**SickKids VS Cancer Genetics:**

**Cracking the Tumour Code with Gene Sequencing**

COLD OPEN

HANNAH: Izaan is born a happy and healthy boy. His mother, Saima, considers him a miracle child, their gift from God after ten years of trying for a baby. But at seven months old, Izaan is brought to the SickKids Emergency Department.

DR. DAVID MALKIN: He was essentially inconsolable. Mom was holding him and flipping between her and dad. And this, based on listening to them, was what he was like most of the time. He couldn’t lie down without really screaming. He was having difficulty eating or breastfeeding.

HANNAH: That’s Dr. David Malkin, an oncologist and Director of the Cancer Genetics Program at SickKids. He can see how exhausted Saima is, how terrified she is for her boy. He can also see what’s causing all this—a grapefruit-sized tumour protruding from Izaan’s bum. The tumour is sandwiched between his spine and bladder, pressing on his intestines—and causing terrible constipation. Izaan’s symptoms are already worrying. As the tumour continues to grow, things will only get worse. But the exact nature of the tumour isn’t so easy to decipher. Izaan’s pathologist initially diagnosed it as a soft tissue sarcoma.

DR. DAVID MALKIN: So a sarcoma is a tumor that's derived from either muscle or bone or cartilage or fat.

HANNAH: But they’re not entirely sure what kind of sarcoma it is. It resembles another rare tumour, but it’s not an exact fit. At best, their diagnosis is an educated guess. And that doesn’t sit well with David.

DR. DAVID MALKIN: As an oncologist, not knowing exactly what you're treating always makes you a bit nervous.

HANNAH: So, David enrolls him in a study he co-leads called KiCS, the SickKids Cancer Sequencing Program, one of the world’s leading programs of its kind. It’s where oncologists bring their most difficult cases: kids susceptible to cancer; kids with aggressive, hard-to-treat cancers; and kids with rare or hard-to-classify tumours. KiCS analyzes children’s DNA—and their tumours’ DNA—to figure out what’s causing the cancer, and how to stop it.

A patient’s DNA might reveal mutations that predispose a child to cancer. While their tumour’s DNA might reveal mutations driving the cancer. Like plants and people, tumours have their own genetic code, a blueprint for how they grow and spread. Understanding that genetic code can be key to finding the right treatment. But comprehensive genetic testing like this can take months. And David needs to start treating Izaan now.

So, he starts Izaan on chemotherapy. The plan is to shrink the tumour with chemo, then have surgeons remove what’s left—*without* damaging any organs. But as the days pass, the tumour doesn't shrink. It gets bigger.

DR. DAVID MALKIN: And if this thing keeps on growing again, is resistant to all the therapy that we're giving, then the end result can only be bad.

HANNAH: For Saima, it’s devastating.

SAIMA: I was so upset that time and I might I lose my all hope. I went into totally depression.

HANNAH: David needs to change course. But he still doesn’t know why the treatment isn’t working, or what exactly Izaan’s tumour is. And to answer those questions, he needs KiCS.

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 Cancer Genetics.

ACT ONE

DR. ANITA VILLANI: The collective goal of the huge team that works on KiCS is to understand better how this type of in-depth genetic analysis can help us better understand our patients' diagnoses, try to help shed some light on why they got cancer, try to take a look at how it is responding to treatment.

HANNAH: That’s Dr. Anita Villani, a SickKids oncologist and co-lead of the KiCS program with David.

Anita likes to think of KiCS as a pipeline, a step-by-step process that begins with extensive genetic analysis and ends at the molecular tumour board, a group of oncologists, geneticists, genetic counsellors, pathologists, and scientists who make treatment recommendations based on the findings. Each week, they come together at SickKids to pool their expertise and review cases from KiCS.

If cancer is the supervillain, the molecular tumour board is the Avengers—the best of the best, all united by a singular purpose.

To help Izaan, first they need to find the mutation that’s driving his cancer. And that job belongs to genome analyst Nisha Kanwar.

NISHA**:** I look at the DNA of individuals’ tumors, and that really helps me understand what is a mutation that initiated the tumor. Is there a certain mutation that led to progression or resistance to treatments and things like that. So really the goal is to look at a patient's DNA, to try and find what caused the cancer.

HANNAH: Unlike David, Nisha doesn’t see patients and families–she sees genetic code. But the work is personal to her. And the pressure is serious. Her team, and their patients, depend on her.

NISHA: These are all urgent. These are all essential.

HANNAH: Nisha works on a lot of cases. But she still remembers Izaan’s well.

Nisha: It was probably one of the last days I was coming into work before going off on holidays. And it was odd because I was actually working on a different case and all of the conversation was about this different case.

HANNAH: That case is a patient with a rare kidney cancer. But something about that tumour isn’t right. It’s not behaving like it should. And the mutation that’s driving this strange tumour is in a gene called BCOR, which codes proteins**.**

Around that time, Nisha opens Izaans’ file.

NISHA: And right there, the first thing I see is a B core variant. So, you call it a coincidence. Serendipity, like whatever you call it, like everybody just had to take a pause and sort of go, “How is this happening?”

HANNAH: This could be it, the very mutation that’s driving Izaan’s cancer. Nisha fires off an email to Anita and her colleagues.

DR. ANITA VILLANI: This was a Friday. Nisha writes to say, “Hi all. I'm working on this case of infantile sarcoma and I found a B core variant that might be indicative of a b core ITT.”

HANNAH: That one email triggers a flood of excited responses. Dr. Adam Shlein, KiCS’ Clinical Research Project Manager, writes, “mind blown times two.” Other colleagues review her work and the scientific literature.

NISHA: There’s so few of us at the lab at that point because at the end of year and we were double, triple, quadruple checking it to make sure like is this is this real.

HANNAH: Just a few days before Christmas, it’s confirmed. They’ve found the unique mutation driving Izaan’s tumour, the secret to what’s made it so resistant to chemo. But Izaan is still very sick. And time is of the essence.

ACT TWO

HANNAH: With this new discovery, Izaan’s case is now ready for the molecular tumour board. And the excitement in the room is palpable.

DR. DAVID MALKIN: The idea that what we were doing wasn't working and here was something that the bioinformatics team was giving us that could change the course was really quite exhilarating.

DR. ANITAVILLANI: We were very excited. You know, it's sort of like the thunder that you want to reveal to the crowd.

HANNAH: Unlike some tumours, there is no targeted treatment for what Izaan has. But what the group does discover is this:

DR. DAVID MALKIN: It was way more aggressive than the other kind of sarcoma that we initially were thinking or may have been thinking. And with that information in mind, I knew that there was I would switch his treatment entirely.

HANNAH: David wants to use a combination of four chemotherapy drugs, three of which are very aggressive. And toxic. Which means a greater potential for serious side effects, like nausea, anemia, infection, and bleeding.

DR. DAVID MALKIN: That's the constant battle is how much are you willing to take a child to the edge? And with the hope of a great response, recognizing that, you know, you could end up with other problems down the road.

HANNAH: But with the tumour growing, David isn’t left with much choice.

DR. DAVID MALKIN: I just felt that for Izaan that we had to do something pretty dramatic, or we’re just going to lose the entire game altogether.

HANNAH: Izaan’s parents agree. David begins Izaan on the new, more intensive chemo. Days pass. Then, something remarkable happens—the tumour begins to shrink.

DR. DAVID MALKIN: After a couple of cycles, there was no question that physically you could see this tumour was getting smaller; it felt softer. And then when we did the first imaging MRI, this thing had shrunk by about half of what it had been before we started.

HANNAH: Saima can see her son improving, too.

SAIMA: So we were happy and we are getting hope. Izaan is going to be well soon.

HANNAH: David’s next question is how long to continue the chemo before surgeons can remove what’s left of the tumour. As in so many things in cancer care, it’s a precarious balance.

DR. DAVID MALKIN: As a tumour gets exposed to more and more chemotherapy, they start to acquire resistance to that chemotherapy. They get used to it a little bit. So the worry is always there that if you wait too long, yeah, the surgeon goes and takes it out. But in the meantime, some of these few cells have acquired resistance and they could come back down the road.

HANNAH: David decides to continue the chemo for a total of six cycles. With each subsequent round, the tumour continues to shrink. Everything is looking good. Still, the surgery won’t be so straightforward.

DR. DAVID MALKIN: At the time of surgery, there was still potential challenges that, uh, the surgeons were concerned about that based on where this tumor was. They could damage nerves to his for his walking, for his bowel, for his bladder.

HANNAH: Izaan’s surgery will be spread over two days. On the first, surgeons will approach the tumour from the front of his body; on the second, from the back. All of this makes Saima nervous. She has visions of her child traumatized by the surgery.

Making everything more complicated is the sudden surge of COVID-19. As the disease spreads across Canada, operating rooms start shutting down. So David scrambles to coordinate with surgeons and hospital leadership to get the surgery done quickly. Finally, in the spring of 2020, Izaan goes in for surgery. Saima waits outside with her husband. Hoping and praying.

ACT THREE

HANNAH: The first day of surgery finishes faster than anyone expects. Better yet, there were no complications, no damage to any of the surrounding organs. The second day is a success, too. The surgeons remove whatever is left of the chemo-shrunken tumour. And Izaan begins to heal.

HANNAH: In December 2020, more than eight months after the surgery, I ask David about the last time he saw Izaan.

DR. DAVID MALKIN: What I remember was quite funny as I was leaving I waved and I said a little, bye Izaan, see you next time. And he sort of peeks over his mom's shoulder and gives me a wave of his hands, probably because he knew that. “OK, good. I'm out of here.”

HANNAH: Izaan seems to be doing well. He’s happy. And playful.

SAIMA: I'm always scared, but I know that things are very good. It's back to normal and he's very active now. We are always busy with him to play with him all day.

HANNAH: Izaan is just one of many children whose lives has been saved by KiCS. In the four years in which KiCS has been active, they’ve enrolled just under 500 patients—kids, teenagers, and young adults who otherwise had little hope. They’ve even started to sequence the DNA of adult patients.

DR. DAVID MALKIN: So, uh, just over 80 percent of the alterations that are identified are potentially actionable. About half of those are patients in which we find an alteration in the tumour cells for which there is a drug that could be, at least in theory, used to target it. About 15 percent, we find an alteration in their blood, which suggests that they have a genetic predisposition to the cancer. That may not always change or guide us in terms of treatment, but it does tell us that there may be an impact on other family members. And then there's also a smaller group of patients, about 10 to 15 percent, for whom the genetic alteration we see in the sequencing actually changes the diagnosis.

HANNAH: In other words, it’s working—really, really well. So well, in fact, David wants to expand the program, so even *more* children have access to this kind of sequencing and expertise.

DR. DAVID MALKIN: The KiCS program has demonstrated to me and to our colleagues and really around the world that this is the right way, the best way, the most appropriate way, to take care of kids with cancer. Every child should have access to KiCS sequencing and to the potential therapies that can be enabled by a program such as this.

HANNAH: Genetics-driven, highly tailored treatment is part of a broader trend in medicine. Here at SickKids, we call it Precision Child Health. It’s a vision of a different kind of healthcare, one informed by what makes each patient unique, from their genetic code to their postal code. But this kind of individualized treatment can be expensive, a problem David knows all too well.

DR. DAVID MALKIN: So the actual cost per patient, if you will, once you've done everything and put all the analysis together, still approaches close to ten thousand dollars here.

HANNAH: All of the funding for KiCS comes from donors.

DR. DAVID MALKIN: As this program evolves, as we offer it to more and more children and young adults, that we need funding to maintain that and the funding is substantial. But at the end of the day saving lives is worth it.”

EXTRO

HANNAH: From SickKids Foundation, this is SickKids VS. Thanks for listening. If you want to support work like this, visit sickkidsfoundation.com/podcast to donate. And if you like this podcast, please subscribe and rate us on Apple podcasts, Spotify, or wherever you listen to SickKids VS.

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