SickKids VS Rare Disease Transcript

COLD OPEN

Hannah: In March 2022, a four-year-old boy named Michael received the first gene therapy designed to treat his very rare, very distinct disease. The drug had been approved by Health Canada just a few months earlier, and Michael would be the first recipient in a clinical trial.

That day, the room was heavy with nervous anticipation. Michael was sedated and lying on a surgical table. He was surrounded by his medical team and his parents. His dad Terry said a prayer. He prayed that the drug wouldn't hurt Michael. He prayed that it would work. That it would reach every cell in Michael's brain and replace the missing protein needed to halt the disease. Which by then, had robbed Michael of the ability to walk or speak.

Terry: It was stressful at the beginning because you're like, "oh my God, am I doing the right thing?" Because, you know, gene therapy isn't 100 percent safe. The second side of it was, you know, we had no idea what was going to happen. We didn't know if that gene therapy was going to turn around and we were going to see Michael talking in a month or if, you know, it was going to just stop the disease. We had no idea.

Hannah: Everything about this was unprecedented. It was the first drug developed for Michael's disease, which is called SPG50, short for spastic paraplegia. It's a recently recognized neurodegenerative disorder with only 80 known diagnoses worldwide, most of them children. Michael's drug is also one of the earliest *gene* therapies, which work by targeting the underlying genetic variant.

For SickKids, it would be the first clinical trial of an individualized gene therapy, and the first involving just one participant. In other words, Michael would be the first human test case. His experience would determine if the drug could be used for other people with SPG50.

After the prayer, Michael's parents said their goodbyes and left the room. Then it was over to Dr. Jim Dowling, a SickKids neurologist and scientist specializing in rare genetic diseases. He would be overseeing the treatment, delivered with a needle to Michael's spine.

Jim: It was both awe-inspiring and scary and hopeful. It's hard to encapsulate a single emotion of the day. We had this thing that had been made, and really you get one shot at it. Got a special tube. If the tube dropped, then, there's no gene therapy. And just all these things that had not really been tried before. I think there was a feeling of historic-ness to the process that we were trying something that could have a real impact not just on Michael, but could be setting a paradigm for other clinical work moving forward.

Hannah: The stakes were high, and the impact potentially enormous. Would this therapy work for Michael? Would it reach other kids with SPG50? How would this trial inform the emerging field of gene therapy? And what would it all mean for the promise of precision medicine.

You're listening to SickKids VS, where we take you to the frontlines of child health. I'm Hannah Bank and this is SickKids VS Rare Disease.

ACT 1

Hannah: It took about a year for Michael to get a diagnosis. The family's quest followed a common path: Terry and his wife Georgia noticed that Michael was missing certain milestones. He was four months old, but not grabbing for toys or lifting his arms. A visit to their family doctor led to a paediatrician, who referred them to SickKids to see specialists in neurology and infectious disease. When everything came up empty, they were sent to Jim's clinic for undiagnosed neuro-genetic disorders. Michael's blood was analyzed using an advanced type of whole-genome sequencing, which uncovered SPG50. Terry describes the disease this way.

Terry: And so the disease, the way it works is, children become paralyzed from the waist down by the age of ten. They become quadriplegic by the age of 20, and most of them are non-verbal.

Hannah: Because SPG50 is a newly identified disorder, the average lifespan of patients is still unclear. But the current understanding is that SPG50 is life-limiting – and certainly life-altering.

Terry: The realization that Michael had this terrible disease just kind of set in. They told us that he most likely be paralyzed, that he'll be severely mentally disabled, and just to go home and love him and give him the best life we possibly can.

Hannah: SPG50 is considered an *ultrarare* disease, a class of disorders that affect only one in 50,000 people. So far, SPG50 is well below that. When Michael was diagnosed in 2019, he was the only known person in Canada with SPG50. For conditions *this* uncommon, drug companies have little financial incentive to invest in research. Which means rare and ultrarare diseases don't often have treatments. The collective toll of this is immense.

Hannah: Here's Dr. Jim Dowling.

Jim: There are individual rare diseases like SPG50, and it might seem like one child, but there's more than 8,000 individual rare diseases. If you put together everyone in Canada with those 8,000 rare diseases, there's more than a million people. And 50 percent of all of those million people with rare disease are children. And of those individuals, 25 percent will die before the age five. It's a staggering number of individuals, and also it's a staggering impact on the health of those individuals and obviously on their families and on their communities and the health care system.

Hannah: Here's Michael's mom, Georgia.

Georgia: Pretty much in a split second, all your dreams for your child are gone. Everything that you hope for them is no longer there. You're just on survival mode. You're like, okay, how am I going to get through this? How am I going to help them? What can we do?

Hannah: The night they got the diagnosis, Terry and Georgia went online and found a family in Boston whose child has a subtype of the same disease. SPG47 instead of SPG50.

Terry: They were actually working on a gene therapy for SPG47, and they kind of told us, you know, this is what you need to do. They were kind of guiding us over that one phone conversation. And then I just started researching like crazy over the next two days. I kind of just went down the rabbit hole, to be honest with you. And I read up everything I humanly could on gene therapy.

Hannah: What happens next could be its own podcast episode, or an entire series. Terry and Georgia decided to go at it alone. If no drug existed for SPG50, then they would raise the money and get one made. When Terry wasn't working his day job as a managing director at a large bank, he would spend every waking moment finding a cure for Michael. Georgia would manage the house and look after their three kids.

Georgia: I mean, we had no option. So we discussed it, Terry told me about it. We looked into it together, we researched it, and then I was just like on board because we had no choice. There was nothing for Michael. It was either accept it and just move on – or try. So, together we had to try.

Terry: So at this point in time, he was around 18 months of age. So he was very delayed in his mental capacity. He wasn't able to walk. He was starting to become spastic. So his toes and his ankles started to become spastic, as in stiff. And obviously the disease was on its way.

Hannah: Terry immediately went in search of a team. He went to conferences and met with biotech companies and scientists. He taped up posters of Michael, with a plea to help cure his disease.

Terry: And I found that there was this conference down in Boston where it's meant for gene therapy and the doctors that do gene therapy. And I flew out there and I met six of the seven world experts. And I asked them all the same thing: if this was your child, what would you do? And they all said gene therapy.

Hannah: A gene therapy is a drug that modifies the genetic error causing disease. Gene therapies are still relatively new and they're not suitable for all genetic disorders. Only a handful have been developed, and even fewer have been approved for patient use. When Terry and Georgia began their quest, the landscape was even more stark.

Jim: When Terry first started the process, there was no path for this. If you look across rare disease in Canada, there wasn't a single gene therapy that existed that you could give to patients at that point. I mean, there were some that were in clinical trials, but those were multi-million-dollar industry-sponsored trials. So the idea that a family foundation would start this, and go through all the process, and

then have a therapy seemed just almost fantastical at the moment that he was thinking about it.

Hannah: It's hard to overstate what an enormous undertaking it is to develop a drug from concept to clinical trial. Especially if, like Terry, you have a job, a family, and zero knowledge about science and medicine. Oh, and also during a global pandemic.

But astonishingly, it happened. Terry found a leading gene-therapy scientist to develop the drug. He hired a lab to test if it worked and it was safe. He got the drug approved for a clinical trial in Canada and the U.S. And he found a manufacturer willing to make the dose.

The whole process involved more than 100 people from a dozen research groups and labs around the world. It took three years and three million dollars, raised from golf tournaments, galas, lemonade stands, and a key anonymous donation. There were plenty of heartbreaking twists and turns. But also, lots of luck and good will.

Terry: Things just always go wrong, unfortunately. Like we had a batch of drug that went bad. We were shipping another batch for something else, and it went through Texas during the snowstorm and *it* went bad.

We had another shipment that was coming from Spain and was going to Quebec. And along the way there was another storm and they got stuck in a warehouse somewhere. But the dry ice needed to be replaced because if the dry ice in the box didn't get replaced, we would lose five months and $1 million. And the shipper had called every hour to make sure that the ice was being replaced. And he did that for three days.

During COVID, we couldn't find the specific needle we needed or the materials. So we had to call these manufacturers and find this random company that purchased it and beg them to give us two or three needles. It's just, you know, there were so many hurdles along the way that we kind of had to just go through, otherwise things would have just been paused.

Hannah: For Terry and Georgia, every delay gobbled precious time. Every setback gave the disease a stronger foothold, taking more from Michael.

On December 30, 2021—three years after Terry started his quest—he got word that Health Canada approved Michael's therapy for a clinical trial. On January 2, Terry called SickKids. Would they run the trial on Michael?

ACT 2

Hannah: The last time Jim and Terry had spoken was when Jim had diagnosed Michael with SPG50. Three years later, Jim was astounded to hear that Terry had developed a gene therapy for Michael.

Jim: I was very excited to see where he had progressed and my immediate thought was, okay, well, we have to see how we can make this happen for him. But I think probably there was some good, healthy skepticism to look at this and say, okay, this is actually feasible. Can we really do this?

Hannah: SickKids President Dr. Ronni Cohn convened a meeting with hospital executives and legal and ethics staff. They were joined by leaders of SickKids' new Precision Child Health group, whose core mission is to advance a monumental new approach to medicine that aims to customize care for each patient. Michael's therapy would be the *ultimate* precision medicine – a drug made just for his disease. A drug that targeted his precise genetic glitch.

But still, there were considerations: What were the ethical and safety implications of doing a trial on one patient? Did SickKids have the expertise to do it safely? Even though the drug had been thoroughly tested in animal models, there was no guarantee that Michael wouldn't have serious side effects. In the end, all the boxes were checked. And everyone understood that the opportunity and impact were too important – not just for Michael, but other rare-disease patients.

Jim: This represented a totally new avenue of thinking about things. Doing a single patient gene therapy was really not something that had been widely attempted before. And so I think we felt this was an opportunity to be at that forefront of an emerging technology that we all think is going to be extremely important. And I think there was also a real sentiment that, a) we could treat Michael and b) we could at the same time learn all these important lessons about how one does therapy in this setting -- a single patient, a new therapy, a treatment that hasn't been used before – and what that whole process looks like,

and that we could take that learning and apply it to all the other rare-disease patients that we take care of where there aren't therapies yet.

Hannah: And so began the mammoth task of designing a clinical trial. Basically, it's a detailed playbook about how the drug will be delivered and what to monitor after. Jim led the design of the trial. He consulted colleagues in oncology, who had been involved in clinical trials with a small number of patients. And he drew from his own experience leading a gene therapy trial for another rare disease.

Jim: What we're developing is a whole protocol for every step of what we're going to do, from the development of the drug itself to its dosing to its monitoring thereafter. And we have to be very precise about every element that we add to that, because we have to make sure that we're doing everything in the safest way possible, the most effective, and also in the most ethically acceptable way that we can. I mean, just to give an example, like the trial manual itself is, you know, 100 or 150 pages. And we have to put all that together just to treat and monitor for this one therapy.

Hannah: For Michael's drug, the corrected gene was packaged in a benign virus. If all went well, the virus would infect Michael's brain cells and release the genetic instructions to produce the missing protein. It was a single, very high dose. And once it was delivered, there was no turning back.

Jim: So with gene therapy, you get the therapy, and basically that's it. There's no additional dosing. The thought is that the therapy will be very long lasting. May not last for a lifetime, but will last for several years. That element of things is completely different because the idea often with the single-patient trials is that you would start a medicine and then you might stop it and see how things are going. Or if side effects started developing, you would stop the medicine. So here, that's not an option.

Hannah: The procedure took two hours, and Michael went home the next morning. He would return to SickKids every week for the first month, a critical period for monitoring.

Jim: We know from other gene therapy studies that the immune system can attack the gene therapy product. That often that happens in the first couple of weeks after the therapy is given. So we obviously monitored extremely closely in

the beginning. He's also been on pretty high-dose immunosuppression medicines. And so as we've been peeling away those medicines, we've also been watching to see if side effects have come out. And there's a little bit of a, you know, what would a side effect look like? And again, because there haven't been that many individuals who've ever received gene therapy through their spinal fluid, certainly none at the dose that he's received, there is a little bit of not having to predict what we might see without actually knowing. So, putting a broad net on what we're watching.

Hannah: Of course, everyone is also watching for changes in Michael's disease progression. But these aren't clear or immediate.

Jim: We do know that it does take some time for the therapy to actually start working. And so it takes a couple of weeks until the gene therapy starts making the RNA and the protein that's needed to replace that. And then you can imagine it might take some time until the new proteins there that it's actually doing the function it's supposed to, and there may be some more time for that to improve the function of the neurons of the brain cells. And then *that* might take some more time to then actually change function.

Hannah: It seems unlikely that the gene therapy will reverse the effects of Michael's progressive disease. But the hope is that the drug will slow it down. That it will preserve and maybe improve the function of his body and mind. It may take a year or two to see these changes.

Jim: Of course, we're really hoping that it's going to make things better for Michael. This is a relentlessly progressive condition. And if progression could be halted, and Michael is able to continue to do the things that he's able to do now in terms of, you know, being really amazingly interactive and he can do some standing, he's able to work with electronic devices. And, if you've met him, he's a very joyful child. And so to see that preserved in and of itself, I think would be really a major achievement for the therapy.

Hannah: After this quick break, I'll speak with Terry and Jim about how Michael's doing, and how SickKids is learning from his experience.

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ACT 3

Hannah: It's been more than a year since Michael received the therapy. He's been coming to SickKids every three months as part of his monitoring schedule. And soon, this will decrease to just once a year. Because the clinical trial is still active, we can't talk about Michael's side effects. But we can say that Terry and Georgia have noticed signs of improvement. Michael can now point, grasp toys, and stand while supported.

The SPG50 clinical trial has expanded to two more patients, both in the U.S. The goal is to dose 10 patients. Terry hopes this data will be compelling enough to convince the American Federal Drug Administration to bring the therapy to market. This would mean that insurance providers and governments could help pay for the drug. The cost right now is about $1.4 million per dose.

Terry's focus has also expanded to the inequities of rare-disease research. He recently quit his job and started a biotech company. Using lessons learned from SPG50, he aims to develop gene therapies for five other rare diseases. The ultimate goal is to smooth the path for other families, so they don't have to go through what he did.

Terry: We need to think outside the box. There's things that can be done to give these kids a better life and we need to do it. And it can't be just, you know, one family at a time. It needs to be, you know, government funding to change their lives.

Hannah: In March 2023, the Canadian government announced new funding for rare diseases – for better access to screening and drugs. It's an important acknowledgement of the barriers faced by patients and families. But, with so few treatments available, investing in drug *development* is vital. To that end, Jim is working with colleagues to expand the scope of the neuro-genetic clinic. They want to rapidly diagnose patients *and* develop gene therapies to cure them. For Jim and the SickKids team, Terry's efforts have inspired new urgency and understanding about what is possible for rare-disease treatments.

Jim: What we've learned from with Michael is the power of an early diagnosis with broad-based genetic testing. The idea of figuring out what type of therapy would be the most effective for the individual's type of genetic disease, and then the pathway of how to rapidly develop it, and implement it, and what's needed to be in place and how one monitors, both from safety and effectiveness, are all lessons that we're learning, including also as well, you know, how we interact with regulators, and with ethics, and how the whole process needs to go.

Hannah: Beyond the potential impact on Michael and other children, the SPG50 gene-therapy trial is a critical stepping-stone to develop other gene therapies. And these pursuits, no matter how they turn out, build a path toward a new paradigm of precision medicine.

Jim: Supporting the development of a therapy for one child is likely to lead to our ability at SickKids to start developing a therapy for 100 children and then 1,000 children. And then, you know, ultimately, my dream is that we're making individualized therapies for every child with rare disease. As we learn the lessons from rare and ultra rare disease, that's going to teach us how we can treat *everybody* in this individualized, precise way.

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