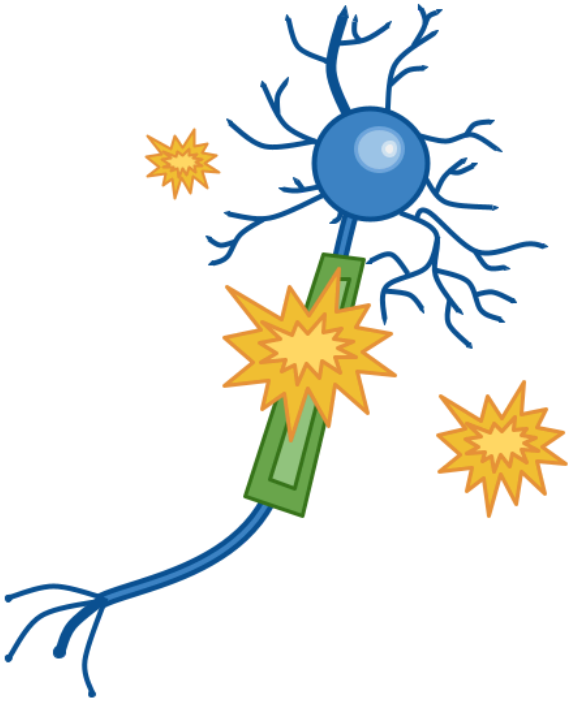
Forgetting Alzheimer's with CRISPR

A Comprehensive Review by Anaïs Lohier



Anaïs Lohier is in her third year at the California Polytechnic State University, majoring in Business Administration with a concentration in Quantitative Analysis and minors in French and Biology. The French-American grew up in Berkeley, California, with a passion for human anatomy and the medical field. Upon graduating, she plans to attend graduate school to obtain a Masters in Bioinformatics at Brown University.

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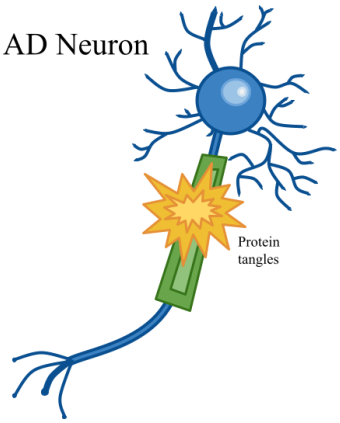
What is Alzheimer's Disease

Imagine waking up one morning and not being able to recall your address, or even the names of your close relatives. This is the devastating reality for millions of people suffering from Alzheimer's disease. Alzheimer's is a neurodegenerative brain disorder marked by a decline in memory, identity, and independence. In the United States alone, approximately 5.8 million people have been diagnosed with Alzheimer's as of 2019, and it is estimated that by 2050 this number will increase to 15 million. There is currently no real cure for this disease, but what if scientists could rewrite the very genetic code that causes Alzheimer's?

Firstly, What Causes Alzheimer's Disease?

On a molecular level, Alzheimer's disease (AD) is caused by neuropathological changes in the brain (Bhardwaj, 2021). According to the Aging division of the National Institutes of Health (NIA), two key proteins are the root cause of such changes: tau and amyloid-beta. In healthy amounts, tau normally binds to and stabilizes the structure of neurons. In AD however, abnormal chemical changes cause tau to detach from the structure and combine with other tau molecules to form tangles inside neurons. These tangles block the neuron's transport system, which harms the communication between neurons (Duan, 2021). Amyloid-beta is an important protein for interneuron communication and neuron development, but abnormal levels of this naturally occurring protein clump together to form plaques that disrupt cell function in Alzheimer's patients (NIA, 2024a). The disease is believed to be mostly caused by external factors rather than inheritance of these faulty tau and amyloid-beta genes. Interestingly, only 5% of recorded AD cases are early-onset and caused by these inherited genetic mutations. The remaining 95% of cases stem from external factors such as age, lifestyle, and pre-existing medical conditions (Konstantinidis, 2022).



Current Treatment Options

There is still no cure for Alzheimer's. There are some medications, such as antipsychotics and immunotherapy treatments, that target glutamate, an amino acid that tries to counteract the neuron communication by stimulating the neurons, but they only provide temporary relief and do

not stop the disease from progressing (NIA, 2023b). Additionally, these drugs come with many side effects, including confusion, dizziness, and depression to list a few. Lifestyle changes are also frequent with AD patients, who commonly live in memory care, or assisted care facilities as their disease progresses, whose costs run higher than many other types of senior care (Shuman, 2025). In the past twenty years, there have been over 400 failed clinical trials for AD treatments, with only one drug able to enter the market, which helps manage patient symptoms by targeting glutamate (NIA, 2023b). With a staggering 99.5% failure rate, scientists are turning to genetic engineering to find a cure (Bhardwaj, 2021).

Scientists are now looking at the genes linked to Alzheimer's to slow or even prevent the buildup of harmful amyloid-beta proteins that cause the disease. Researchers have identified the PSEN1 gene as one of the key drivers in amyloid-beta production. Mutations in this gene can disrupt the balance between the harmless amyloid-beta 40 and the more toxic amyloid-beta 42— which has been found to clump together and form plaques in the brain at higher rates than its counterpart— leading to AD progression (Konstantinidis, 2022). Using genetic engineering, researchers hope to correct this imbalance and reduce the buildup of these harmful plaques, potentially changing the course of the disease. But how exactly can they do this?

Enter CRISPR

Clustered Regularly Interspaced Palindromic Repeats (CRISPR) granted, is quite a mouthful. Despite this humorously long name, this technology has recently revolutionized the face of medicine. CRISPR is a groundbreaking technology that allows scientists to precisely modify DNA by cutting, replacing, or silencing specific genetic sequences with accuracy like never seen before (DeBruhl, CRISPR).

Fun Fact!

CRISPR is adapted from a bacteria's natural immune response. Bacteria actually store parts of a virus' DNA in its own genetic code to recognize and destroy them in the future!

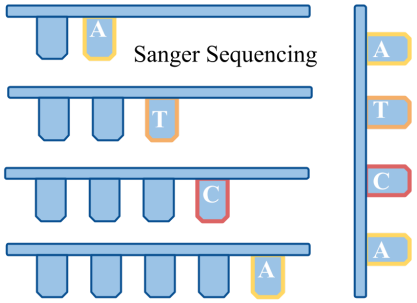
The Experiment

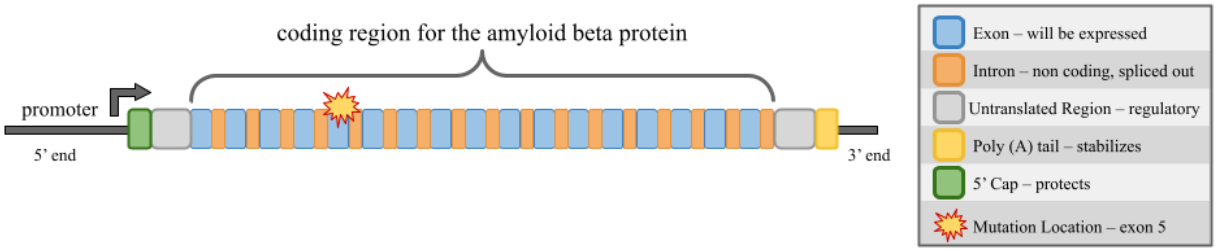
Let's follow along with the experiment performed by Evangelos Konstantinidis and their team to better understand the mechanisms of CRISPR. In their study, published in June of 2022, researchers used CRISPR to restore the ratio of healthy to aggregate-prone amyloid-beta protein

levels in human AD fibroblasts— a connective tissue cell that secretes collagen proteins to help maintain the structural framework of tissues (Sidransky, 2025). Here's how they did it:

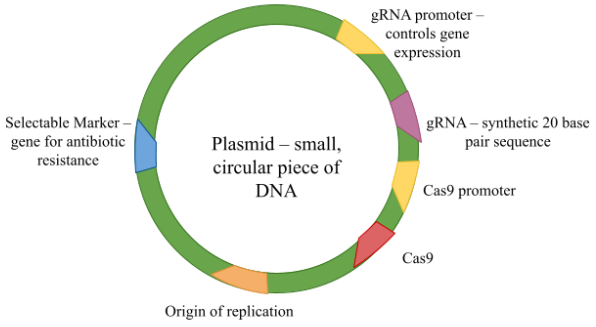
1. Since PSEN1 is known to be a commonly mutated in AD patients, researchers studied what creates this mutation firstly by isolating the gene in AD-affected cells using PCR— a technique that amplifies DNA by repeatedly heating to separate strands, cooling for primer binding, and using an enzyme called DNA polymerase to make new copies (DeBruhl, Isolating DNA).

2. Once the gene was isolated and amplified, researchers used Sanger Sequencing to determine the DNA sequence by adding fluorescent synthetic nucleotides that terminate replication, producing fragments that are then analyzed through a chromatogram to reveal the sequence (DeBruhl, DNA Sequencing). Doing so revealed a point mutation, named M146L, where an Adenine nucleotide is replaced by Cytosine in the fifth exon—regions of a gene that contain instructions for making proteins (DeBruhl, Gene Components).

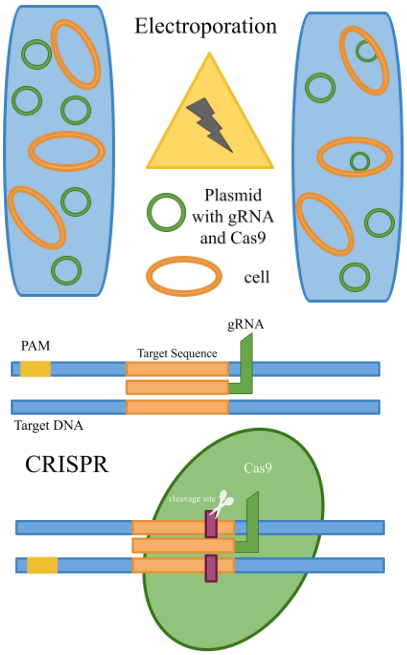




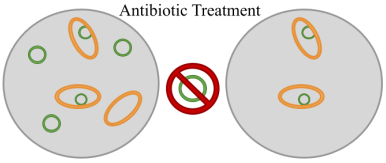
3. After identifying the point mutation, researchers used CRISPR, a gene-editing tool consisting of a Cas9 nuclease that cuts DNA and a guide RNA (gRNA) that directs the system to a specific sequence. They designed a 20-base-pair gRNA to selectively bind to the mutant allele (version of a gene like eye color inherited from each parent) while avoiding the healthy sequence (DeBruhl, CRISPR and Genetic Diseases).



4. The CRISPR components were introduced into human fibroblast cells using electroporation, a technique that temporarily neutralizes the cell membrane's charge, allowing a plasmid (a circular piece of DNA that can accept, carry, and replicate another piece of DNA) containing Cas9 and the gRNA to enter the cell (DeBruhl, Expressing and Purifying a Protein). The location of the mutation also provided a unique opportunity for precise editing, as it is next to a protospacer adjacent motif (PAM) site, which is needed for CRISPR-Cas9 recognition and serves as a marker that helps bacteria distinguish foreign DNA from its own (DeBruhl, CRISPR).



5. Once inside the cell, Cas9 created a double-strand break of the DNA at the target site, triggering the cell's natural repair mechanisms. The primary repair pathway involved non-homologous end joining (NHEJ), which is a cell's first line of defense per se when damaged, and known to be an error-prone process that frequently introduces small insertions or deletions of DNA bases at the break site (DeBruhl, CRISPR).
6. To ensure that only successfully edited cells remained, researchers used puromycin as a selection marker. Cells that had successfully taken up the plasmid carrying the CRISPR-Cas9 components were resistant to puromycin, while unedited cells were eliminated by the antibiotic treatment (DeBruhl, GMO Animals).



After completing the steps outlined above, researchers analyzed their findings by putting the transformed cells once again through the PCR and Sanger Sequencing processes, and found that 95% of these edits resulted in frameshift mutations (a mutation that shifts the reading frame of a gene), which by chance led to premature stop codons (a sequence of three nucleotides that tell a cell to stop making a protein) that effectively disabled the mutant PSEN1 allele (DeBruhl, Overview of Transcription & Translation). Researchers found that this genetic disruption helped restore the amyloid beta 42/40 ratio, which decreases the amyloid beta in the brain that are found to cause Alzheimer's. They also used two

Fun Fact!

You can buy the very same plasmid these researchers used online! https://www.addgene.org/62988/

different verification methods to analyze off-target effects, and found that this only occurred in less than 1% of cases. This is important to consider, as they could lead to unintended genetic changes which could potentially disrupt gene function or regulation, and a major source of safety concern (DeBruhl, Genetic Diseases & Gene Therapy).

Easy as…CRISPR?

CRISPR has not only opened tremendous possibilities for treating Alzheimer's but is already being used to treat diseases such as sickle cell anemia (that causes misshapen blood cells) and transfusion-dependent thalassemia (broken proteins necessary in blood) (Henderson, 2024). While such possibilities are very exciting, CRISPR has raised many ethical and moral questions and sparked much debate regarding its application. Let's analyze some of these claims.

Fun Fact!

Although CRISPR was first discovered in bacteria in 1987, it took over 36 years for it to be commercially approved, with the first CRISPR based treatment receiving FDA approval in 2023.

Claim 1 – Medical Use of CRISPR Leads to Using CRISPR for Genetic Enhancement

The opponent in the following argument is Sandy Sufian, an associate professor of health humanities and history at the University of Illinois Chicago who focuses on disability studies and ethics. Sufian graduated from New York University with a doctorate in Middle East History and Masters in Public Health in epidemiology and biostatistics from Oregon Health Sciences University. Defendants for this argument are led by Julian Savulescu, director of the Oxford Centre for Practical ethics, who focuses on the ethics of emerging technology from reproduction and enhancement of physical and cognitive performance through drugs or genetic manipulation.

Opponents	*Defense*
Cost Implications: Genetic changes, whether for enhancement or treatment, risk being accessible only to the wealthy, widening social inequalities and creating a genetic divide (Rueda, 2024).	Validation of Fears: New technology often faces skepticism. Like Artificial Intelligence (AI), CRISPR has aided various fields while sparking debate about its future use (Savulescu, 2015).

Slippery Slope: Technology could enhance traits such as intelligence just as easily as it could treat diseases (Sufian, 2021).	Everything is a Slippery Slope: Just because technology could be used for non-essential purposes doesn't warrant a complete ban (Savulescu, 2015).
Ableist Perspective: CRISPR reduces diversity and innately describes those with chronic disabilities as inferior (Sufian, 2021). Comparing CRISPR and eugenics, used for genetic selection in WWII, both devalue people with genetic conditions to achieve specific outcomes (Sufian, 2021).	CRISPR Guidelines: Global guidelines (with varying degrees of regulations) for CRISPR use in somatic editing, in order to prevent the mishandling of this technology (Genetic Literacy Project, 2024).

Analyzing the Evidence

CRISPR does not have any inherent limitations, but it is important to consider the global regulations for the use of CRISPR for therapeutic treatments. Therefore the slippery slope argument is definitely one to be considered in the context of such regulations, but also necessary to consider the dignified inability to control an individual's free will. Having more medical treatments for genetic diseases is also not inherently negative. Many other medical advancements—such as insulin for diabetes or cochlear implants for hearing loss— have provided life-changing benefits without directly leading to discrimination of people with these conditions. The eugenics comparison is interesting, but it is important to consider the difference in intent between CRISPR and eugenics, as well as the circumstances: CRISPR is currently being used in a medical treatment context, whilst WWII was arguably the most heinous time period in history. Cost implications of CRISPR treatment is also a great point. Comparing CRISPR to hospice and memory care though, which in 2024 amounted to a median of $181 per day, totaling $500,000 to $660,000 over an average 8–10 year Alzheimer's diagnosis (Shuman, 2025). If approved, this CRISPR treatment might have higher upfront costs, but one must also consider the price of memory and quality of life, which is, well, priceless.

Fun Fact!

Casgevy, the world's first approved CRISPR-based cell therapy that targets sickle cell anemia and TDT, costs a hefty $2.2 million per patient!

My Opinion

I believe the critiques of CRISPR rely on speculation and stem from fear of the potential disruption caused by CRISPR. I definitely agree with the cost considerations of CRISPR, but find this to be moreso a critique of the American healthcare system rather suitable for this discussion at hand. I believe the ableist and eugenics claims are quite interesting, but unfairly pointed towards CRISPR technology. One could make the same comparisons to any other form of medical treatment. Although there are strict regulations on gene editing and a lengthy approval process before new medications can enter a market, I do acknowledge the fact that someone can use CRISPR technology for feats other than what is intended. With this in mind, I think it is important to maintain enforcement of regulations and maintain skepticism of new technologies but also welcome new treatments for common diseases.

Claim 2 – Unintended Consequences such as Off-Target Mutations

Opponents of this claim are led by Dr. Greg Licholai, who is the chief medical and innovation officer at ICON plc, as well as a professor of Sustainable Innovation at both Harvard and Yale University, and writes about innovation for Forbes. Proponents are long time researchers in the field of biomedical and clinical research, including Jennifer Couzin-Frankel, reporter on biomedical and clinical research with works anthologized in the Best American Science Writing series and honored by the National Academies of Science Communication Award and National Institute for Health Care Management Foundation Award.

Opponents	*Defenses*
Unfit Validation Methods: Sanger sequencing is typically used to validate gene edits, but it often fails to identify large changes in the genome, such as major deletions. Larger structural variations can occur at both on-target and off-target sites, potentially leading to unintended effects. (Höijer, 2022).	Medical Advances: Multiple new approaches have significantly reduced the risk of off-target mutations, such as improved engineering of Cas9, and using anti-CRISPR proteins to neutralize CRISPR activity where it is not needed, reducing the chance of off-target effects (Mengistie, 2024).

Negative Effects: Some studies show that CRISPR may cause cells to lose their cancer-fighting ability, and damage genes more than previously understood (Licholai, 2018).	Conflicting Data: In other studies, CRISPR has not been found to increase risk of recurring illness any more than chemotherapy, a common treatment for cancer (Couzin-Frankel, 2023).

Analyzing the Evidence

Essentially all medical treatments place a patient at risk of side effects in some regards, although it is true that theoretically CRISPR could introduce new genetic diseases into the population from a long-term standpoint. Therefore, it is important to understand the rate at which this occurs and if it is greater than when compared to other treatment methods. The issue here lies in the fact that there is not enough long term data to make a conclusive statement, and as of now is a very polarizing debate. It is also important to point out that sources found for the opponents regarding the safety of CRISPR are perhaps not recent enough to still hold ground. While such concerns were raised early on in CRISPR developments, researchers since then have been able to engineer Cas9 variants to be more precise in their editing, though long term safety and efficacy remains under investigation.

My Opinion

I feel strongly against the concern for negative side effects of CRISPR, considering the fact that there are extensive side effects for many prescription drugs available to consumers— birth control pills can cause nausea, mood changes, breast cancer, heart attack, stroke, and death— and that in recent findings CRISPR has been found to be more precise than other options (Cleveland Clinic, 2023). I also believe the ethical consideration is arguably the most important factor to consider, as it is unethical to not pursue possible treatment effects if they exist, especially if they are underdeveloped.

Claim 3 – Safety of CRISPR Treatment Delivery to the Brain

Researchers are primarily leading the discussion of this claim as it is still evolving and difficult to gather specific conclusions regarding the safety of CRISPR delivery to the brain. Researchers

such as Gaia Colasante, Yan Zou, Gokul Ramadoss, and Mohammad Chehelgerdi are all current or recent PhD candidates in San Francisco and London, who have found conflicting findings regarding the developments of new methods and of their commercial use.

Opponents	*Defendants*
Extra Risk: Delivering CRISPR to the brain presents unique risks that are not yet thoroughly studied. Neurons respond differently to CRISPR than other cell types and take longer to repair, which could lead to unpredictable outcomes, such as larger mutations or unintended consequences in the brain's genetic makeup (Ramadoss, 2024).	Recent Success: A 2020 study found success in treating epilepsy and cognitive defects in rats, by using a CRISPR technology that allowed for precise regulation of the gene rather than directly editing the genome which can reduce risk of unintended neural mutations (Colasante, 2020).
Research Needed: Recent studies have delivered CRISPR across the blood–brain barrier (that protects the brain from harmful substances in the blood) but more research is needed to understand its safety and efficacy and this feat remains in its early stages (Chehelgerdi, 2024).	Brain Barrier Entrance: Existing CRISPR brain delivery methods include deactivated viruses and synthetic delivery capsules made of fats or polymers. But, researchers recently designed a nanocapsule for noninvasive CRISPR brain delivery by coating the Cas9 and sgRNA in a positively charged polymer shell that can penetrate the blood-brain barrier and was deemed more efficient than other mechanisms in mice (Zou, 2022).

Analyzing the Evidence

Although the animal testing stage is essential for human treatment, rat brains are significantly different than that of humans. Analyzing the blood-brain barrier is important, as it is highly selective in what can pass through into the brain, and opponents are correct that more research is necessary considering none of these methods have been commercialized. That being said, there

have been many promising developments of various delivery methods of CRISPR across the blood brain barrier.

My Opinion

I agree that there is extra risk in delivering CRISPR to a human brain, and that it is important to be extremely careful in understanding the various approaches in crossing the blood-brain barrier whilst protecting neuron health. I acknowledge the fact that CRISPR has been commercially approved for other diseases, but I think the sensitivity required for targeting a human brain requires extra considerations. I find it interesting that other experiments have focused solely on the delivery of CRISPR to the brain and am curious if researchers have been able to test the culmination of the gene editing and delivery in one experiment and the effectiveness of this.

Moral and Philosophical Considerations

After understanding some of the controversial claims surrounding CRISPR technology, it is also important to examine the subject more broadly from a moral and philosophical perspective. This opens the discussion further and extends to government authorities, public opinion, and even professionals from the agricultural industry.

The discussion is primarily led by researchers, such as Jennifer Doudna who pioneered CRISPR, as well as philosophers such as Greg Licholai who graduated with a masters in business administration and doctor of medicine from Yale and Harvard, respectively.

- ***To Use CRISPR:*** CRISPR is promising for people with inherited diseases as it can precisely target and correct harmful mutations. CRISPR has successfully been used to treat conditions such as sickle cell anemia, and there are many other diseases that could potentially be treated using this technology. Its applications also extend beyond medicine, offering potential benefits in agriculture by creating disease-resistant crops and improving food security (Henderson, 2024). In the end, intentionally refraining from life-saving research because of a fear for consequences is not moral (Savulescu, 2015). This approach considers utilitarianism, an ethics system that considers morally right actions to be those that produce the greatest good for the greatest number of people (DeBruhl, Ethics).

- ***Or to not to use CRISPR:*** Critics of CRISPR apply the deontological ethics system, based on an absolute set of principles and the dignity of human life, by emphasizing the duty to respect human life in its natural form rather than changing it at the genetic level (DeBruhl, Ethics). Expanding on such considerations, CRISPR in the context of long term implications raises concerns about unintended genetic consequences for future generations and the potential for misuse, such as genetic enhancement rather than disease prevention (Licholai, 2018). The high cost and experimental nature of CRISPR also create issues with accessibility, which can potentially exacerbate healthcare disparities and limit the benefits of CRISPR only to those who can afford it (Rueda, 2024).

Considering all stakeholders of CRISPR, including researchers, patients, and big pharma, I ultimately believe there are more benefits to implementing the technology than banning it entirely– thereby following the utilitarianism ethics system. If regulated carefully, CRISPR's ability to cure genetic diseases and improve quality of life outweighs its risks. I believe that the concerns regarding genetic enhancement as well as cost are not completely unique to CRISPR technology, and the potential of the technology outweighs such concerns.

Final Thoughts

After better understanding the mechanisms of CRISPR and considering some of the moral and ethical claims, what now? Let's go back to the beginning and compare CRISPR techniques to non-genetic engineering methods:

- Available medications manage symptoms rather than addressing the root cause of the issue. While these methods are often considered safer and more widely accepted, they may require lifelong treatment and lack the potential for permanent cures.
- Contrastingly, genetic engineering methods directly modify an organism's DNA to correct mutations, thereby offering a potential cure rather than just managing symptoms, but have yet to be commercialized or truly successfully tested.

In Alzheimer's treatments, given the fact that CRISPR is currently the closest method to a cure, it is the better solution. Genetic engineering generally represents a groundbreaking advancement in medicine, holding the potential to revolutionize disease treatment and prevention. While non-genetic methods will continue to be an important part of healthcare, genetic engineering

provides a more effective, long-term solution. However, ethical considerations, accessibility, and continued research should be prioritized to ensure these technologies benefit society as a whole.

What's next?

We've learned about Alzheimer's and analyzed one research article in depth to learn the mechanisms of CRISPR as a potential cure, as well as opened the discussion regarding some of the claims and moral considerations regarding this technology. Yet, this is only the beginning. There is much more to be discovered regarding the future of CRISPR, and scientists and critics alike are eager to find out what the endless possibilities of this technology entail. The question remains, will Alzheimer's be cured in our lifetime? What CRISPR breakthroughs remain undiscovered, and how soon will CRISPR-based treatments become widely available? As research advances, the answers to these questions will shape the future of medicine and redefine the boundaries of genetic science.

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