Are Genetic Tweaks Made by Gene Therapy Handed Down to Offspring?

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The possibility of finding a treatment or even a cure for genetic disorders such as muscular dystrophy or hemophilia has taken a giant leap forward in recent years with the advent of gene therapy as a way to modify a defective gene or group of genes.

But would those changes be handed down to that person’s offspring?

In general the answer is no, except in a very specific circumstance that isn’t being pursued by pharmaceutical researchers as a potential therapy. But to understand why

those genetic changes are not handed down, we must first grasp how gene therapy works.

How Gene Therapy Works

The general approach of gene therapy is to deliver a functioning copy of a gene to cells that are diseased because they lack that functioning gene. In those cells, the gene is then used as a blueprint to create the missing or non-functioning protein encoded by that gene. And while the concept is simple — deliver genes to cells so they can make the right proteins — a significant practical hurdle has been how to deliver that genetic material (DNA or RNA) to the appropriate cells within the affected organs or tissues.

One common method of delivery is to use a type of non-harmful virus called adeno-associated virus (AAV) as the vector. An AAV particle is made up of two parts: a hollow protein ball called the “capsid” that serves as a sort of GPS-guided delivery system, and the genetic material that is contained inside as cargo. In the case of a gene therapy vector, the viral genes that are required for AAV to replicate are replaced with the therapeutic gene.

When it comes to gene therapy, there’s one characteristic of using an AAV as the vector that can make it useful or not so useful, depending on what kind of tissue you’re trying to modify.

“With AAV, the gene that’s being delivered doesn’t integrate into the genome. It exists as a piece of DNA that sits outside of the genome,” says Sharon Hesterlee, Director of Gene Therapy in Pfizer’s Rare Disease Research Unit. “In the body, the cells continue to use it to make proteins, but if the cells divide a lot, like in blood disorders, you would dilute and lose that effect. Non-integrating vectors like AAV are mostly used to deliver genes to muscle tissue, brain tissue — tissues with cells that don’t divide very much.”

Another vector being investigated as a delivery method is the lentivirus — a group of retroviruses that also includes HIV. “These viruses integrate into the DNA, which is a nice permanent fix. And because of that, she explains, “If you have a target tissue with actively dividing cells, like blood, you want to use an integrating virus like lentivirus, because it’s integrated into the genome and copied with each cell division.”

That trait of lentivirus may pose a risk that the corrected gene could integrate where it wasn’t intended to, such as into an oncogene, a gene with the potential to cause cancer. But, Hesterlee explains, “lentivirus trials take an ex vivo approach to try to avoid that risk.” That is, the virus carrying the corrected gene is delivered to a sample of the target

cells in a lab before adding those cells into a patient, thus ensuring that the gene is only integrated into the intended site.

However, just because lentivirus is integrated into the genome, that doesn't mean it is handed down to the offspring. For that to happen, the changes to the genome must be made to what is known as the germline — that is, cells that produce eggs or sperm, Hesterlee explains. "There is a miniscule possibility of that happening," says Hesterlee, "because the ex-vivo approach of lentivirus trials means that 'free' virus isn't inserted directly into patients."

Why Making Changes to the Germline Isn't Being Actively Pursued

While the technology currently exists to perform germline editing — that is, gene editing that occurs within sex cells and could then be handed down to an offspring — it's not something that's being widely pursued for various reasons, including a lack of information on the full extent of risks and benefits and the fact that future generations can't give consent to changes being made, even if the reason to perform germline editing is to edit out a serious genetic disease forever.

In a paper in the journal Nature in early August, researchers in Oregon reported using CRISPR-Cas9 gene editing technology to successfully alter viable human embryos at the four to eight cell stage to eliminate a mutation that often causes hypertrophic cardiomyopathy, a type of heart failure. But the research sparked further discussion about the ethics of germline editing.

"Even doing gene editing to correct a genetic disease — we're just not there yet, thinking through the ethics and morality of it," Hesterlee said of the prevailing sentiment in the biomedical field. "With germline editing, the technology is still in its infancy compared to something like gene therapy using AAV. And furthermore, there are still many ethical questions that we must address collectively as a society."

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