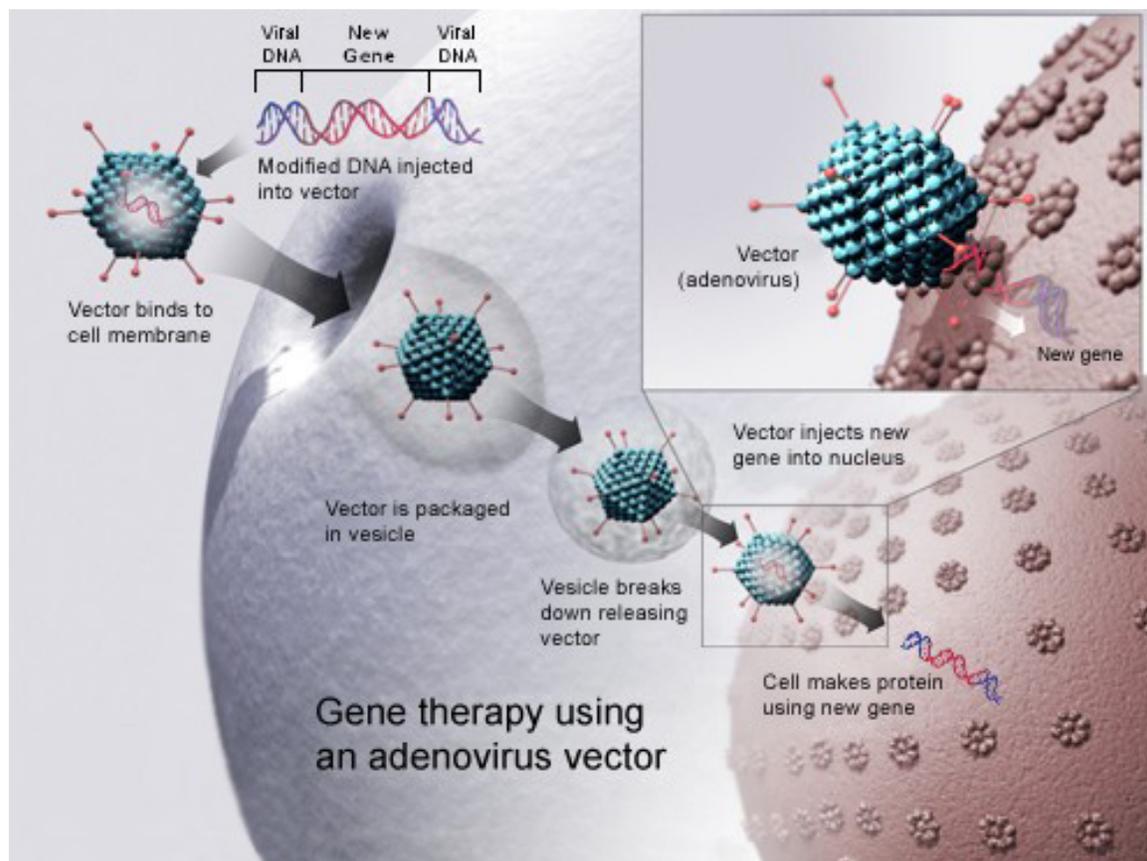


Ethical Considerations in Phase I studies: Gelsinger Case

Gene Therapy Clinical Trial

This case study focuses on a Phase I gene therapy trial conducted at the University of Pennsylvania (UPenn) in 1999. Gene therapy is a therapeutic technique that uses DNA as a pharmaceutical agent to treat or prevent disease¹. When the concept was introduced in 1972, it was received with enormous excitement because of its potential to treat diseases that standard drug therapy and surgery could not. In 1990, the first FDA-approved gene therapy experiment in the United States was conducted for the treatment of [adenosine deaminase deficiency](#). So in 1999, when the clinical trial at UPenn began, gene therapy research was still in its infancy.



** One method for delivering a gene therapy is to package the DNA that encodes a therapeutic protein into “vectors” (usually lentivirus- and adenovirus-based) and transfer these “vectors” into cells. The products of the therapeutic proteins are designed to correct the effects of the mutation that causes the targeted disease.*

Dr. James M. Wilson (University of Pennsylvania Research Team)

Dr. James M. Wilson was the co-investigator and sponsor of this gene therapy clinical trial. At the time of the trial, Wilson was one of the leading gene therapy researchers in the world: he was director of the Institute of Human Gene Therapy and professor and

chair of the Department of Molecular and Cellular Engineering in UPenn's School of Medicine.

Prior to his move to UPenn, Dr. Wilson had founded Genovo Inc., which had the rights to market his discoveries related to gene transfer². By 1999, Genovo had provided more than \$4 million a year to the Institute. Dr. Wilson and his family had a 30% nonvoting equity stake in Genovo and UPenn had a 3.2% equity stake³. In 1994, UPenn's Conflict of Interest Standing Committee had reviewed Wilson's involvement with Genovo. They conducted a detailed investigation and raised some important concerns, ultimately concluding that Wilson's research program could lead to important medical advances that could benefit the public. UPenn did not seek to end Dr. Wilson's financial arrangements with the company.

Clinical Trial Design

Dr. Wilson and his colleagues designed a Phase 1 trial to test the safety of an adenoviral gene therapy being developed by Genovo for treatment of ornithine transcarbamylase (OTC) deficiency, a rare X-linked genetic disease of the liver that interferes with the metabolism of ammonia. Complete OTC deficiency usually leads to death during infancy. Recognizing the additional ethical issues that arise in studies of children, the researchers decided to conduct the Phase 1 study in adults with partial OTC.

The protocol was reviewed and approved by several oversight bodies including the United States Food and Drug Administration, and human subjects review boards at both UPenn Medical Center and Children's Hospital of Philadelphia. The informed consent document cited risks related to liver injury with a 1 in 10,000 risk of serious unpredicted complications that could include death. The informed consent document also included a one-sentence statement about Dr. Wilson's relationship with Genovo: "Please be aware that Dr. James M. Wilson and Genovo Inc. have a financial interest in a successful outcome from the research involved in this study."⁴

Jesse Gelsinger

As a young child, Jesse was diagnosed with partial OTC. Despite suffering from a few episodes of hyperammonemia (excess ammonia in blood) throughout his life, by early 1999 his disease was controlled by strict adherence to a low-protein diet and cocktail medication regime comprising 32 pills a day.

Gelsinger had wanted to enroll in the Phase 1 trial when he first learned about it from his physician at age 17 but had to wait until he was of consenting age. When he signed up for the trial at the UPenn just 4 days past his 18th birthday, he knew that he would most likely not benefit from the treatment; after all, the goal of the trial was to test safety. However, Gelsinger was excited about the promise of this therapy. During a late night talk with his father just days before the trial, Gelsinger had said: "The worst that could happen is that I could die and maybe help doctors figure out a way to save sick babies."⁵

Gelsinger was the last of 18 volunteers to be enrolled in the trial. On the day of his adenoviral infusion, his ammonia levels were above the range for inclusion but he was given the dose regardless. 18 hours following the first infusion of the adenovirus vector, Gelsinger developed altered mental status and jaundice. Deteriorating liver function was followed by a blood-clotting disorder, kidney failure, lung failure and eventually brain death. He was dead 98 hours after the infusion.

Gelsinger was the first reported death of a participant in a gene therapy trial.

Discussion Questions

Consider the following questions as you start the discussion. You are encouraged to discuss about other ethical aspects of the case as well.

1. How would you assess the individual risk-benefit ratio for Gelsinger? Do considerations of societal level alter your assessment?
2. Using the information provided (as well as that you find on your own), do you think that conflict of interest was an important issue in this case? Do you believe it was sufficiently disclosed?

Please be respectful of others' opinions and the controversial nature of this case. As with all ethical issues, there is no clear answer.

Sources:

¹http://en.wikipedia.org/wiki/Gene_therapy

² Steinbrook, Robert. "The Gelsinger case." *The Oxford textbook of clinical research ethics* (2008): 110.

³ Hensley S. Targeted Genetics' Genovo deal leads to windfall for researcher. *Wall Street Journal* Aug. 10, 2000: B12.

⁴ Raper SE, Batshaw ML, Wilson JM, et al. Consent to act as a subject in an investigational study (January 1999), CHOP IRB#1994-7-794, Penn IRB #366-0, "Recombinant adenovirus gene transfer in adults with partial ornithine transcarbamylase deficiency."

⁵ "Gelsinger P. Jesse's Intent." <http://www.sskrplaw.com/gene/jessieintent.html>