

Hi, I'm Jen Phillips, and this is USH TALKs. Today, I'm going to give you a crash course in Gene Therapy 101 and address some of the most common questions people have on this topic. We'll talk about what gene therapy is, how it works, who it's for, and when it might be available.

So let's dive right in with the first question-- what is gene therapy? In general terms, it's a medical intervention that's designed to treat the genetic cause of a disease. Humans have tens of thousands of genes, each of which encodes instructions for use in chemical building blocks to assemble a functional molecule. In most cases, this functional molecule is a protein.

In this cartoon, I'm illustrating the coding region of a normal gene by a series of green circles. The information in this code is read and translated into a protein of a prescribed shape and size, which then goes on to have some important function, for example, in vision. However, if there is a mistake in the instructions, then the shape and function of the resulting protein are affected and this is the basis of genetic disease. The goal of gene therapy is to try to figure out ways of restoring that normal protein form and function by addressing the problem at its source, which is at the genetic code or as part of the translation process.

So how does this work? Basically, there are three main ways that people are working on to try to approach gene therapy. The first way is to provide a replacement copy of the instructions, basically delivering a healthy copy of the gene to the appropriate body tissue so that it, instead of the native incorrect instructions, will be used to build a protein. And then, hopefully, that protein will be able to correct some of the damage that was done by having an incorrect protein there for as long as it's been.

A second way people are approaching this is figuring out ways to read past the error. The genetic information is arranged linearly, which goes from upstream on the left to downstream on the right. But during the process of translation, there are a few time points where an intervention could happen that would help being able to just skip over that bad part and proceed past it toward the good protein coding information on the other side of the mistake.

The third, and newest way, is also the most direct way. And in this scenario, it's repairing the error at the source, basically swapping out the bad information for the good and restoring the ability of the native gene to be able to code for a normal, functional protein. And the therapeutic approach that's chosen for a particular type of disease or a particular type of gene is going to vary depending on a lot of different details.

So moving on, who is gene therapy for? Well, there are a couple of criteria that are important for considering hypothetical gene therapy in the first place. Targeted therapy for a specific gene is only going to work in a person

who has a disorder in which that particular gene has been identified. Now in a complex disorder, like Usher Syndrome, that can be caused by mutations in many different genes, it's really important to have a genetic diagnosis to know which gene is affected in your particular case and which gene therapy might be appropriate for you.

Secondly, it's important to monitor the progress of your condition so that you know, for example, how far your vision loss has progressed. There are certain therapies that may be more or less appropriate depending on these conditions, so it's very important to stay in touch with how things are progressing and know which therapy is right for you when they do become available. Probably the most common question I get about gene therapy is, when will a treatment be available for me? So the process of going from preliminary research to an effective medical treatment that's available in your doctor's office is a very long one.

Research from a number of different fields can inform preclinical studies that are addressing a particular approach to gene therapy. Some of these may pan out to the point where they can enter into clinical trials, which go in multiphase ways, and only a few of the things that actually enter clinical trials typically are going to end up being available in your doctor's office. So there is definitely a winnowing process, but that means it's more important than ever to increase the input into the first ends so that there will be more options available on the other end of things.

Regarding Usher Syndrome, there is currently one clinical trial underway right now that's a gene therapy to treat Usher Syndrome type 1B. The approach that they're using is the first one that I described where it's a gene replacement therapy designed to supply patients with a better copy of the USH1B gene than what they were born with. In addition to this, we don't know the outcome of this yet so we don't know when it will be available for patients with Usher type 1B.

Additionally, a lot of research is happening all around the world exploring gene therapies of different types for virtually all the different kinds of Usher syndrome. So we'll need to see significant preclinical success in order for any of those things to advance to clinical trials, but a lot of good people are working on it and there are lots of good reasons to remain hopeful. I know that the waiting is really hard, even as this work is underway, so there are a few things that you can do while you wait to make sure that you're in the best possible position when a gene therapy does become available.

First of all, as we discussed, know your genotype. Second of all, continue to monitor your condition, especially your vision. And finally, stay connected with the Usher family through the USH Trust and the Blue Book so that you'll be the first to know when something comes your way that might be effective. Until next time, this is Jen Phillips for USH TALKs.

