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## Caution Over Gene Therapy Puts Hopes on Hold; [FINAL Edition]

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**Full Text** (1649 words)

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Like most 2-year-olds, Max Randell is a bundle of exuberance, gaining new mastery over the world with every passing day. But unlike most children his age, Max has just about reached the prime of his life.

Max has Canavan disease, a rare inherited disorder that destroys young brains, dragging toddlers into a near coma by age 4 and typically killing them before the age of 10. The Chicago-area boy's parents believe that his only hope for any semblance of a childhood is an experimental gene therapy developed at Jefferson Medical College in Philadelphia, now under federal review.

But given gene therapy's many troubles of late--including a teenage patient's death in Philadelphia and revelations of numerous research lapses at other sites around the country--Max's doctor and parents fear that officials will demand extraordinary evidence that the Canavan treatment is ready for human testing, and perhaps withhold a go-ahead until it's too late for Max.

"I hate that all this happened right now," said Max's mother, Ilyce, speaking of the current wave of negative attention on gene therapy. "We don't have the luxury of waiting."

That urgency infuses an emotional debate that has drawn federal regulators, scientists and patients into what amounts to a rare public tribunal over an entire branch of experimental medicine. At stake is gene therapy's scientific credibility, and perhaps even its economic future, in what experts are calling the "post-Gelsinger era." The term refers to Jesse Gelsinger, whose September death at Penn marked the first death attributed to a gene therapy experiment and a turning point in public confidence in the field.

On one side are those who believe that gene therapy has become something of a rogue branch of medical science in which patients, their families and even some doctors have become deluded by unrealistic hopes--and by hype from gene therapy's growing cadre of scientist-investors and venture capitalist backers.

With the decade-old field still lacking a single cure and facing numerous questions about financial conflicts of interest, some critics are even calling for a temporary halt to gene therapy pending further studies in animals and a review of ethics rules.

"No one seems ready to start saving lives, and it's too valuable an area of research to not do it right and to lose the public confidence," said George Annas, a professor of health law and bioethics at Boston University. "I say take a voluntary moratorium."

On the other side are many scientists, patients and family members who acknowledge that the field has had a few mishaps but who believe it's been unfairly tarnished by overly close news media scrutiny and by activists opposed to genetic research. If the negative rhetoric doesn't stop soon, these supporters warn, the field may get curtailed just as it's about to produce results.

"The controversy has gotten so overblown," said Carl Feldbaum, president of the Biotechnology Industry Organization. "That could hurt the very people we're trying to help."

Both views will be aired at a three-day National Institutes of Health meeting beginning tomorrow at which officials will consider the Canavan treatment along with broader questions about how best to regulate gene therapy.

Few experts believe that NIH will endorse a moratorium on gene therapy. But there is evidence that the past six months' events may already be taking a toll on the beleaguered specialty's supply of volunteers. A gene therapy experiment for cystic fibrosis at Johns Hopkins University School of Medicine, for example, has now gone several months with no patients, said Pamela Zeitlin, a professor of pediatrics who is running the study.

Zeitlin had no trouble attracting volunteers for an earlier version of the study, and she had planned to start the new version in December. But because of trouble finding willing patients, the first volunteer will be treated just this month. Meanwhile, many asked about Gelsinger's death and never returned.

"We've had many more potential volunteers with concerns about risk," Zeitlin said, "or who planned to start and then had second thoughts and didn't enroll."

Scientists at other gene therapy centers said it's too soon to say whether the current climate of distrust is slowing enrollment. Indeed, some noted, if some patients are thinking twice about getting new genes, others are responding to gene therapy's crisis in just the opposite way: by scrambling to get into studies before a feared crackdown occurs.

When a Boston research hospital last month responded to all the attention on the field by temporarily halting its hemophilia gene therapy experiment, for instance, patients with the bleeding disorder seethed with anger. Beth Israel Deaconess Medical Center said it suspended the study to make sure that no potential risks to patients had been overlooked. But the study had already been fully approved and had experienced no problems, suggesting to angry critics that the shutdown, which was reversed two weeks later, represented a capitulation to a mere wave of fear.

"It sent a very bad message, a terrible message," said Michael Coyne, a Pittsfield, Mass., board member of the National Hemophilia Foundation whose 9-year-old son, Conor, has the clotting disorder. "If a trial is going to be shut down, it should be shut down for medical rationale, not political rationale."

That reaction miffed hospital officials, who complained that all the hoopla surrounding gene therapy had left them trapped between competing pressures.

"What if we say, 'Damn the torpedoes, full speed ahead, everything is fine!' And what if something had happened to someone in those two weeks?" asked Michael Rosenblatt, Beth Israel's interim president. "Would patients still support the hospital then?"

Abbey Meyers, president of the National Organization for Rare Disorders, was equally upset with hemophilia patients' desperate demands for access--but for a very different reason.

"These people are disappointed that this is going to delay their treatment, but they don't understand there has been a betrayal here," said Meyers, a former member of the NIH gene therapy oversight committee, which is meeting this week in Bethesda.

"They haven't been told the truth," Meyers said, about how unlikely it is that they will be helped, or about the risks of participating. "We've got to get some rules around this to make sure it's being done properly."

Biotechnology industry representatives have already said they are willing to impose upon themselves new rules to allay public concerns. And a recent letter to medical research leaders from Jordon Cohen, president of the Association of American Medical Colleges (AAMC), said the association would embark upon several initiatives to reverse the "erosion of public trust" that had been prompted by recent events.

But some critics are concerned that the proposed changes may prove more cosmetic than substantial. One federal health official, speaking on condition of anonymity, was especially critical of the Feb. 18 AAMC letter, calling it a blueprint for "damage control" instead of a proposal to more thoroughly protect medical volunteers.

The letter describes plans for a conference call among the deans of medical centers recently targeted by the FDA, with the goal of learning how federal investigators conducted their inquiries. That information should be used to develop a "strategic response plan," the letter said, to help other institutions develop more effective

public communications in the event they come under similar scrutiny.

Moreover, the letter stated, the association had scheduled a meeting with The Washington Post's editorial board, and would help coordinate "other media outreach activities as appropriate."

"I wouldn't call it 'damage control,' it's just about good communication," Cohen said in an interview last week, noting that the letter also describes planned efforts to educate scientists about federal regulations. "We need to get the facts out there so people are not operating on rumors or bad information."

But if the facts are that gene therapy is not working and may even cause harm, then those facts are not likely to emerge from a young field that is under growing financial pressures to succeed, Meyers and other critics said.

Perhaps, some said, that explains why so much was made last week of some very preliminary findings from a gene therapy study of hemophilia, published in the journal *Nature Biotechnology*.

Results of the study, which involved only three patients, rained upon news organizations in the form of faxes and repeated phone calls made by a public relations company hired by Avigen, a California biotechnology company that sponsored the research. According to a company news release, "even the lowest dose is effective."

Yet the amount of clotting factor found in the gene-treated patients' blood was barely detectable, outside scientists said. And the measure of clinical effectiveness used in the study--essentially patients' personal assessments that they were feeling less pain--was all but invalid, experts said, because the patients knew they'd received a new treatment. Volunteers who know they've received a new drug predictably report feeling better, because of the so-called placebo effect.

Declarations of the treatment's "efficacy," said the University of Michigan's Randy Kaufman, a hemophilia expert who cloned the gene involved in the most common form of the disease, are "a lot of hype."

Still, experts said, it's difficult to ignore the wishes and demands of patients and their family members, including Illyse Randell, who want their personal shot at the latest that medicine has to offer.

The experiment that Randell craves would involve an injection of genetically engineered viruses directly into Max's brain. It has never been tried in people, and the goal for now is just to see if it causes damage, not to see if it can actually protect dying brain cells.

Randell said she understands that distinction, and that participation in this kind of study is really for the good of future patients. But her words also illustrate how difficult it can be for a patient or parent to stop hoping.

"We're at the point where Max is almost 2 1/2, and soon he's going to start losing ground," Randell said. "He can't wait until winter to be treated."

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