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AMT-130: The First Gene Therapy for Huntington's Disease

Gene therapy, first used in 1990, is a type of treatment for genetic disorders that works in one of the following three ways: gene addition, gene editing, and gene silencing [1, 2]. Today, gene therapy is used to treat conditions like blood disorders, blood vessel and heart disease, cancer, infectious diseases, and neurological disorders [3]. In 2025, the first gene therapy for Huntington's disease (HD) was developed [4].

HD is an autosomal dominant neurodegenerative disorder caused by cytosine-adenine-guanine (CAG) trinucleotide repeats occurring 40 to 120 times—whereas they normally range from 10 to 35 repeats—in the huntingtin (HTT) gene, which leads to the production of an abnormally long version of the huntingtin protein [5]. At the beginning of 2025, only medications that could help alleviate the symptoms associated with HD existed. However, in September of that year, a University College London (UCL) research group announced the first gene silencing therapy for HD, called AMT-130 [4].

The gene therapy AMT-130 uses a one-time infusion of an adeno-associated virus 5 (AAV5) vector encoding an engineered microRNA for the HTT gene (miHTT). That AAV5 vector is designed to reduce HTT mRNA levels and, consequently, huntingtin protein levels. The first step is to deliver the AAV5 vector to the caudate nucleus and the putamen via neurosurgery using real-time MRI scanning. Once the AAV5 vector transduces neurons, the endogenous

machinery expresses miHTT, which in turn binds to partially complementary HTT mRNA and prevents its translation into the huntingtin protein by promoting its degradation through endogenous enzymes. As a result, overall huntingtin protein levels decrease, slowing HD progression by up to 75%. This means that the cognitive decline you would expect to experience in one year would actually take four years, ultimately increasing life expectancy [5].

A key advantage of AMT-130 is it requires one neurosurgery for visible impact, while enabling lasting transduction of vulnerable neurons. However, the most common disadvantages of AMT-130 are from the surgical procedure itself [5]. Not only does the surgery last between twelve and eighteen hours, but it also costs $1-4 million per patient before insurance [4, 6]. Further, several side effects associated with the surgical procedure include epistaxis, major depression, postoperative delirium, and suicidal ideation. Moreover, the side effects from the gene therapy itself include central nervous system inflammation and severe headaches. Nonetheless, patients with central nervous system inflammation improved with glucocorticoid medication [5].

If I or someone I care about had HD, I would consider AMT-130, but my decision would strongly depend on the stage of HD the person had. If this person were in the early stage (largely functional with symptoms including minor involuntary movements) of HD, I would choose AMT-130; however, if this person were in the middle (somewhat functional) to late (nonfunctional) stage of HD, I would not choose AMT-130 [7]. In the early stage of HD, although the surgery has its costs and risks, they are justified if the procedure can prevent death by HD. At this stage, not enough damage, like neuron death, has occurred, so AMT-130 would help slow HD progression, allowing patients to live a longer and healthier life. Nonetheless, in the middle to late stage of HD, enough damage has already been done. Since AMT-130 does not

reverse neuron death, I would encourage patients to spend their remaining time with loved ones rather than recovering from the surgical procedure.

My grandmother's Parkinson's disease shapes this view. She is currently in the late stage of the disease, and the medication she takes for her tremor makes her so nauseous she can barely be present when she is with me. Watching her trade the ability to interact with others for a treatment that does not give her her life back makes me nervous about aggressive treatments in the middle to late stages of neurodegenerative disorders. So if someone I loved were in the middle to late stages of HD, I would rather help them savor whatever authentic moments they have left than ask them to spend those moments in recovery, even if that meant saying goodbye sooner.

The recent announcement of the AMT-130 gene therapy for HD is very promising. It is currently the best option for slowing HD progression, especially in early-stage patients who can increase their life expectancy. Ultimately, AMT-130 not only shifts HD treatment from purely alleviating symptoms toward real disease modification, but it also paves the way for microRNA-based gene therapy as a powerful strategy for other neurodegenerative diseases [5].

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