

The Biotech Death of Jesse Gelsinger
By Sheryl Gay Stolberg
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The jagged peak of Mount Wrightson towers 9,450 feet above Tucson, overlooking a deep gorge where the prickly pear cactus that dots the desert floor gives way to a lush forest of ponderosa pine. It is said that this is as close to heaven as you can get in southern Arizona. Jesse Gelsinger loved this place. So it was here, on a clear Sunday afternoon in early November, that Paul Gelsinger laid his 18-year-old son to rest, seven weeks after a **gene-therapy** experiment cost him his life.

The ceremony was simple and impromptu. Two dozen mourners -- Jesse's father; his mother, Pattie; his stepmother, Mickie; and two sisters, a brother, three doctors and a smattering of friends -- trudged five miles along a steep trail to reach the rocky outcropping at the top. There, Paul Gelsinger shared stories of his son, who loved motorcycles and professional wrestling and was, to his father's irritation, distinctly lacking in ambition. Jesse was the kind of kid who kept \$10.10 in his bank account -- "You need \$10 to keep it open," Gelsinger explained -- but those assembled on the mountaintop agreed that he had a sharp wit and a sensitive heart.

At Gelsinger's request, the hikers had carried Jesse's medicine bottles filled with his ashes, and now they were gathered at the edge of the peak. Steve Raper, the surgeon who gave Jesse what turned out to be a lethal injection of new genes, pulled a small blue book of poetry from his pocket. "Here rests his head upon the lap of Earth," Raper read, reciting a passage from an elegy by Thomas Gray, "a youth to Fortune and Fame unknown./Fair Science frowned not on his humble birth." Then the surgeon, the grieving father and the rest scattered Jesse's ashes into the canyon, where they rose on a gust of wind and fell again in a powerful cloud of fine gray dust. "I will look to you here often, Jess," Paul Gelsinger said sadly.

Jesse Gelsinger was not sick before died. He suffered from ornithine transcarbamylase (OTC) deficiency, a rare metabolic disorder, but it was controlled with a low-protein diet and drugs, 32 pills a day. He knew when he signed up for the experiment at the University of Pennsylvania that he would not benefit; the study was to test the safety of a treatment for babies with a fatal form of his disorder. Still, it offered hope, the promise that someday Jesse might be rid of the cumbersome medications and diet so restrictive that half a hot dog was a treat. "What's the worst that can happen to me?" he told a friend shortly before he left for the Penn hospital, in Philadelphia. "I die, and it's for the babies."

As far as government officials know, Jesse's **death** on Sept. 17 was the first directly related to **gene therapy**. The official cause, as listed on the **death** certificate filed by Raper, was adult respiratory distress syndrome: his lungs shut down. The truth is more complicated. Jesse's **therapy** consisted of an infusion of corrective genes, encased in a dose of weakened cold virus, adenovirus, which functioned as what scientists call a vector. Vectors are like taxicabs that drive healthy DNA into cells; viruses, whose sole purpose is to get inside cells and infect them, make useful vectors. The Penn researchers had tested their vector, at the same dose Jesse got, in mice, monkeys, baboons and one human patient, and had seen expected, flulike side effects, along with some mild liver inflammation, which disappeared on its own. When Jesse got the vector, he suffered a chain reaction that the testing had not predicted -- jaundice, a blood-clotting disorder, kidney failure, lung failure and brain **death**: in Raper's words, "multiple-organ-system failure." The doctors are still investigating; their current hypothesis is that the adenovirus triggered an overwhelming inflammatory reaction -- in essence, an immune-system revolt. What they do not understand yet is why.

Every realm of medicine has its defining moment, often with a human face attached. Polio had Jonas Salk. In vitro fertilization had Louise Brown, the world's first test-tube baby. Transplant surgery had Barney Clark, the Seattle dentist with the artificial heart. AIDS had Magic Johnson. Now **gene therapy** has Jesse Gelsinger.

Until Jesse died, **gene therapy** was a promising idea that had so far failed to deliver. As scientists map the human genome, they are literally tripping over mutations that cause rare genetic disorders, including OTC deficiency, Jesse's disease. The initial goal was simple: to cure, or prevent, these illnesses by replacing defective genes with healthy ones. Biotech companies have poured millions into research -- not for rare hereditary disorders but for big-profit illnesses like cancer, heart disease and AIDS. As of August, the government had reviewed 331 **gene-therapy** protocols involving more than 4,000 patients. Just 41 were for the "monogeneic," or single-**gene**, defect diseases whose patients so desperately hoped **gene therapy** would be their salvation.

At the same time, the science has progressed slowly; researchers have had trouble devising vectors that can carry genes to the right cells and get them to work once they are there. Four years ago, Dr. Harold Varmus, the director of the National Institutes of Health, commissioned a highly critical report about **gene therapy**, chiding investigators for creating "the mistaken and widespread perception of success." Since then, there have been some accomplishments: a team at Tufts University has used **gene** therapy to grow new blood vessels for heart disease patients, for instance. But so far, **gene therapy** has not cured anyone. As Ruth Macklin, a bioethicist and member of the Recombinant DNA Advisory Committee, the National Institutes of Health panel that oversees **gene-therapy** research, says, bluntly, "**Gene therapy** is not yet **therapy**."

On Dec. 8, the "RAC," as the committee is called, will begin a public inquiry into Jesse's **death**, as well as the safety of adenovirus, which has been used in roughly one-quarter of all **gene-therapy** clinical trials. The Penn scientists will report on their preliminary results, and investigators, who at the RAC's request have submitted thousands of pages of patient safety data to the committee, will discuss the side effects of adenovirus. Among them will be researchers from the Schering-Plough Corporation, which was running two experiments in advanced liver cancer patients that used methods similar to Penn's. Enrollment in those trials was suspended by the Food and Drug Administration after Jesse's **death**. The company, under pressure from the RAC, has since released information showing that some patients experienced serious side effects, including changes in liver function and blood-cell counts, mental confusion and nausea; two experienced minor strokes, although one had a history of them. Once all the data on adenovirus are analyzed at the Dec. 8 meeting, the RAC may recommend restrictions on its use, which will almost certainly slow down some aspects of **gene-therapy** research.

The meeting will be important for another reason: it will mark an unprecedented public airing of information about the safety of **gene therapy** -- precisely the kind of sharing the RAC has unsuccessfully sought in the past. Officials say **gene therapy** has claimed no lives besides Jesse's. But since his **death**, there have been news reports that other patients died during the course of experiments -- from their diseases, as opposed to the **therapy** -- and that the scientists involved did not report those deaths to the RAC, as is required. This has created a growing cloud of suspicion over **gene therapy**, raising questions about whether other scientists may have withheld information that could have prevented Jesse's **death**. That question cannot be answered until all the data are analyzed. But one thing is certain: four years after the field was rocked by Varmus's highly critical evaluation, it is now being rocked again, this time over an issue more fundamental than efficacy -- safety.

"I think it's a perilous time for **gene therapy**," says LeRoy Walters, a bioethicist at Georgetown University and former chairman of the RAC. "Until now, we have been able to say, 'Well, it hasn't helped many people, but at least it hasn't hurt people.' That has changed."

No one, perhaps, is more acutely aware of **gene therapy**'s broken promise than Mark Batshaw, the pediatrician who proposed the experiment that cost Jesse Gelsinger his life.

At 54, Batshaw, who left the University of Pennsylvania last year for Children's National Medical Center, in Washington, is tall and gangly with slightly stooped shoulders and a shy smile that gives him the air of an awkward schoolboy, which he once was. As a child, Batshaw struggled

with hyperactivity: he didn't read until the third grade; in the fourth, his teacher grew so irritated at his constant chatter that she stuck his chair out in the hall. The experience has left him with a soft spot for developmentally disabled children, which is how he has become one of the world's foremost experts in urea-cycle disorders, among them OTC deficiency.

The urea cycle is a series of five liver enzymes that help rid the body of ammonia, a toxic breakdown product of protein. When these enzymes are missing or deficient, ammonia -- the same ammonia that you scrub your floors with," Batshaw explains -- accumulates in the blood and travels to the brain, causing coma, brain damage and **death**. OTC deficiency is the most common urea-cycle disorder, occurring in one out of every 40,000 births. Its genetic mutation occurs on the X chromosome, so women are typically carriers, while their sons suffer the disease. Severe OTC deficiency is, Batshaw says, "a devastating disease." Typically, newborns slip into a coma within 72 hours of birth. Most suffer severe brain damage. Half die in the first month, and half of the survivors die by age 5. Batshaw was a young postdoctoral fellow when he met his first urea-cycle-disorder patient in 1973, correctly diagnosing the disease at a time when most other doctors had never heard of it. Within two years, he and his colleagues had devised the first treatment, a low-protein formula called keto-acid. Later, they came up with what remains standard **therapy** to this day: sodium benzoate, a preservative, and another type of sodium, which bind to ammonia and help eliminate it from the body.

But the **therapy** cannot prevent the coma that is often the first sign of OTC and ravages the affected infant. By the time Batshaw joined the faculty at Penn in 1988, he was dreaming of a cure -- **gene therapy**. Patients were dreaming, too, says Tish Simon, former co-president of the National Urea Cycle Disorders Foundation, whose son died of OTC deficiency three years ago. "All of us saw **gene therapy** as the hope for the future," Simon says. "And certainly, if anybody was going to do it, it had to be Mark Batshaw."

Gene therapy became a reality on Sept. 14, 1990, in a hospital room at the National Institutes of Health, in Bethesda, Md., when a 4-year-old girl with a severe immune-system deficiency received a 30-minute infusion of white blood cells that had been engineered to contain copies of the **gene** she lacked. Rarely in modern medicine has an experiment been filled with so much hope; news of the treatment ricocheted off front pages around the world. The scientist who conducted it, Dr. W. French Anderson, quickly became known as the father of **gene therapy**. "We had got ourselves all hyped up," Anderson now admits, "thinking there would be rapid, quick, easy, early cures."

Among those keeping a close eye on Anderson's debut was Jim Wilson, a square-jawed, sandy-haired Midwesterner who decided to follow his father's footsteps in medicine when he realized he wasn't going to make it in football. As a graduate student in biological chemistry, Wilson had taken a keen interest in rare genetic diseases. "All I did," he says, "was dream about **gene therapy**."

Today, as director of the Institute for Human **Gene Therapy** at the University of Pennsylvania, Wilson is in an excellent position to make that dream a reality. Headquartered in a century-old building amid the leafy maple trees and brick sidewalks of the picturesque Penn campus, the six-year-old institute, with 250 employees, state-of-the-art laboratories and a \$25 million annual budget, is the largest academic **gene-therapy** program in the nation. In a field rife with big egos, Wilson is regarded as first-rate. "Present company excluded," Anderson says, "he's the best person in the field."

Batshaw was banging on Wilson's door even before Wilson arrived at Penn in March 1993, and within a month they were collaborating on studies of OTC-deficient mice. Their first task was to develop a vector. Adenovirus seemed a logical choice.

There had been some early problems with safety -- a 1993 cystic fibrosis experiment was shut down when a patient was hospitalized with inflamed lungs -- but Wilson and Batshaw say they

figured out how to make a safer vector by deleting extra viral genes. Adenovirus was the right size: when its viral genes were excised, the OTC **gene** fit right in. It had a "ZIP code," on it, Batshaw says, that would carry it straight to the liver. And while its effects did not last, it worked quickly, which meant that it might be able to reverse a coma, sparing babies from brain damage. "It wasn't going to be a cure soon," Batshaw says, "but it might be a treatment soon."

The mouse experiments were encouraging. Mice that had the **therapy** survived for two to three months even while fed a high-protein diet. Those that lacked the treatment died. "It wasn't subtle," Wilson says. "We felt pretty compelled by that." But when the team contemplated testing in people, they ran smack into an ethical quandary: who should be their subjects?

To Wilson, the answer seemed obvious: sick babies. Arthur Caplan, the university's resident bioethics expert, thought otherwise. Caplan says parents of dying infants are incapable of giving informed consent: "They are coerced by the disease of their child." He advised Wilson to test only stable adults, either female carriers or men like Jesse, with partial enzyme deficiencies. The National Urea Cycle Disorders Foundation agreed. When Batshaw turned up at their 1994 annual meeting asking for volunteers, so many mothers offered to be screened for the OTC **gene** that it took him four hours to draw all the blood.

By the time Mark Batshaw and Jim Wilson submitted their experiment to the Recombinant DNA Advisory Committee for approval, the panel was in danger of being disbanded. Varmus, the N.I.H. director, who won the Nobel Prize for his discovery of a family of cancer-causing genes, had made no secret of his distaste for the conduct of **gene-therapy** researchers. He thought the science was too shoddy to push forward with human testing, and it bothered him that so few experiments were focusing on genetic diseases. It irked him to have to sign off on protocols the RAC approved, and it irked him even more to see biotech companies touting those approvals, like some kind of N.I.H. imprimatur, in the business pages of the papers. "Some days," says Dr. Nelson Wivel, the committee's former executive director, who now works for Wilson at Penn, "it felt as though the RAC was helping the biotech industry raise money. Dr. Varmus hated that." At the same time, the pharmaceutical industry and AIDS activists were complaining that the RAC was redundant: the F.D.A. already reviewed **gene-therapy** proposals. So in mid-1995, after seeking the advice of an expert panel, Varmus reorganized the RAC, slashing its membership from 25 to 15 and stripping it of its approval authority -- a decision that, some say, has enabled **gene-therapy** researchers to ignore the panel and keep information about safety to themselves. "The RAC," complains Dr. Robert Erickson, a University of Arizona medical geneticist who served on the panel, "became a debating society."

The Batshaw-Wilson protocol was among the last the committee would ever approve. The plan was for 18 adults (19 eventually signed up, including Tish Simon, but the last patient was never treated, because of Jesse's **death**) to receive an infusion of the OTC **gene**, tucked inside an adenovirus vector, through a catheter in the hepatic artery, which leads to the liver. The goal was to find what Wilson calls "the maximum tolerated dose," one high enough to get the **gene** to work, but low enough to spare patients serious side effects. Subjects would be split into six groups of three, with each group receiving a slightly higher dose than the last. This is standard fare in safety testing. "You go up in small-enough increments," Wilson explains, "that you can pull the plug on the thing before people get hurt."

The experiment stood in stark contrast to others that had earned Varmus's scorn. It was paid for by N.I.H., which meant it had withstood the rigors of scientific peer review. It was aimed at a rare genetic disease, not cancer or AIDS. It was supported by plenty of animal research: Wilson and his team had performed more than 20 mouse experiments to test efficacy and a dozen safety studies on mice, rhesus monkeys and baboons. Still, it made Erickson, one of two scientists assigned by the RAC to review the experiment, uneasy.

He was troubled by data showing that three monkeys had died of a blood-clotting disorder and severe liver inflammation when they received an earlier, stronger version of the adenovirus vector

at a dose 20 times the highest dose planned for the study. No one had injected adenovirus directly into the bloodstream before, either via the liver or otherwise, and the scientists admitted that it was difficult to tell precisely how people would respond. They planned to confine the infusion to the right lobe of the liver, so that if damage occurred it would be contained there, sparing the left lobe. And they outlined the major risks: bleeding, from either the **gene-therapy** site or a subsequent liver biopsy, which would require surgery; or serious liver inflammation, which could require an organ transplant and might lead to **death**.

Both Erickson and the other scientific reviewer thought the experiment was too risky to test on asymptomatic volunteers and recommended rejection. But in the end, Batshaw and Wilson prevailed. They offered up Caplan's argument that testing on babies was inappropriate. And they agreed to inject the vector into the bloodstream, as opposed to putting it directly into the liver. That decision, however, was later reversed by the F.D.A., which insisted that because the adenovirus would travel through the blood and wind up in the liver anyway, the original plan was safer.

The RAC, in such disarray from Varmus's reorganization that it did not meet again for another year, was never informed of the change.

Jesse Gelsinger was 17 when his pediatric geneticist, Dr. Randy Heidenreich, first told him about the Penn proposal. He wanted to sign up right away. But he had to wait until he was 18.

Paul Gelsinger was also enthusiastic. A trim 47-year-old with intense blue eyes, Gelsinger, who makes his living as a handyman, gained custody of his four children nine years ago, when he divorced their mother, who suffers from manic depression. He had been having some difficulty with Jesse then; the boy was in the midst of an adolescent rebellion and was refusing to take his medicine. "I said: 'Wow, Jess, they're working on your disorder. Maybe they'll come up with a cure.'"

Jesse's was not a typical case of OTC deficiency: his mutation appears to have occurred spontaneously in the womb. His disease having been diagnosed when he was 2, Jesse was what scientists call a mosaic -- a small portion of his cells produced the missing enzyme. When he watched what he ate and took his medicine, he was fine. But one day last December, Paul Gelsinger arrived home to find his son curled up on the couch. He had been vomiting uncontrollably, a sign, Paul knew, that Jesse's ammonia was rising. Jesse landed in the hospital, comatose and on life support. When he recovered, he never missed another pill.

On June 18, the day Jesse turned 18, the Gelsingers -- Paul, Mickie and the children -- flew to Philadelphia to see Paul's family. They played tourists, visiting the Liberty Bell and the Rocky statue, where Jesse was photographed, fists raised, a picture that would circulate in the newspapers after his **death**. On the 22nd, they went to the University of Pennsylvania, where they met Raper, the surgeon, who explained the experiment and did blood and liver-function tests to see if Jesse was eligible. He was, and his treatment was scheduled for the fall. Jesse would be the youngest patient enrolled.

On Sept. 9, Jesse returned to Philadelphia, this time alone. He took one duffel bag full of clothes and another full of wrestling videos. Paul Gelsinger planned to fly in a week later for the liver biopsy, which he considered the trial's most serious risk.

The treatment began on Monday, Sept. 13. Jesse would receive the highest dose. Seventeen patients had already been treated, including one woman who had been given the same dose that Jesse would get, albeit from a different lot, and had done "quite well," Raper says. That morning, Jesse was taken to the interventional-radiology suite, where he was sedated and strapped to a table while a team of radiologists threaded two catheters into his groin. At 10:30 a.m., Raper drew 30 milliliters of the vector and injected it slowly. At half past noon, he was done.

That night, Jesse was sick to his stomach and spiked a fever, 104.5 degrees. Raper was not particularly surprised: other patients had experienced the same reaction. Paul Gelsinger called; he and Jesse talked briefly, exchanging I love yous. Those were the last words they ever spoke. Early Tuesday morning a nurse called Raper at home; Jesse seemed disoriented. When Raper got to the hospital, about 6:15 a.m., he noticed that the whites of Jesse's eyes were yellow. That meant jaundice, not a good sign. "It was not something we had seen before," Raper says. A test confirmed that Jesse's bilirubin, a breakdown product of red blood cells, was four times the normal level. Raper called Gelsinger, and Batshaw in Washington, who said he would get on a train and be there in two hours.

Both doctors knew that the high bilirubin meant one of two things: either Jesse's liver was failing or he was suffering a clotting disorder in which his red blood cells were breaking down faster than the liver could metabolize them. This was the same disorder the scientists had seen in the monkeys that had been given the stronger vector. The condition is life-threatening for anyone, but particularly dangerous for someone with Jesse's disease, because red blood cells liberate protein when they break down.

By midafternoon Tuesday, a little more than 24 hours after the injection, the clotting disorder had pushed Jesse into a coma. By 11:30 p.m., his ammonia level was 393 micromoles per liter of blood. Normal is 35. The doctors began dialysis.

Paul Gelsinger had booked a red-eye flight. When he arrived in the surgical intensive care unit at 8 Wednesday morning, Raper and Batshaw told him that dialysis had brought Jesse's ammonia level down to 72 but that other complications were developing. He was hyperventilating, which would increase the level of ammonia in his brain. They wanted to paralyze his muscles and induce a deeper coma, so that a ventilator could breathe for him. Gelsinger gave consent. Then he put on scrubs, gloves and a mask and went in to see his son.

By Wednesday afternoon, Jesse seemed to be stabilizing. Batshaw went back to Washington. Paul felt comfortable enough to meet his brother for dinner. But later that night Jesse worsened again. His lungs grew stiff; the doctors were giving him 100 percent oxygen, but not enough of it was getting to his bloodstream. They consulted a liver-transplant team and learned that Jesse was not a good candidate. Raper was beside himself. He consulted with Batshaw and Wilson, and they decided to take an extraordinary step, a procedure known as ECMO, for extracorporeal membrane oxygenation, essentially an external lung that filters the blood, removing carbon dioxide and adding oxygen. It had been tried on only 1,000 people before, Raper says. Only half had survived.

"If we could just buy his lungs a day or two," Raper said later, they thought "maybe he would go ahead and heal up."

The next day, Thursday, Sept. 16, Hurricane Floyd slammed into the East Coast. Mickie Gelsinger flew in from Tucson just before the airport closed. (Pattie Gelsinger, Jesse's mother, was being treated in a psychiatric facility and was unable to leave.) Batshaw spent the day trapped outside Baltimore on an Amtrak train. He ran down his cell phone calling Raper; when it went dead, he persuaded another passenger to lend him his. The ECMO, Raper reported, appeared to be working. But then another problem cropped up: Jesse's kidneys stopped making urine. "He was sliding into multiple-organ-system failure," Raper says.

That night, at his hotel, Paul Gelsinger couldn't sleep. He left his wife a note and walked the half mile to the Penn medical center to see Jesse. The boy was bloated beyond recognition; even his ears were swollen shut. Gelsinger noticed blood in Jesse's urine, an indication, he knew, that the kidneys were shutting down. How can anybody, he thought, survive this?

On the morning of Friday the 17th, a test showed that Jesse was brain dead. Paul Gelsinger didn't need to be told: "I knew it already." He called for a chaplain to hold a bedside service, with prayers for the removal of life support.

The room was crowded with equipment and people: 7 of Paul's 15 siblings came in, plus an array of doctors and nurses. Raper and Batshaw, shellshocked and exhausted, stood in the back. The chaplain anointed Jesse's forehead with oil, then read the Lord's Prayer. The doctors fought back tears. When the intensive-care specialist flipped two toggle switches, one to turn off the ventilator and the other to turn off the ECMO machine, Raper stepped forward. He checked the heart-rate monitor, watched the line go flat and noted the time: 2:30 p.m. He put his stethoscope to Jesse's chest, more out of habit than necessity, and pronounced the **death** official. "Goodbye, Jesse," he said. "We'll figure this out."

Wilson reported the **death** immediately, drawing praise from government officials but criticism from Arthur Caplan, who says they should have made the news public, in a news conference. In the weeks since, the Penn team has put every detail of Jesse's treatment under a microscope. It has rechecked the vector to make certain it was not tainted, tested the same lot on monkeys, re-examined lab and autopsy findings. Wilson's biggest fear was that Jesse died as a result of human error, but so far there has been no evidence of that. "That's what's so frightening," French Anderson says. "If they made a mistake, you would feel a little safer."

The **death** has rattled the three doctors in various ways. Wilson has asked himself over and over again whether he should have done anything differently. "At this point, I say no, but I'm continuing to re-evaluate constantly." He has been besieged by worry, about the morale of his staff, about whether his institute's financial sponsors would pull out, about whether patients would continue to volunteer, about whether he would lose his bravado -- the **death** knell for a scientist on the cutting edge. "My concern," he confessed, over dinner one night in Philadelphia, "is, I'm going to get timid, that I'll get risk averse."

Raper has thrown himself into his work, trying to live up to his promise to "figure this out." There are a number of possible explanations, he says: the vector may have reacted badly with Jesse's medication; Jesse's status as a mosaic may have played a role; or perhaps the early testing in monkeys, which showed that the stronger vector had deleterious side effects, was more of a harbinger of danger than the doctors realized. An answer may take months, but he is determined to find one; only by understanding what happened to Jesse, and how to prevent it in others, can the research continue. "That," Raper says, "would be the best tribute to Jesse."

Of the three, Batshaw seems to have taken it the hardest. He is not a particularly religious man, but a few days after Jesse died he went to synagogue to say Kaddish, the Jewish mourner's prayer. He struggles with the idea of personal responsibility. He has cradled many a dying child in his career, but never before, he says, has a patient been made worse by his care. "What is the Hippocratic oath?" Batshaw asks rhetorically, looking into the distance as his fingers drum the tabletop. He pauses, as if to steel himself, and says, "I did harm."

Paul Gelsinger does not hold the doctors responsible, although he is acutely interested in knowing what other scientists knew about adenovirus before Jesse died. He has experienced a deep spiritual awakening since losing his son; in dying, he says, Jesse taught him how to live. He speaks frequently of God, and of "purity of intent," which is his way of saying that Jesse demonstrated an altruism the rest of us might do well to emulate. "I hope," he said on the mountaintop that Sunday afternoon, "that I can die as well as my son has died."