Duchenne

Hannah Bank: Listen up. Gavriel Rosenfeld is ready to make music. He isn't a pro. And he can't read sheet music. But the 19-year-old from England taught himself to play piano. Just give him a sec to warm up.

Gavriel Rosenfeld: Ok, I figured it out.

[MUSIC]

Hannah: Gavriel's fingers are dancing over piano keys. He's chosen to play "Clocks" by Coldplay. It's a song he loves that originally came out in 2002—the same year Gavriel was born—and its lyrics are full of urgency with phrases like "closing walls," "ticking clocks," and "cursed missed opportunities." They're themes Gavriel wrestles with every day of his life.

Gavriel: From a very young age, music has been my way of just expressing myself. If I've had a bad day, I'll sometimes bang on the piano more aggressively than others, just to let out a bit of frustration. It's really just a release in me. It's not enough of a release for me, believe it or not. I need to go for a run. I've been needing to do that for ages, but unfortunately, I just can't really be bothered to get around to it.

Hannah: The reality is Gavriel can't run. Not anymore. He's got Duchenne Muscular Dystrophy—a rare, life-threatening disease that's steadily weakening the muscles in his body. So when he passionately plays songs on the piano he does so from a wheelchair.

Duchenne, as Gavriel calls it, currently has no cure. The disorder's genetic mutation is linked to the X chromosome, so it mostly happens in boys. Gavriel was only four years old when he was diagnosed with Duchenne. Nothing dramatic changed overnight. But as Gavriel grew, he noticed his friends started running a little faster than him.

Gavriel: Nah, I didn't really understand. I just thought, I don't know, maybe I was just slightly slower physically. That's it.

Hannah: Leg cramps kicked in.

Gavriel: They were pretty bad as a kid. I mean, I was crying. My parents used to give me Ibuprofen or Nurofen. Then, you know, just lie with me. "Mommy's here. Daddy's here." Just to make sure that, you know, I was reassured at that stage.

Hannah: Then Gavriel couldn't walk anymore. He wasn't even a teenager.

Gavriel: I haven't stepped foot on this earth in seven years.

Hannah: Now Gavriel's arms are getting weaker. And both his heart and breathing muscles are also at risk.

Gavriel: Anything from bathing to dressing, you know, you name it—it affects me. I mean, I'm being told I probably will never walk again, and that's a scary thought. It's not just for now. It's for, you know—please, God, in the future, I want to raise a family. You know, physically things matter. You know, people have said to me, "Take it one day at a time." I don't have time—I don't have time to do that.

Hannah: The clock is ticking. But Gavriel has the rare chance to help scientists slow down or even reverse the disease in other boys with Duchenne. The first step? Sending a small sample of his skin cells thousands of kilometres away—to SickKids.

Hannah: You're listening to SickKids VS, where we take you to the frontlines in the fight for child health. I'm Hannah Bank. And this is SickKids VS Duchenne.

ACT ONE

Hannah: When you first meet Dr. Ronald Cohn, it's easy to feel intimidated by the sheer volume—and weight—of his titles: Paediatrician. Geneticist. Researcher. President and CEO of SickKids. Honestly, though, he just prefers Ronni. That's what Gavriel calls him, too.

Dr. Ronald ("Ronni") Cohn: It's essential for my own mental health—and has proven to be incredibly helpful even for my current position—to have, really, the privilege to experience what the frontline looks like when it comes to clinical service, what the issues are when it comes to research. So I actually think it's a huge advantage for me in my current role to still be able to be connected to clinical care and research.

Hannah: Ronni learned the importance of keeping close ties to patients during summer vacations as a kid.

Ronni: So I got into medicine through my grandfather, who was a family medicine practitioner of the sort of type that doesn't really exist anymore these days, because he practiced in an office that probably looked more like a living room than like a real physician's office. And I just loved sitting there for hours and hours at a time and watching him—how he would treat and interact with his patients.

Hannah: As Ronni grew, so did his curiosity about medicine, genetics, and research on a particular protein called dystrophin. It's the same protein that causes all sorts of problems for Gavriel and other boys with Duchenne.

Ronni: And what happens as a result of the loss of dystrophin in muscle is that these muscle fibers become somewhat fragile and go through cycles of being destroyed and then repairing themselves. You replace the newly formed muscle fibers that initially are being repaired with fat or scar tissue. And the more of that fat and scar tissue you produce, the bigger the impact on the actual muscle strength of the boys. Depending on what kind of standard of care access you have with physical therapy and access to prednisone, which is currently the only drug that somewhat stabilizes the disease, they lose ambulation and become wheelchair bound at the age of 12 to 14.

Hannah: When Ronni graduated medical school in 1996, most men with Duchenne died before they turned 20.

Ronni: The trajectory has now changed to a life-threatening disease. So these boys do get, now, much older. We have even a few adults—young men—up to the age of 40 or so with all the

respiratory support, cardiac support. But the ability in terms of what they are able to do because of this profound muscle weakness is usually quite limited.

Hannah: Through the ups and downs of his relationships with patients and their parents, Ronni has developed a deeper appreciation for the power of diagnosis—even when there's no cure for certain genetic diseases.

Ronni: And to tell you the truth, it has been probably the single most, so far, humbling experience in my own professional life: that I probably underestimated the power of having an answer for many years of my career when we didn't have the technology in our hand. I often told my families, "Let's take away that pressure to find a label," because they had lots of things we can—and need to—be taking care of independent of the diagnosis.

But then when technology arrived through genome sequencing and we were able to start providing diagnoses sometimes for families who have been searching for an answer for years, I realized what an unbelievable relief it is if you don't necessarily have a treatment.

Hannah: You might already be familiar with genome sequencing. It's a process where a sample of DNA gets taken from your blood and examined for mutations that could lead to a disease like Duchenne.

There's even more promising technology called CRISPR with the power to physically edit genes. But when studies about CRISPR first start coming out, Ronni doesn't pay much attention to them.

Ronni: It was such a different language. I never found the time to read it, because I didn't understand it. The only scientists who really knew deeply about CRISPR were microbiologists. Really, nobody else knew about it.

Hannah: Less than a decade ago, an article about revolutionizing the treatment of genetic disorders gets published in a U.K. newspaper. Ronni's inbox gets **flooded** about the story.

Ronni: Within 24 hours I had like 40 emails from parents asking me, "Do you think it can help my child with this mutation or that mutation?" So I finally read it, was mesmerized, and still today—many years later—I'm still mesmerized by even the idea that we can think about fixing a genetic mutation.

Hannah: CRISPR might sound like the brand name for a salad spinner. But Ronni says to think of it as tiny scissors that can reach nearly any region within the human body. Those scissors can clip out faulty or mutated portions of genes before they get corrected.

Ronni: I remember going to my director of my laboratory—asking him, what do you think about this? Let me know. And if you believe that this is as exciting as I think it is then scrap everything we are doing now in our laboratory and start doing research just on this.

ACT TWO

Hannah: As soon as Ronni introduces CRISPR to his team, everyone gets excited about the technology's potential to treat genetic diseases like Duchenne.

Ronni: Everybody in my laboratory was willing to almost put behind what they were working on.

Dr. Zhenya Ivakine: It's very appealing because if we can correct the cause of the disease at its root level—and the root is DNA—it can be potentially a curative therapy.

Hannah: That's Dr. Zhenya Ivakine, a scientist who was Ronni's lab director at the time.

Zhenya: So, in this case, we don't have to give medications on and on and on. So that potentially can actually provide a real cure.

Hannah: The lab actively gets going in this new direction in 2014.

Ronni: I started thinking about my very close friends in the U.K., who have a boy with Duchenne Muscular Dystrophy, who is now a young man.

Hannah: He's talking about Kerry and Doron Rosenfeld—and their son Gavriel.

Ronni: We are very close. Gavriel is not a patient of mine, he's a friend of mine.

Gavriel: My parents met him at a conference once, and it kind of went from there. He's been around as long as I can remember.

Hannah: Gavriel is of interest, in part, because his Duchenne is caused by a mutation where a tiny portion of his genes are duplicated. *What if* Ronni and his team can correct the mutation in a small sample of Gavriel's cells? Could they then also fix it in a living organism? Ronni calls Kerry.

Ronni: I remember asking her, "Would you be willing for us to try this in the muscle cells of your son, Gavriel?" And she is an incredibly intelligent individual who asked me 1,000 questions and, at some point, I didn't have answers anymore for the questions. And I remember her quote saying, "Alright, I'm going to send you these cells. And if it all works, then we're going to make a movie out of it. I want to be played by Angelina Jolie."

Gavriel: Ronni took some skin cells from my left arm. There's still a mark there.

Hannah: First, Ronni's team receives and analyses the skin sample.

In 2015, they successfully remove the duplicated genes right from Gavriel's cells. A thrilling achievement. But we're still talking about victory in a Petri dish.

Now comes the tricky part: the team is going to recreate Duchenne—along with Gavriel's genetic duplications—inside a young mouse. They're doing this to see if they can inject CRISPR into the mouse to find and cut out genetic duplications. If the team can accomplish this, they can show how to make a living organism healthy again—*before* more serious symptoms of Duchenne appear. That could ultimately lead to the discovery of a new treatment for the disease.

Ronni: You really want to know whether that works in the whole-body organism.

Hannah: At first, things are working as planned.

Ronni: Creating something like this would usually take a year at least, if not two. And here, within a few months, we have this mouse model, we're all excited it had muscular dystrophy, no dystrophin—everything we were expecting.

Hannah: But then the team runs into a problem. While they can demonstrate that their mouse displays Duchenne, they can't actually correct anything at the genetic level.

Ronni: We injected the scissors into the mouse with an associated virus carrying it. And nothing happened. So I initially thought, oh my God, maybe this doesn't work in a mouse.

Hannah: The team keeps trying. For weeks. Then months. Then over a year. But they still can't make the experiment work. The setback is daunting, and it's taking a toll.

Ronni: We as scientists, we set a certain amount of expectations for us that this is just going to work. And when it's so directly related to individual patients and families—in this case, even somebody I know who is so dear to my heart—all the time that passes by, it is a pressure. There's a certain amount of pressure, and I remember—for a long time—we were having regular meetings to just talk about the ethical impact of the work we do. And there is as much of a psychological motivation to actually make this happen.

Hannah: The pressure weighs on the team. For two years they persist. Then, one day in 2017, a graduate student in the lab cracks the case. It turns out that when the team introduced Gavriel's mutated genes into the mouse, by chance, a few parts of the gene got flipped in the process.

Zhenya: What it means is a portion of the gene just basically goes not from left to right anymore, but now from right to left. And by doing it, we broke the gene in a way that we did not plan.

Ronni: So it took us a long time to figure out why the experiment didn't work. I remember this Saturday afternoon when I was at home and my post doc sent me a picture of successfully removing the duplication in the cells.

Hannah: Finally. There's visual proof showing the mouse's genes are fixed and that normal functioning is restored. The breakthrough is widely celebrated and means Ronni and his team can develop their findings even further into a potential treatment to help boys with Duchenne.

Ronni: And that was kind of my eureka moment in science.

Hannah: Once again, Gavriel and his parents are top of mind. Ronni pulls out his phone.

Ronni: I remember I sent them a text saying, I need to talk to you, and I need to show you something. It was the next day when I spoke to the parents. On the Sunday. It was at that point an unbelievable, exciting moment for all of us. As much as, as I said before, we were trying to set expectations to be realistic, but at that moment, it was just great.

ACT THREE

Hannah: Right now, Ronni and his team are looking to advance their work by collaborating with an industry partner. They're hoping their breakthrough might, one day, help prevent Duchenne from devasting the lives of young boys.

Ronni: The proof of concept has been done. We would like to develop this further and see where it can go into a clinical trial.

Hannah: The team is also exploring how to help older children, like Gavriel. That's why they're initiating gene editing work in more senior mice with Duchenne.

Zhenya: We would like to understand until what age it is possible to completely reverse development of the disease.

Hannah: The team has already done research on another type of muscular dystrophy and found that they can start treating early signs of paralysis in mice. It's another major finding, and one that motivates the team to keep going.

Zhenya: We can actually, partially, reverse progression of the disease. And so this is my hope: that we can accomplish the same for Duchenne.

Hannah: For Gavriel, and others with Duchenne, time is of the essence.

Gavriel: I've kind of come up with an idea. There's a YouTube I once saw that did a segment called "30 Things I Like to Do Before I'm 30," and I'm starting to think of those. One of them is skydiving—the reason being is because it's completely out of my comfort zone. And, you know, every sinew in your body tells you not to jump out of the plane, which is exactly what I'll be doing. Medically there is actually nothing holding me back. But the guy who's strapped to me, the instructor, is going to have to do the running, when we land, for me.

Hannah: Gavriel's still working on his list. He's already gone scuba diving—with dolphins—and he's an avid horseback rider. Plus, he's got support from Ronni, whose team is diligently working behind the scenes to buy boys with Duchenne more time.

Ronni: It has been fascinating to even witness over the last few years how this genome technology has moved forward in an unprecedented speed. You know, what we started thinking about eight, seven years ago is now so much further advanced. This technology is constantly developing and constantly getting better, so I can't even begin to think how much better it's going to be in a few years from now.

Gavriel: I'd say there's plenty of hope, even though I'm a moody old man, probably. Yeah, I'd definitely say there's a lot to look forward to. The future is now. Time is ticking.

[MUSIC]

EXTRO

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