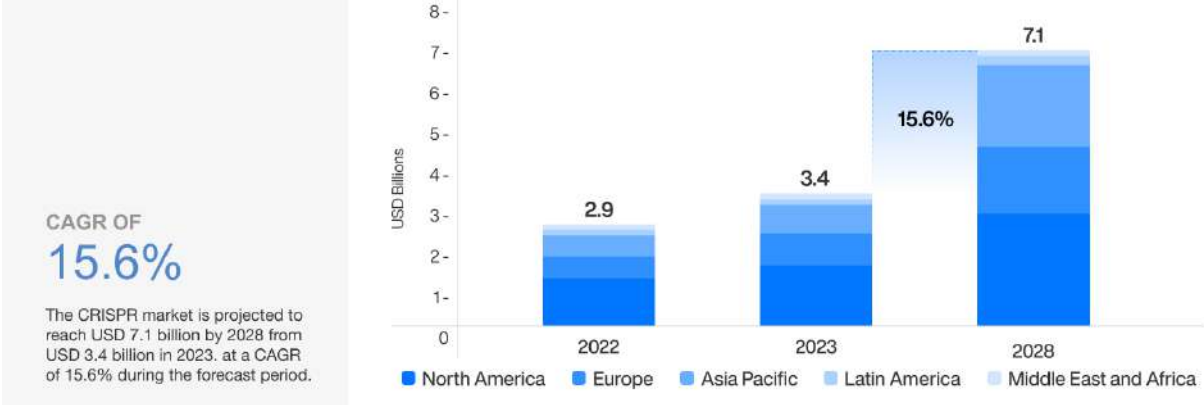
Multiplexing Led Scalability

The process of programming CRISPR Cas9 systems to target multiple genes simultaneously is called multiplexing and it is considered one of the major advantages over preceding genetic editing tools.^{xxviii} Multiplexing is highly scalable and cost-effective, allowing scientists to simultaneously examine complex gene and protein interactions for large-scale genetic studies.^{xxix} These gene and protein interaction studies may lead to the identification of therapeutic targets in pharmaceutical research and lead the scientific community to develop a deeper understanding of dysregulated cellular signaling in cancer^{xxx} and other genetic disorders.^{xxxi} The versatility and applicability of CRISPR is what positions the technology for high-potential market growth.



CRISPR Market Projections and Industry Growth

Figure 2: CRISPR Market Expansion.



Source: ARK Investment Management, 2023.^{xxxiii}

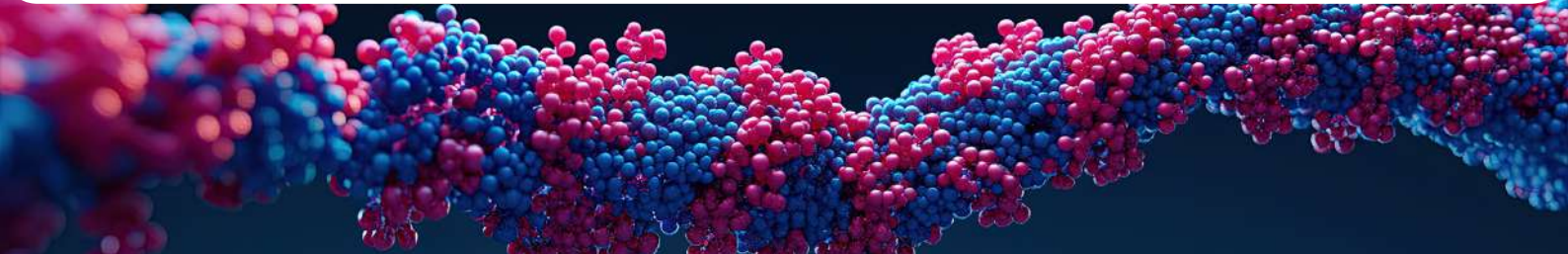
Currently, CRISPR remains the most heavily invested genetic editing technique. Moreover, CRISPR-generated revenue is expected to grow with a compounded annual growth rate (CAGR) of 15.6% from 2023 to 2028, pushing the USD 3.4 billion revenue in 2023 to reach USD 7.1 billion by 2028.^{xxxii} Figure 2 depicts CRISPR-generated revenue in the marketplace, with the dominant driver for CRISPR being pharmaceuticals and medical therapies.

The optimistic upside in the projected growth is a testament to the expanding influence of gene editing in critical industries including medicine and healthcare. This is particularly true for the North American region, which is forecasted to retain its current dominant position as the largest market, followed by Europe and the Asia-Pacific region.^{xxxiv} The projected steady growth among all global regions is driven by the accelerated democratization of the technology alongside global collaborative research efforts.

One of the most successful and famous research efforts is the Human Genome Project (HGP), which

successfully reduced the costs of sequencing a genome to <\$0.08 per finished base. For context, the project had originally intended to reduce the costs of genome sequencing to <\$0.25 per finished base.^{xxxv} Between 2004 and 2022, the sharp declines in genomic sequence costs, alongside the exponential increase in the number of genome sequences, illustrate a rapid democratization of the technology.

The plummeting costs of genome sequencing have helped its applications scale. This trend is demonstrated by the marked acceleration of sequencing volume after 2016 when genomic sequencing costs dropped to below \$1,000 per genome.^{xxxvi} Genome sequencing costs are likely to decline even further in the future due to improvements in nanopore sequencing^{xxxvii} and other new sequencing technologies, leading to an expansion of the field in both the research and clinical domains. Further research into clinical applications and safety risks is certainly necessary as medical researchers have yet to address many of CRISPR’s technical and practical challenges.



CRISPR Challenges and Emerging Solutions

Despite CRISPR Cas9 systems' promise to enable effective, efficient, economic, and scalable solutions to genetic modifying therapeutics, a few technical challenges remain. More specifically, CRISPR technologies must better protect against off-target effects and improve its delivery methods. Off-target

effects refer to accidental genomic rearrangements or chromosomal deletions due to unfavorable and unintended DNA damage response. Table 1 outlines these technical challenges and their proposed solutions.

Table 1: CRISPR Technical Challenges and Proposed Solutions.

Challenge	Proposed Pathway
<p>gRNA Mismatch Tolerance</p> <p>Mismatch tolerance refers to the margin of error for CRISPR-Cas9 systems to still recognize and cut DNA despite slight mismatches.</p> <p>CRISPR Cas9 systems are designed to tolerate potential mismatches to increase the tools' versatility. However, higher tolerance to mismatches leads to unintended binding and cutting at similar but non-target sequences, leading to off-target effects.^{xxxvii} This is an exceedingly difficult area to address as gRNAs must also be flexible and robust enough to tolerate mismatches while minimizing the risks of targeting incorrect sequences. Even more challenging, studies have shown that Cas9 tolerance for mismatches is higher in vitro (in the lab) than in vivo (in living organisms). This may be the case due to cellular factors that influence gRNA-DNA interactions.^{xxxix} These tolerance differences would render clinical applications far riskier and more challenging as lab research moves toward patient applications.</p>	<p>Truncated gRNAs</p> <p>Truncated gRNAs are more precise, making them less susceptible to mismatches.</p> <p>Truncated gRNAs shorten the number of nucleotides in the DNA sequence, making the truncated gRNAs more precise to specific targets when compared to the standard gRNAs. Truncated gRNAs have been proven to increase sensitivity to mismatches so that they are less tolerant of off-target binding.^{xi} Other studies are investigating the mechanistic aspects of mismatch tolerance and offer insights into how structural distortions in DNA may accommodate mismatches.^{xii}</p>
<p>Cas9 Persistence</p> <p>Cas9 activity could persist longer than intended, creating more opportunities for off-target effects.</p> <p>Cas9 may remain active past its intended use, allowing for more opportunities to bind to sequences that are similar but are not the intended target.^{xiii} When this happens, there are increased risks of unintended DSBs.^{xiii} These off-target effects are particularly prone to large chromosomal rearrangement^{xiv} like deletions, translocations, and inversions.^{xv}</p>	<p>Transient Delivery</p> <p>Transient delivery methods minimize Cas9 activity.</p> <p>To minimize the duration of Cas9 activity, researchers have developed 'transient delivery' methods^{xvi} (like ribonucleoprotein (RNP) complexes^{xvii} and extracellular vesicles (EVs)^{xviii}), and non-integrating viral vectors^{xix} that make temporary introductions of genetic material to cells. This makes them active for a shorter period hence reducing the chances of making unintended DSBs ransient delivery methods minimize Cas9 activity.</p>
<p>Repair Outcome Unpredictability</p> <p>DNA repair mechanisms introduce some uncertainty, particularly when without a repair template.</p> <p>The cell's DNA repair mechanisms (NHEJ or HDR) can lead to off-target effects.ⁱ NHEJ repairs DSBs by linking two broken ends of DNA without a homologous DNA template¹, which serves as a guide for new DNA synthesis. Therefore, NHEJ is often considered error-prone relative to the template-based HDR repair mechanisms.ⁱⁱ</p>	<p>Augmenting HDR Efficiency</p> <p>Various solutions focus on improving repair outcome predictability by engineering specific repair outcomes.</p> <p>Solutions have ranged from improving HDR efficiency through synchronized cells in attempts to phase out NHEJⁱⁱⁱ, or engineering NHEJ factors to favor specific repair outcomes.^{iv}</p>

In addition to addressing off-target effects, the scientific community must also improve gene editing delivery methods. Oftentimes, Cas9 proteins are too large to absorb into the intended cells, limiting their delivery. Other times, physical barriers like the blood-brain barrier protecting neural tissue

also become a biological barrier to gene editing delivery. Researchers are developing a variety of gene editing material delivery methods applicable to CRISPR Cas9, outlined in Table 2, and a few other genetic editing methods described later in this paper.

Table 2: CRISPR Delivery Methods.

Delivery Method	
<p>Viral Vectors</p>	<p>Adeno-Associated Virus (AAV) vectors have proven effective in delivering gene editing in vivo because of their lower risk of inducing an immune response and ability to convert both dividing and nondividing cells, and long-term gene expression. However, they can only package and deliver small genetic materials.^{iv} Lentivirus and Adenoviruses can carry larger genetic material relative to AAVs but carry higher risks of unintentional genetic material transfer to host genes and adverse immune responses.^{vi}</p>
<p>Non-Viral Vectors</p>	<p>Lipid nanoparticles (LNPs) are particles with lipid (fat) layers that deliver therapeutic substances, like encapsulated CRISPR components, into cells. LNPs are considered a safer alternative to viral vectors due to being non-viral and have reduced risks of triggering an immune response.^{vii} Meanwhile, EVs are membrane-bound particles that carry biomolecules like proteins, lipids, and nucleic acids. They are non-viral and transport molecules between cells.^{viii}</p>
<p>Physical Delivery</p>	<p>Physical delivery methods are far less common and typically entail electroporation, which is a technique where electrical pulses are used to induce temporary pores in cell membranes to allow necessary genetic editing material to enter cells.^{ix}</p>

Ongoing research in CRISPR Cas9 has focused on addressing challenges in off-target effects and improving delivery methods through advanced gRNA design, engineering Cas 9 variants, and developing alternate delivery systems. CRISPR

systems are still in the early to mid-stages of research, but they have significant potential to transform the pharmaceutical industry as they advance through preclinical and clinical trials.



Base Editing: DNA's Spell Check

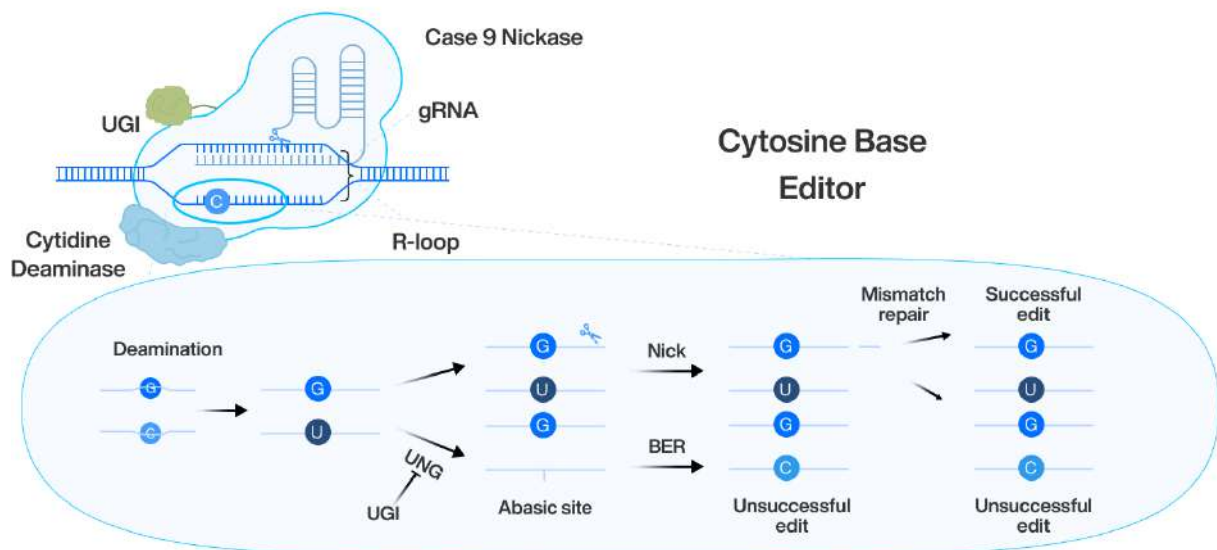
Even as CRISPR Cas9 revolutionized genetic editing at the dawn of the 21st century researchers continue to refine and optimize the systems' methods. Scientists have also turned to exploring other tools that address CRISPR's limitations.

In 2019, David Liu's laboratory at Harvard University pioneered a potentially revolutionary medical technique called base editing.^{ix} Like CRISPR Cas9, base editing performs targeted edits to genetic code. But while CRISPR Cas9 achieves this by introducing DSBs and then repairing those breaks, base editing is designed to correct single nucleotide polymorphisms (SNPs) without prompting DSBs in DNA strands.^{ixi} Figure 3 illustrates cytosine base editing using a modified CRISPR Cas9 system. Cas9 nickase, which is modified for the base editing

process, is guided by gRNA to the sequence target and cuts a single DNA strand.

DNA is composed of four nucleotide bases: adenine (A), thymine (T), cytosine (C), and guanine (G). These bases pair specifically—A pairs with T, and C pairs with G—to form the double-helix structure of DNA. In RNA, uracil (U) replaces thymine (T) and pairs with adenine (A) during transcription. The cellular mismatch repair process replaces the base G with an A on the broken strand. Meanwhile, the cytidine deaminase enzyme will convert C to U on the target strand. In this process, C changes to G while T changes to A. During DNA repair, the cytidine deaminase changes one DNA letter (say, C) into another letter (say, U). When this happens, the cell will repair itself by replacing the U with the right letter.

Figure 3: Cytosine Base Editing.



Source: CRISPR Medicine News.^{ixii}



The new approach should theoretically reduce off-target effects. However, recent studies have found that base editing has not eliminated the risks of accidental modifications to non-targeted genes.^{lxiii} More specifically, while base editors are designed to modify SNPs, most modify multiple nucleotides within the targeted genome loci.

Each nucleotide, consisting of a deoxyribose, a phosphate group, and a nitrogenous base, has a pair (adenine - thymine, A-T) or (cytosine - guanine, C-G), enabled by hydrogen bonds and forming the nitrogenous base. Adenine is paired with thymine (and cytosine is paired with guanine) because the molecules are structurally complementary i.e., they provide the structure for the double-helix shape fundamental to DNA strands.

Base editing refers to the editing of these base pairs. The editing process incorporates a Cas protein (most commonly Cas9) and a deaminase enzyme to induce precise modifications in the nucleotide, and a gRNA to guide the base editor to the targeted location in the sequence. Once the base editor, consisting of the Cas protein, deaminase enzyme,

and gRNA, reaches the targeted location in the sequence, it converts the nucleotide base to the desired base. After the base substitution, the cell's natural repair processes will repair the sequence using the modified information, permanently changing the sequence's new genetic information. For example, a cytosine base editor (CBE) may target a C-G base pair and convert it to a T-A pair, requiring a C to be swapped for a T. Likewise, an adenine base editor (ABE) would convert adenine to guanine.

Base editing only recently entered human clinical trials; thus, the current literature insufficiently captures the gravity and causes of its off-target mutations. However, there is a growing collection of existing literature that employs biological models, such as using transgenic mice, to study how off-target effects may affect patients in ongoing human clinical trials.^{lxiv} A 2023 study found severe CBE-induced off-target mutations in transgenic mice, leading to unintended consequences in gene expression, including inducing developmental delay, obesity, and various complex diseases.^{lxv}



Further Developments for Base Editing

Most genetic disorders are caused by single-gene mutations, which require the correction of an individual mutation or SNP. Generally, the known base editing off-target effects are caused by one or more of the following occurrences:

- » **Bystander Mutations:** When several base editors are directed to the same editing window, which is the gRNA-directed target site denominated by several nucleotides [nts] in length, deaminase over-activity may lead to the modifications of multiple Cs and As within this window. Deaminase are enzymes that convert nucleotide bases in base editing. This is because deaminase over-activity could result in more unintended edits. Chromatin structures are part of the sequence that needs to be 'switched out.' Chromatin structures that are too accessible to enzymes pose a higher risk of unintended edits, while overly condensed chromatin may prevent enzymes from binding effectively, making intended edits more difficult to achieve.
- » **Enzyme and gRNA Mis-Specificity:** Designing the appropriate components of the base editing system can also be an incredibly daunting task.

Base editing enzymes, like C (cytidine deaminase) or A (adenine deaminase), must be compatible with the genome editing goals. For example, Cas9 proteins should be engineered to prevent DSBs without compromising their ability to recognize or bind to specific DNA sequences. Beyond the basic functionalities of base editors, optimized base editors should be designed to minimize the editing window and reduce bystander mutations.

- » **Ineffective Delivery Methods:** Base editing treatments are mostly delivered directly to human tissue. Early clinical human trials have reported fatal immune responses.^{lxvi} While not all immune responses may be lethal, they will induce unintended genetic mutations. Most base editors deliver therapeutics via plasmid DNA molecules meant to carry genes, and recent research suggests that this delivery method would cause prolonged off-target gene expressions and trigger undesirable immune responses.^{lxvii}

Going forward, ongoing research in base editing will include improvements to base editor specificity, the optimization of gRNA design, and the development of effective delivery methods to minimize immune response and off-target effects. The development of advanced methods in base editing and CRISPR must start from a solid foundation of responsible development and trust in the research community and its relationship with clinicians and patients.



Enhancing Trust: Ethical Considerations in Genomic Editing

“Men ought not to play God before they learn to be men.”

- Walter Isaacson, *The Code Breaker*

Fueled by technical advancements and supportive market growth, gene editing technologies are constantly evolving and improving, ushering in new promises for the pharmaceutical industry and healthcare.

However, the challenge in genetic editing is not simply in overcoming technical hurdles—such as off-target effects, delivery efficiency, editing precision, and base editing specificity. As science progresses, these obstacles will be refined, and new techniques for gene editing will inevitably emerge. The greater challenge lies in grappling with the profound ethical question: what should humanity be allowed to edit, and where must the limits be set?

This debate serves greater relevance as market potential accelerates with research developments, often forcing innovation to be at odds with responsible development.

On one hand, genome-editing-based therapeutics expand the medical interventions available for patients and their healthcare teams, offering increasingly powerful medical protocols

for chronic and deadly conditions. As a result, a compelling and carefully considered argument can be made that genomic editing should not only be permitted but also supported. However, this must be approached with caution and thoughtful deliberation. Beyond the clinical applications, gene editing methods are likely to accelerate the scientific comprehension of novel diseases, furthering medical advances beyond genomic editing-based therapeutics by expanding the medical community’s understanding of complex biological processes.

Meanwhile, the perils of genetic engineering extend beyond technical and scientific uncertainties regarding reliability and safety. They also encompass broader societal concerns, such as equitable access and the potential for irresponsible use. As the tools are still in their preliminary stages, many of their technical challenges remain unresolved. Nevertheless, ethical discussions must account for both the current risks and the future implications of these challenges.



Unintended Edits

Unintended alterations to the genetic code pose significant risks to patient safety, potentially worsening existing conditions or, in more severe cases, triggering new medical complications. While uncertainty is common in most medical procedures and treatments, the unintended consequences of genetic modifications often result in severe and irreversible harm.

Moving forward, advancements in design and development from the scientific community, thorough and prudent clinical testing by the pharmaceutical industry, and rigorous oversight from regulators will undoubtedly enhance the efficiency and effectiveness of genetic editing. However, significant risks remain with the current state of the technology, and as proposals for its application move from the lab to broader society, new risks will inevitably emerge.

Equitable Access

Gene editing therapeutics are costly and unavailable to most populations. In this scenario, only the economically advantageous would find genetic editing services accessible – limited to high-income nations with high GDP per capita, including North America, Europe, and parts of East Asia.^{lxviii} Since most of the global population lives in countries with a GDP per capita below \$15,000, the most advanced medical treatments would be unaffordable for much of the world.^{lxix} To reduce this potential inaccessibility and inequality, companies must lower the costs of research and development (R&D) and other operational expenses, allowing them to maintain fair profit margins while offering medical services at affordable prices. Fortunately, R&D costs tend to be higher during the initial stages of a technology but typically decrease as the technology matures. For instance, the costs of genomic sequencing have already dropped significantly. However, the clinical operations and enterprise processes needed to deliver gene-editing therapies to patients remain expensive.



Governance

Governance frameworks are essential to regulating and overseeing the research, development, and deployment of gene-editing technologies. Standardized procedures are critical in mitigating risks to human health and safety. The deployment of these technologies must prioritize patient autonomy, informed consent, and transparency to foster trust in the face of ongoing risks and uncertainties. Currently, there is insufficient clarity on what constitutes genetic editing for the 'primary purpose of medical therapeutics.' Additionally, inconsistent national policies create the potential for 'regulatory havens,' while the absence of binding international agreements inadequately deters unauthorized clinical applications.

The reluctance to reach a binding global agreement on genetic editing stems from several complex factors, including:

1. Scientific and Technological Uncertainty:

The field is rapidly evolving, which poses challenges for creating lasting regulations. There is uncertainty about the long-term effects of gene editing technologies and the potential for unintended consequences.

2. Cultural Differences in Addressing Ethical Conversations:

Cultural and religious views on the sanctity of life and the role of human intervention play a significant role in shaping discussions on the boundaries between therapeutic treatments and enhancements. These diverse perspectives must be carefully considered when establishing global coalitions and

regulatory frameworks for this often controversial technology.^{lxx} For example, some may argue that genetic therapy should encompass preventive gene-editing treatments aimed at reducing the risk of patients developing diseases in the future. Conversely, others may view such interventions as enhancements rather than therapies, particularly when they address non-life-threatening conditions or traits.^{lxxi lxxii}

3. Economic Interests: Achieving and sustaining a leadership position in biotechnology and gene editing will contribute to many national interests, particularly in national security and economic competitiveness. This is evident in the strategic investments made by China^{lxxiii} which has designated gene editing as a key technology, and the United States,^{lxxiv} where both federal and private capital have allocated resources to gene editing.

4. National Security Interests: National interests are likely to drive substantial growth and investment in the gene-editing sector across major global economies, as both private and public enterprises seek to capitalize on research advancements and market opportunities. The intense competition between nations and companies will propel gene editing to new and exciting frontiers, but it may also complicate the landscape of patents and intellectual property as entities vie for recognition and exclusive rights to the technology. A notable example is the recent case in which the Broad Institute of MIT and Harvard prevailed over UC Berkeley in a dispute concerning the recognition and ownership of gene-editing innovations.^{lxxv}



Trustworthy Framework: Aligning Market Incentives with Ethical Development

Targeted Funding and Grants

Both private and public entities may encourage responsible development by offering grants focusing on developing safeguards and risk assessment tools related to gene editing technologies. To ensure the diversity and robustness of varying perspectives, these grants may require interdisciplinary teams of scientists, ethicists, and policy experts. Moreover, targeted grant funding could also include prioritizing resources allocated to addressing genetic diseases or conditions with limited treatment options, ensuring that the most critical ailments are addressed with higher urgency.

Tax Incentives

Governments may seek to provide tax breaks for companies that adhere to ethical guidelines and policies governing gene editing research and development. These policies could materialize in tiered systems that offer additional tax incentives for companies that invest in long-term safety studies or research focused on surveilling gene therapies in clinical applications. Enterprises that can prove higher levels of ethical commitment could qualify for enhanced tax benefits that allow organizations to reinvest the tax benefits into their research, which withholds the highest long-term safety monitoring programs and includes extended follow-up studies with patients who have received their gene therapies.

Patent and IP Policies

Gene editing therapeutics that address conditions of higher urgency may be entitled to faster patent approvals, in nations where these processes are applicable. An example of this is the U.S. Federal Drug Administration's 'Breakthrough Therapy' designation,^{lxvii} which allows an expedited review of drugs intended to treat life-threatening diseases, or the European Union's counterpart, the Priority

Medicines Scheme.^{lxviii} National governments should continue to provide consistent guidance that encourages researchers to present preliminary clinical evidence that demonstrates substantial improvements over existing therapies for serious conditions. Moreover, additional funding for programs that offer direct and streamlined grants for promising treatments that meet rigorous safety and efficacy standards in gene editing should be considered.

Encouraging Accessibility Through Aligned Economic Incentives

The declining costs of genomic sequencing technologies and processes do not directly translate into an increase in the accessibility of genetic editing services. This is because there are several steps that follow the scientific processes of genomic sequencing and gene editing that would allow patients to receive clinical treatment. Increasing accessibility in genetic editing-based medical therapeutics requires a decline in scientific research costs and a reconstruction of the medical systems that underlie patient care. These restructures would differ across nations, cultures, and organizations, but must be undertaken to truly increase the accessibility of gene editing therapeutics.





Conclusion

The rapid advancements in gene editing are propelling humanity into a new era, one where the ability to reshape our biology sparks profound ethical questions about our relationship with life itself. As we stand at the crossroads of possibility, the path forward demands not only a rigorous assessment of the field's scientific achievements and limitations but also a careful balance of globally coordinated efforts to ensure responsible progress.

From a technical perspective, several priorities must guide this journey: (1) refining editing technologies to minimize off-target effects, (2) deepening our understanding of gene functions and interactions, (3) developing reversible editing methods as a vital safety mechanism, (4) establishing clear guidelines distinguishing permissible from prohibited applications, (5) fostering inclusive public dialogues on the societal implications, and (6) addressing concerns about equity and access to these innovations.

Gene-editing technologies have arrived at

a pivotal moment in their evolution. They hold the extraordinary potential to allow humanity to design its own biology, and by extension, shape its future. The technological strides in efficiency, precision, and delivery have been nothing short of remarkable, and the market forecasts for this burgeoning industry are filled with optimism. However, even the most seasoned experts recognize that gene editing remains a novel and evolving field, requiring ongoing advancements in both its technical processes and the ethical frameworks that govern its use.

As we move forward, the industry must collaborate closely with researchers and policymakers to implement robust governance structures that align market incentives with ethical imperatives and engage the public in the technology's responsible development. Unlocking the ability to rewrite the code of life is a power that demands not only technological excellence but also wisdom, foresight, and a profound respect for the fragility and sanctity of human existence.

Author:

Helene Huang

Senior Research Associate, CTT

Research Assistance:

Jan Riecke

Research Intern, CTT

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