# A Comparative Analysis of CRISPR-Cas9 and Gene-Lowering Approaches for the Treatment of Huntington's Disease

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**Abstract**

Huntington's disease is a severe autosomal dominant inherited disease, which means a person will suffer from this disease even if only one allele is mutated. The disease is caused by CAG trinucleotide repeat expansion in 4th chromosome, HTT gene, and only a little approach could be helpful to treat this disease from now. Today, approximately 5 out of every 100,000 people will suffer from this disease all around the world. This article explores two groundbreaking technologies that emerged at the end of 2025, marking the first time Huntington's disease has ever been successfully treated. Two rivaling approaches are at play: CRISPR-Cas9 editing of the gene responsible for Huntington's disease (HTT), and gene-lowering, which involves the degradation of the mRNA produced by miRNA. In previous research, the gene-lowering method functioned in mutant Huntington mRNA, instead of targeting the gene itself. This paper compares the benefits and shortcomings of these two prevailing methods for curing Huntington's disease. According to this paper, the gene-lowering method is relatively mature, and it is getting increasingly closer to being released in the market as a drug. The CRISPR-Cas 9 method is theoretically more efficient due to its once-and-for-all characteristic, and could be more convenient. However, both treatments are all facing the delivery challenge. This paper provides a comprehensive comparison of two novel approaches for treating Huntington's disease, providing a roadmap for where this research needs improvement, and may progress in the future.

## Introduction

Huntington's disease is classified as a neurodegenerative disorder. This means that it will damage some specific areas of the people's central nervous system. The source of Huntington's disease is a mutation of the HTT gene (Tong et al., 2024). This particular gene is located on the 4th chromosome. For many patients, within the HTT gene, the 1st exon will continuously copy a "CAG" mutation into the gene, termed a trinucleotide repeat expansion. In people unaffected with Huntingtons, the CAG sequence within the HTT gene only exists around 6~35 times; however, patients with Huntington's disease can have as many as 40 times the number of CAG insertions (Mühlbäck et al., 2024). The HTT protein is an essential protein for human neurons to survive, grow properly, and assist in intracellular transport within the central nervous system (CNS). However, mutated copies of the HTT protein have an abnormal length, leading to misfolding and build-up within the CNS, where it can become toxic and cause neuronal death. (Palaiogeorgou et al., 2023). In summary, the CAG repeat expansion in the HTT gene results in a misfolded protein that accumulates in the CNS, driving the neurodegenerative process characteristic of Huntington's disease.

Huntington's disease has three primary symptoms: movement disability, cognitive dissonance, and psychiatric disorder (some serious psychological problems such as depression, bipolar) (Mehanna & Jankovic, 2024). The impacts to movement can be divided into two parts:

involuntary motion disorder and voluntary movement disorder. Involuntary movement can cause patients to exhibit dance-like twitching, which is an apparent symptom of Huntington's disease, and is done unintentionally by the patient. The voluntary movement disorder presented by Huntington's causes patients to lose the ability to move and operate their muscles efficiently, or in some cases, completely lose the ability to move at all. What's more, cognitive impairment can greatly impact the lives of those affected. Patients can begin to exhibit a loss of attention, the ability to change their minds or switch between perspectives in different contexts, and the loss of future planning (Andriessen et al., 2025). Language can also decline as the disease progresses. Besides that, patients might exhibit psychiatric symptoms such as anxiety, depression, and aggression, which greatly impact the patient's quality of life.

Researchers have spent decades trying to elucidate the mechanisms leading to Huntington's disease, to develop therapies that could stop the progression of the disease, or prevent it altogether. The first step was discovering the gene responsible for the disease (*HTT)*, which was finally found in 1993, and represented a breakthrough in the field (Alkanli et al., 2023). Today, tests for the repeat expansion of the *HTT* gene are the most reliable biomarker used to diagnose a patient and are considered a genetic biomarker (Lepinay & Cicchetti, 2023). However, there are other biomarkers that can be used to diagnose or predict the onset of Huntington's. Protein-based biomarkers detection of the mutant Huntingtin protein in the blood (Lepinay & Cicchetti, 2023), neurofilament light chain (NfL), which can be found in the cerebrospinal fluid (Coppens et al., 2023). Finally, non-invasive imaging such as MRIs and PET scans (Farag et al., 2025), and motor control and clinical assessments could be efficient instruments to measure and present the results(Mestre et al., 2018). Each of these biomarker-based diagnosing methods is carefully considered and employed by physicians when diagnosing patients with Huntington's disease (Byrne et al., 2022). That being said, there are limitations to each of these biomarker-based diagnostic tools, and none is completely efficient. A major obstacle in biomarker development is the lack of standardised, sensitive detection methods validated by rigorous statistical analysis. (Przybyl et al., 2021).

There has been considerable effort put into developing treatments for patients with Huntington's disease, and two have emerged that have relatively high efficiency. The first is gene-lowering therapy (RNA interference) and the second is Gene-editing therapy (CRISPR-Cas approach) (Alkanli et al., 2023; Belgrad et al., 2025). Gene-lowering therapy. uses siRNA or miRNA to target the mRNA of the mutated *HTT* gene, thereby preventing the production of the toxic protein (Fihurka et al., 2023). siRNA (small interfering RNA) and miRNA (microRNA) are two different RNAs that act to identify the mutated *HTT* mRNA gene product and to denature (break down) the mutated mRNA(Alkanli et al., 2023). But this method has an apparent limitation: it is difficult to efficiently deliver siRNA and miRNA through the blood-brain barrier (BBB), a highly selective biological barrier located between blood and CNS, and it has the purpose of blocking any harmful substance in blood from entering the brain (Chen et al., 2025). Additionally, these RNAs can degrade within the intestinal tract and blood due to pH and other factors, potentially limiting their effectiveness (Vignone et al., 2022). So, this approach is relatively safe because it will not modify DNA, but it faces some problems that are still waiting to be solved.

The second method employed to treat Huntington's Disease is a CRISPR Cas-9 therapeutic strategy. CRISPR-Cas9 is a gene editing tool that acts like a precise pair of scissors that can cut off the mutated part of a gene. By targeting the tandem repeats in the mutated HTT gene, researchers may be able to prevent production of the mutated protein and restore production of the healthy HTT gene protein (Ling et al., 2025). For instance, targeting of caspase activity, targeting of mitochondrial dysfunction, Targeting of Transcriptional dysregulation, and targeting of mHTT (Fields et al., 2021). Researchers will use these targets to target the mutated HTT gene, then, using CRISPR, will induce a double-strand break in the DNA. (Alkanli et al., 2023). Through this process, the researchers can effectively target the cells impacted by the mutated HTT gene and use CRISPR technology to repair it.

Both approaches, in theory, hold great promise for treating Huntington's disease. However, each therapeutic strategy takes a different approach, which in turn, presents its own distinct challenges.

**1. UniQure (Gene-lowering approaches)**

A company called UniQuire, located in Amsterdam, Netherlands, has taken a gene-lowering therapeutic strategy for treating Huntington's Disease. Gene-lowering involves using RNA to find and denature the mRNA (protein-coding product of a gene), and then suppressing its ability to be made into a protein. The miRNA and its possible carriers cannot cross through the Blood-Brain Barrier efficiently, so UniQure tried a new method, using nuclear magnetic resonance as a leading approach, implementing the intrastriatal injection. This injection means directly injecting the drug into the corpus striatum, so the drug can bypass the BBB(Evers et al., 2018). A gene-lowering therapeutic strategy is particularly apt in the case of Huntington's disease, since the mutated HTT gene mRNA transcripts can be well established for a given patient ahead of treatment. This means that the risks could be lower for the patient, given that no DNA will directly be edited, but rather the products of the gene are edited. Although this technology is new for the treatment of Huntington's disease, it has been used before. One of the examples of this technology is RNA interference (RNAi) for cancer diagnosis and therapy (Yoon et al., 2022). In this approach, plasmonic nanomaterials, such as gold or silver, are attached to mRNA and used to kill cancer cells through the process of heating them (given that gold and silver strongly absorb light) through a process called photothermal therapy. This research approach for the treatment of cancer is well underway in Korea, and new materials are in the process of exploration (Alkanli et al., 2023).

Another emerging technology using RNA as a therapeutic is siRNA. First, specially designed dsRNA (double-stranded RNA) is delivered into the human body (Dar et al., 2021). Next, an enzyme named Dicer will cut the dsRNA into several smaller siRNAs (silencing RNAs), each with a size of only around 21~23 nucleotides (nt). The newly formed siRNAs are able to form a complex with a protein called the Argonaute, which, when combined, is called the RISC complex. The entire RISC complex works as a silencer to cut off or silent target mRNA. Inside cells, the Dicer enzyme will load double-strand miRNA onto Argonaute protein (Pratt & MacRae, 2009). Then, RISC will unwind the miRNA, and drop one strand named passenger strand and keep another strand named guide strand (Deerberg et al., 2013). After this, RISC is activated. It will patrol and scan mRNAs in the cell. Once it finds any mRNA that is 100% matched with a

guide strand, Argonaute protein will slice the mRNA. If the mRNA is only partially matched, RISC will bind with this mRNA and prevent it from being translated (Iwakawa & Tomari, 2022).

While these technologies offer immense promise, they also require additional troubleshooting before they are ready for patient use. The central difficulty is that they require an immense amount of labor to generate the necessary components, because they must be individualized per patient. For example, miRNAs used to treat patient diseases must be produced such that they exactly mimic the structure of a naturally produced miRNA. If these miRNAs are too dissimilar from a naturally occurring mRNA, scientists risk activating the immune system of the patient and causing immune rejection, which can be fatal (Kotowska-Zimmer et al., 2022). Due to existing technical limitations, it is possible to produce isomers, or miRNAs with the same molecular formula that have a different structure, leading to a completely different function within the human body. This has the potential to be very dangerous, so additional research and troubleshooting are necessary to expand these methods so they are ready for patient use.

**Section 2: Spark Therapeutics (CRISPR-Cas approach)**

The other company working quickly to establish a treatment for Huntington's disease is Spark Therapeutics, located in Philadelphia, PA, USA. Their treatment approach involves directly editing the mutated HTT gene so that the HTT mRNA produced will not have the tandem repeats associated with Huntington's Disease. This approach relies heavily on CRISPR-Cas9.

CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) is the most advanced technology in gene editing at present. The CRISPR-Cas9 system uses a customized gRNA to scan the DNA looking for an exact complement to its sequence. Once found, the Cas9 nuclease induces a double-strand break (DSB) in the DNA at the location of interest. This can be used to achieve the inactivation of genes (gene knockdown), the removal of a gene (gene knockout), and the insertion of a different gene (insertion). While CRISPR-Cas9 is a great candidate for treating Huntington's disease, one major problem exists: how do we get the CRISPR-Cas9 components into the brain? To overcome this limitation, Spark Therapeutics has exerted two approaches. First, they developed new Cas9 proteins with smaller size. Traditional Cas9 is oversized and hard to go across the BBB, but the new Cas9 protein named SaCas9from staphylococcus aureus can be packed in single AAV perfectly, which is more efficient to be delivered (Dai et al., 2026). Second, they exerted a directed evolution on AAVs that will be used to deliver drugs for the purpose of letting AAV spread wider in patients' brains. They selected AAV kinds in Non-Human Primates (NHP) and found some AAVs that are efficient in infecting humans such as AAV Ep+. Those new AAV kinds can cover a larger scale of treatment in single injection, which allows the therapy to become more efficient (Tecedor et al., 2025).

CRISPR-Cas9 therapy has had immense success for treating life-threatening genetic diseases. First, Casgevy was the first ever FDA approved treatment for sickle cell disease in December of 2023. It is the therapy for reversing sickle cell disease and ß-thalassemia (Goswami et al., 2025). Scientists used CRISPR to cause an HPFH3 genotype (cut off HBD and HBB). HBB is an essential gene, mutations of which will cause ß-thalassemia, which prevents

the hemoglobin to progress from its neonatal form to its adult form, and sickle cell disease. Some people are born with the HPFH3 genotype, but some aren't, and the deletion of HBB and HBD is totally harmless (Goswami et al., 2025).

Second, scientists used CRISPR to cure Duchenne Muscular Dystrophy, which is a genetic muscular issue (Happi Mbakam et al., 2022). Humans contain a gene named the DMD gene. It is one of the biggest genes in the human body, and it produces a kind of protein named dystrophin in order to increase the strength of muscle cells. Some people don't have this gene, so when they contract their muscles, their muscle cells break. Most of them will die due to heart or breathing problems by 18-30 years old (Erkut & Yokota, 2022). So scientists used CRISPR to cut the problematic genetic part, then let the body repair it by itself. The best outcome was that 60% of the dystrophin expression ability was restored. Although the result and efficiency of this approach are not that stable, it provides us with huge development and direction guidelines (Chemello et al., 2023).

Regarding this approach, scientists have already gotten some results for the treatment of HTT, but are also facing some problems. One major result is the CRISPR-Cas13d technology (Hart et al., 2026). This technology will only cut RNA, instead of DNA. Scientists finished gRNA and off-target tests, HTT patients' cell tests, and rat tests; and the results were all better than they thought (Morelli et al., 2023). What's more, Cas13d can stay in body and work for a long period, so the cost will be lower (Treichel & Bazzini, 2022).

The second strategy utilizes the combination of PAM (Protospacer Adjacent Motif) and SNPs (single nucleotide polymorphisms) to reach allele-specified editing. The PAM sequence is a kind of identification tool. When Cas9 protein is sliding on DNA, PAM will be used to identify a kind of sequence such as NGG (N represents any kind of nucleotide from A, G, C, T) (Klanschnig et al., 2022). Only when it identifies the sequence successfully, the Cas9 protein will start working (Silverstein et al., 2025). For example, mHTT and the normal HTT gene are considerably homogeneous, only some special SNPs tend to occur between the two alleles. Due to the strict needs on a specific PAM sequence (e.g. NGG) of SpCas9 to activate DNA modification (Mojica et al., 2009), our alleles from both parents, one of the SNPs in an allele can produce a PAM, but another can't (Zhuang et al., 2025). The Spark Therapeutic then tested more than 8000 patients and confirmed some SNP points that can produce the PAM. They picked some SNP points, and made sure that the points would only produce one kind in the mHTT gene and another in the normal HTT gene, and finally, they located the kinds that will occur in mHTT and then cut off the whole mHTT gene sequence (Alkanli et al., 2023; Feng et al., 2025). However, this kind of technology is limited to be used on a considerably large scale due to the limitation of specificity. The general version of Cas9 protein,SaCas9, could cover a large variety of SNPs and can be used to treat a larger range of patients. But the SaCas9 has a backwardness that is its oversize and difficulty of delivery. Newly developed Cas9, SpCas9, is smaller and can be delivered into the brian more efficiently, but it loses parts of ability to cover patients as wide as SaCas9 do (Ran et al., 2015) (Yang et al., 2023).

Spark Therapeutics has successfully constructed a large-scale map for PAM-altering SNPs (PAS), which covers thousands of patients (Fang et al., 2023). Besides that, Spark Therapeutics operated an experiment successfully that the precision of PAS altering could be

extremely high because there was no off-target effect (Shin et al., 2022). They aim to cover around 60% to 70% of Europeans about their PAS points, and create a one-and-done therapy for patients (Fang et al., 2023).

**Section 3: Assessing Huntington's Disease Treatment Modalities**

There are several commonalities shared between UniQuire and Spark Therapeutics' approaches to treating Huntington's disease. For instance, both approaches aim to reduce the amount of hTT mRNA in the brain, thereby reducing the accumulation of the toxic protein within the brain, leading to the development of Huntington's disease. Secondly, both companies took a similar approach to increase target specificity and precision. In UniQuire's gene-lowering approach, target specificity relies on the natural mechanism of base pairing to target the hTT mRNA for degradation (Yao et al., 2024). Similarly, the CRISPR-Cas9 approach used by Spark Therapeutics uses a gRNA to find complementary *in vivo* DNA to target for direct editing. Both approaches rely on homology and complementarity to achieve the goal of reducing hTT protein buildup *in vivo.*

In addition to the mechanisms of action, sharing many core commonalities with respect to their biological function, there are shared delivery and mechanistic challenges. The BBB is one of the biggest hurdles to treating diseases located in the central nervous system. Spark Therapeutics' CRISPR-Cas9 approach faces many challenges: in normal cells, delivery may disrupt cell integrity (Aussel et al., 2025). When carriers attempt to enter cells, the cell membrane can sometimes be disrupted, resulting in decreased efficacy. However, both Spark Therapeutics and UniQuire have developed a similar design strategy in which the BBB is surpassed altogether. Through this approach, MRI technology is used to drill small holes into the skull and insert thin hollow tubes, called cannula, into the precise regions of the brain where the HTT gene is expressed. Next, the treatments are delivered into the thin cannula. In a Nature article published in October, 2025, the scientist Kostyk remarks that "it's not a minor procedure" (Dolgin, 2025). So, while this method may allow researchers to edit brain tissue, it is not a simple or trivial pursuit. Furthermore, the cost is a widely known concern of both of the two therapeutic strategies. High cost could be a huge obstacle for patients to use the two methods.

There are remarkable differences between these two approaches as well. Both therapeutic approaches act on different molecular targets. UniQure's gene-lowering approach targets mRNA. Some argue that targeting the mRNA instead of the DNA is a safer strategy because its effects are reversible, reducing concerns about irreversible and risky outcomes that come with permanently changing the DNA sequence using CRISPR-Cas9 (Bhati et al., 2025; Ghosh & Tabrizi, 2017). Spark Therapeutics, on the other hand, uses gRNAs to target particular sequences and induce mutations using CRISPR-Cas9. This approach may be more convenient, as only a single treatment may cure, or at least significantly reduce the disease burden (Bao et al., 2026). However, it is extremely risky because the process is irreversible. If off-target effects occur, patients may suffer unknown and potentially severe mutations, particularly given that no longitudinal studies have been done to monitor long-term side effects of CRISPR-Cas9 treatments, given the novelty of the technology.

Moreover, the durability of the two approaches also differs. Gene-lowering approaches provide reversible therapy, so durability is limited—sometimes relatively short—depending on the condition and technique used. For example, uniQure's AMT-130 offers effects lasting nearly 30 months, or over two years, per administration (Mwape et al., 2026). On the other hand, CRISPR-based treatments offer nearly permanent durability. By modifying DNA, which is stably replicated, the effects persist (Cohn et al., 2025). This is convenient and comfortable for patients, avoiding repeated MRI cannula brain injections. However, this permanence also means that if modifications go wrong, the resulting issues may be difficult to correct. Although there are only two methods on the way from now, they give patients all around the world large hope, encourage patients to keep conflicting with Huntington's disease and never give up.

**Conclusion**

A disease once thought to be nearly impossible to treat, Huntington's disease now has two promising treatment approaches. Once thought of as a near impossibility, the treatment of the first ever patient with Huntington's disease in late 2025 marks an incredible turning point in our ability to treat neurological diseases (Dolgin, 2025).

Promising results have been seen through two different approaches: targeting DNA or mRNA. While each presents its own challenges and benefits, additional research is necessary to fully elucidate the safety and efficacy of these treatments over time. In both cases, immune responses, off-target effects, and delivery methods must be carefully monitored to ensure the best patient outcomes. Advancements in this technology will not only benefit CRISPR and gene-lowering technologies but will also impact all forms of in vivo drug delivery. Furthermore, the need for accuracy can better ensure patient safety and guarantee that each treatment produces a positive effect. These two technologies still have a long way to go, but clarifying the direction of development will make technological progress more efficient and clearer.

The development of the drugs for the treatment of Huntintgon's disease could be an extremely conducive deal. Thousands of families are suffering from Huntington's disease every single year. The success of this sort of technology could be life-saving for all patients of Huntington's disease in the world.

**Reference**

Alkanli, S. S., Alkanli, N., Ay, A., & Albeniz, I. (2023). CRISPR/Cas9 Mediated Therapeutic Approach in Huntington's Disease. *Molecular Neurobiology*, *60*(3), 1486–1498. https://doi.org/10.1007/s12035-022-03150-5

Andriessen, R. L., Oosterloo, M., Molema, J., Daemen, M. M. J., Linden, D. E. J., & Leentjens, A. F. G. (2025). Pharmacological Treatment of Neuropsychiatric Symptoms in Huntington's Disease: A Systematic Review. *Movement Disorders Clinical Practice*, *12*(4), 418–431. https://doi.org/10.1002/mdc3.14343

Bao, C., Channell, C. I., Tseng, Y. H., Bailey, J., Sbaiti, N., Demirkol, A., & Tsang, S. H. (2026). Chronic In Vivo CRISPR-Cas Genome Editing: Challenges, Long-Term Safety, and Outlook. *Cells*, *15*(2), 156. https://doi.org/10.3390/cells15020156

Belgrad, J., Summers, A., Landles, C., Greene, J. R., Hildebrand, S., Knox, E., Sapp, E., Yamada, N., Furgal, R., Miller, R., Osborne, G. F., Chase, K., Luu, E., Freedman, J., Bramato, B., McHugh, N., Benoit, V., O'Reilly, D., Greer, P., … Khvorova, A. (2025). Blocking somatic repeat expansion and lowering huntingtin via RNA interference synergize to prevent Huntington's disease pathogenesis in mice. *bioRxiv: The Preprint Server for Biology*, 2025.06.24.661398. https://doi.org/10.1101/2025.06.24.661398

Bhati, V., Prasad, S., & Kabra, A. (2025). RNA-based therapies for neurodegenerative disease: Targeting molecular mechanisms for disease modification. *Molecular and Cellular Neurosciences*, *133*, 104010. https://doi.org/10.1016/j.mcn.2025.104010

Byrne, L. M., Schultz, J. L., Rodrigues, F. B., van der Plas, E., Langbehn, D., Nopoulos, P. C., & Wild, E. J. (2022). Neurofilament Light Protein as a Potential Blood Biomarker for Huntington's Disease in Children. *Movement Disorders: Official Journal of the Movement Disorder Society*, *37*(7), 1526–1531. https://doi.org/10.1002/mds.29027

Chemello, F., Olson, E. N., & Bassel-Duby, R. (2023). CRISPR-Editing Therapy for Duchenne Muscular Dystrophy. *Human Gene Therapy*, *34*(9–10), 379–387. https://doi.org/10.1089/hum.2023.053

Chen, Y., Sun, X., Xi, Y., Luo, Z., Lai, H., Zhu, D., Zhang, Y., Xu, F., Li, J., Zhou, J., Ding, Y., & Zhang, H. (2025). Pathology-directed drug delivery strategies: How to overcome blood–brain barrier for the treatment of brain diseases. *Acta Pharmaceutica Sinica B*. https://doi.org/10.1016/j.apsb.2025.10.016

Cohn, D. M., Gurugama, P., Magerl, M., Katelaris, C. H., Launay, D., Bouillet, L., Petersen, R. S., Lindsay, K., Aygören-Pürsün, E., Maag, D., Butler, J. S., Shah, M. Y., Golden, A., Xu, Y., Abdelhady, A. M., Lebwohl, D., & Longhurst, H. J. (2025). CRISPR-Based Therapy for Hereditary Angioedema. *The New England Journal of Medicine*, *392*(5), 458–467. https://doi.org/10.1056/NEJMoa2405734

Coppens, S., Lehmann, S., Hopley, C., & Hirtz, C. (2023). Neurofilament-Light, a Promising Biomarker: Analytical, Metrological and Clinical Challenges. *International Journal of Molecular Sciences*, *24*(14), 11624. https://doi.org/10.3390/ijms241411624

Dai, Y., Abudujielili, Z., Ding, Y., Huang, W., Yin, J., Ou, L., Hu, J., Zheng, S., & Li, C. (2026). Self-inactivating AAV-CRISPR at different ages enables sustained amelioration of Huntington's disease deficits in BAC226Q mice. *Science Advances*, *12*(12), eaea8052. https://doi.org/10.1126/sciadv.aea8052

Dar, G. H., Mendes, C. C., Kuan, W.-L., Speciale, A. A., Conceição, M., Görgens, A., Uliyakina, I., Lobo, M. J., Lim, W. F., El Andaloussi, S., Mäger, I., Roberts, T. C., Barker, R. A., Goberdhan, D. C. I., Wilson, C., & Wood, M. J. A. (2021). GAPDH controls extracellular vesicle biogenesis and enhances the therapeutic potential of EV mediated siRNA delivery to the brain. *Nature Communications*, *12*(1), 6666. https://doi.org/10.1038/s41467-021-27056-3

Deerberg, A., Willkomm, S., & Restle, T. (2013). Minimal mechanistic model of siRNA-dependent target RNA slicing by recombinant human Argonaute 2 protein. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(44), 17850–17855. https://doi.org/10.1073/pnas.1217838110

Dolgin, E. (2025). Huntington's disease treated for first time using gene therapy. *Nature*, *646*(8083), 15–15. https://doi.org/10.1038/d41586-025-03139-9

Erkut, E., & Yokota, T. (2022). CRISPR Therapeutics for Duchenne Muscular Dystrophy. *International Journal of Molecular Sciences*, *23*(3), 1832. https://doi.org/10.3390/ijms23031832

Evers, M. M., Miniarikova, J., Juhas, S., Vallès, A., Bohuslavova, B., Juhasova, J., Skalnikova, H. K., Vodicka, P., Valekova, I., Brouwers, C., Blits, B., Lubelski, J., Kovarova, H., Ellederova, Z., van Deventer, S. J., Petry, H., Motlik, J., & Konstantinova, P. (2018). AAV5-miHTT Gene Therapy Demonstrates Broad Distribution and Strong Human Mutant Huntingtin Lowering in a Huntington's Disease Minipig Model. *Molecular Therapy: The Journal of the American Society of Gene Therapy*, *26*(9), 2163–2177. https://doi.org/10.1016/j.ymthe.2018.06.021

Fang, L., Monteys, A. M., Dürr, A., Keiser, M., Cheng, C., Harapanahalli, A., Gonzalez-Alegre, P., Davidson, B. L., & Wang, K. (2023). Haplotyping SNPs for allele-specific gene editing of the expanded huntingtin allele using long-read sequencing. *HGG Advances*, *4*(1), 100146. https://doi.org/10.1016/j.xhgg.2022.100146

Farag, M., Knights, H., Scahill, R. I., McColgan, P., & Estevez-Fraga, C. (2025). Neuroimaging Techniques in Huntington's Disease: A Critical Review. *Movement Disorders Clinical Practice*, *12*(5), 561–576. https://doi.org/10.1002/mdc3.70010

Feng, Y., Shi, J., Li, Z., Li, Y., Yang, J., Huang, S., Zheng, J., Han, W., Qiao, Y., Zhang, J., Liu, Q., Yang, Y., Hu, C., Wu, L., Zhang, X., Tang, J., Huang, X., & Ma, P. (2025). Discovery of CRISPR-Cas12a clades using a large language model. *Nature Communications*, *16*(1), 7877. https://doi.org/10.1038/s41467-025-63160-4

Fields, E., Vaughan, E., Tripu, D., Lim, I., Shrout, K., Conway, J., Salib, N., Lee, Y., Dhamsania, A., Jacobsen, M., Woo, A., Xue, H., & Cao, K. (2021). Gene targeting techniques for Huntington's disease. *Ageing Research Reviews*, *70*, 101385. https://doi.org/10.1016/j.arr.2021.101385

Fihurka, O., Aradi, S., Sava, V., & Sanchez-Ramos, J. (2023). Key Features in the Design and Function of Nanocarriers for Intranasal Administration of Gene Therapy in Huntington Disease. *Journal of Nanotechnology and Nanomaterials*, *4*(2), 55–69. https://doi.org/10.33696/nanotechnol.4.043

Ghosh, R., & Tabrizi, S. J. (2017). Gene suppression approaches to neurodegeneration. *Alzheimer's Research & Therapy*, *9*(1), 82. https://doi.org/10.1186/s13195-017-0307-1

Goswami, S. G., Gupta, P., Arvinden, V. R., Bhargava, N., Iyer, A. R., Saravanakumar, V., Yadav, P., Jha, S. K., Singh, S., Kumar, A., Singh, P., Gunda, P., Jain, S., Mehta, P., Nakamura, Y., Kurita, R., Bajaj, A., & Ramalingam, S. (2025). CRISPR editing of HPFH3 genotype induces γ-globin expression and reverses sickle cell disease and β-thalassemia phenotypes. *Stem Cell Research & Therapy*, *17*(1), 46. https://doi.org/10.1186/s13287-025-04582-1

Happi Mbakam, C., Lamothe, G., Tremblay, G., & Tremblay, J. P. (2022). CRISPR-Cas9 Gene Therapy for Duchenne Muscular Dystrophy. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *19*(3), 931–941. https://doi.org/10.1007/s13311-022-01197-9

Hart, S. K., Müller, S., Wessels, H.-H., Méndez-Mancilla, A., Drabavicius, G., Choi, O., & Sanjana, N. E. (2026). Precise RNA targeting with CRISPR-Cas13d. *Nature Biotechnology*, *44*(1), 64–69. https://doi.org/10.1038/s41587-025-02558-3

Iwakawa, H.-O., & Tomari, Y. (2022). Life of RISC: Formation, action, and degradation of RNA-induced silencing complex. *Molecular Cell*, *82*(1), 30–43. https://doi.org/10.1016/j.molcel.2021.11.026

Klanschnig, M., Cserjan-Puschmann, M., Striedner, G., & Grabherr, R. (2022). CRISPRactivation-SMS, a message for PAM sequence independent gene up-regulation in Escherichia coli. *Nucleic Acids Research*, *50*(18), 10772–10784. https://doi.org/10.1093/nar/gkac804

Kotowska-Zimmer, A., Przybyl, L., Pewinska, M., Suszynska-Zajczyk, J., Wronka, D., Figiel, M., & Olejniczak, M. (2022). A CAG repeat-targeting artificial miRNA lowers the mutant huntingtin level in the YAC128 model of Huntington's disease. *Molecular Therapy. Nucleic Acids*, *28*, 702–715. https://doi.org/10.1016/j.omtn.2022.04.031

Lepinay, E., & Cicchetti, F. (2023). Tau: A biomarker of Huntington's disease. *Molecular Psychiatry*, *28*(10), 4070–4083. https://doi.org/10.1038/s41380-023-02230-9

Ling, S., Zhang, X., Dai, Y., Jiang, Z., Zhou, X., Lu, S., Qian, X., Liu, J., Selfjord, N., Satir, T. M., Lundin, A., Touza, J. L., Firth, M., Van Zuydam, N., Bilican, B., Akcakaya, P., Hong, J., & Cai, Y. (2025). Customizable virus-like particles deliver CRISPR-Cas9 ribonucleoprotein for effective ocular neovascular and Huntington's disease gene therapy. *Nature Nanotechnology*, *20*(4), 543–553. https://doi.org/10.1038/s41565-024-01851-7

Mehanna, R., & Jankovic, J. (2024). Systemic Symptoms in Huntington's Disease: A Comprehensive Review. *Movement Disorders Clinical Practice*, *11*(5), 453–464. https://doi.org/10.1002/mdc3.14029

Mestre, T. A., Forjaz, M. J., Mahlknecht, P., Cardoso, F., Ferreira, J. J., Reilmann, R., Sampaio, C., Goetz, C. G., Cubo, E., Martinez-Martin, P., & Stebbins, G. T. (2018). Rating Scales for Motor Symptoms and Signs in Huntington's Disease: Critique and Recommendations. *Movement Disorders Clinical Practice*, *5*(2), 111–117. https://doi.org/10.1002/mdc3.12571

Mojica, F. J. M., Díez-Villaseñor, C., García-Martínez, J., & Almendros, C. (2009). Short motif sequences determine the targets of the prokaryotic CRISPR defence system. *Microbiology*, *155*(Pt 3), 733–740. https://doi.org/10.1099/mic.0.023960-0

Morelli, K. H., Wu, Q., Gosztyla, M. L., Liu, H., Yao, M., Zhang, C., Chen, J., Marina, R. J., Lee, K., Jones, K. L., Huang, M. Y., Li, A., Smith-Geater, C., Thompson, L. M., Duan, W., & Yeo, G. W. (2023). An RNA-targeting CRISPR-Cas13d system alleviates disease-related phenotypes in Huntington's disease models. *Nature Neuroscience*, *26*(1), 27–38. https://doi.org/10.1038/s41593-022-01207-1

Mühlbäck, A., Hoffmann, R., Pozzi, N. G., Marziniak, M., Brieger, P., Dose, M., & Priller, J. (2024). [Psychiatric symptoms of Huntington's disease]. *Der Nervenarzt*, *95*(9), 871–884. https://doi.org/10.1007/s00115-024-01728-z

Mwape, C., Qureshi, A. A., Saeed, M. Z., Fatima, A., Jamil, A., Mahmood, H., Batool, A., & Khan, A. M. (2026). AMT-130 gene therapy: A promising disease-modifying approach for Huntington's disease. *Annals of Medicine and Surgery*, *88*(1), 1144. https://doi.org/10.1097/MS9.0000000000004574

Palaiogeorgou, A. M., Papakonstantinou, E., Golfinopoulou, R., Sigala, M., Mitsis, T., Papageorgiou, L., Diakou, I., Pierouli, K., Dragoumani, K., Spandidos, D. A., Bacopoulou, F., Chrousos, G. P., Eliopoulos, E., & Vlachakis, D. (2023). Recent approaches on Huntington's disease (Review). *Biomedical Reports*, *18*(1), 5. https://doi.org/10.3892/br.2022.1587

Pratt, A. J., & MacRae, I. J. (2009). The RNA-induced silencing complex: A versatile gene-silencing machine. *The Journal of Biological Chemistry*, *284*(27), 17897–17901. https://doi.org/10.1074/jbc.R900012200

Przybyl, L., Wozna-Wysocka, M., Kozlowska, E., & Fiszer, A. (2021). What, When and How to Measure-Peripheral Biomarkers in Therapy of Huntington's Disease. *International Journal of Molecular Sciences*, *22*(4), 1561. https://doi.org/10.3390/ijms22041561

Ran, F. A., Cong, L., Yan, W. X., Scott, D. A., Gootenberg, J. S., Kriz, A. J., Zetsche, B., Shalem, O., Wu, X., Makarova, K. S., Koonin, E. V., Sharp, P. A., & Zhang, F. (2015). In vivo genome editing using Staphylococcus aureus Cas9. *Nature*, *520*(7546), 186–191. https://doi.org/10.1038/nature14299

Shin, J. W., Hong, E. P., Park, S. S., Choi, D. E., Seong, I. S., Whittaker, M. N., Kleinstiver, B. P., Chen, R. Z., & Lee, J.-M. (2022). Allele-specific silencing of the gain-of-function mutation in Huntington's disease using CRISPR/Cas9. *JCI Insight*, *7*(19), e141042. https://doi.org/10.1172/jci.insight.141042

Silverstein, R. A., Kim, N., Kroell, A.-S., Walton, R. T., Delano, J., Butcher, R. M., Pacesa, M., Smith, B. K., Christie, K. A., Ha, L. L., Meis, R. J., Clark, A. B., Spinner, A. D., Lazzarotto, C. R., Li, Y., Matsubara, A., Urbina, E. O., Dahl, G. A., Correia, B. E., … Kleinstiver, B. P. (2025). Custom CRISPR-Cas9 PAM variants via scalable engineering and machine learning. *Nature*, *643*(8071), 539–550. https://doi.org/10.1038/s41586-025-09021-y

Tecedor, L., Chen, Y. H., Leib, D. E., Ranum, P. T., Keiser, M. S., Lewandowski, B. C., Carrell, E. M., Lysenko, E., Huerta-Ocampo, I., Arora, S., Cheng, C., Liu, X., & Davidson, B. L. (2025). An AAV variant selected through NHP screens robustly transduces the brain and drives secreted protein expression in NHPs and mice. *Science Translational Medicine*, *17*(798), eadr2531. https://doi.org/10.1126/scitranslmed.adr2531

Tong, H., Xu, S., Li, X., Liu, L., Zhou, G., Yang, S., Yin, S., Li, X.-J., & Li, S. (2024). Huntington's Disease: Complex Pathogenesis and Therapeutic Strategies. *International Journal of Molecular Sciences*, *25*(7), 3845. https://doi.org/10.3390/ijms25073845

Treichel, A. J., & Bazzini, A. A. (2022). Casting CRISPR-Cas13d to fish for microprotein functions in animal development. *iScience*, *25*(12), 105547. https://doi.org/10.1016/j.isci.2022.105547

Vignone, D., Gonzalez Paz, O., Fini, I., Cellucci, A., Auciello, G., Battista, M. R., Gloaguen, I., Fortuni, S., Cariulo, C., Khetarpal, V., Dominguez, C., Muñoz-Sanjuán, I., & Di Marco, A. (2022). Modelling the Human Blood-Brain Barrier in Huntington Disease. *International Journal of Molecular Sciences*, *23*(14), 7813. https://doi.org/10.3390/ijms23147813

Yang, Z.-X., Fu, Y.-W., Zhao, J.-J., Zhang, F., Li, S.-A., Zhao, M., Wen, W., Zhang, L., Cheng, T., Zhang, J.-P., & Zhang, X.-B. (2023). Superior Fidelity and Distinct Editing Outcomes of SaCas9 Compared with SpCas9 in Genome Editing. *Genomics, Proteomics & Bioinformatics*, *21*(6), 1206–1220. https://doi.org/10.1016/j.gpb.2022.12.003

Yoon, J., Shin, M., Lee, J.-Y., Lee, S.-N., Choi, J.-H., & Choi, J.-W. (2022). RNA interference (RNAi)-based plasmonic nanomaterials for cancer diagnosis and therapy. *Journal of Controlled Release: Official Journal of the Controlled Release Society*, *342*, 228–240. https://doi.org/10.1016/j.jconrel.2022.01.012

Zhuang, S., Bai, B., & Liu, Y. (2025). CRISPR-based SNP detection technologies advance from classical methods to cutting-edge innovations. *Chemical Communications*, *61*(71), 13345–13358. https://doi.org/10.1039/d5cc03655k