SickKids VS Unexplained Seizures

Hannah: Patrick and Taylor were days from getting married when they noticed something going on with their son Noel. It was June 2023. Their friends and family had travelled to Northern Ontario, where the couple would exchange vows at a lakeside resort. Nine-month-old Noel had a cute little outfit for the occasion. But the weekend before the wedding, Noel started acting strange. His dad Patrick explains.

Patrick: Especially as a new parent, obviously you see babies do a lot of weird things, and you're always just wondering, I don't know, just normal behavior or, you're always second guessing yourself. But then, yeah, he had a sort of weird movement, where I remember Taylor saw it first, and she seemed kind of alarmed. She told me about it, and we just thought it was nothing. And then it happened again. I guess their head sort of drops and then their arms come up. It's really quick. It's like sort of a quick spasm and then he's back to normal. And then sort of immediately you go down a bit of a rabbit hole and you read a lot of scary stuff and, yeah. So, we brought him to the emergency right away.

Hannah: When they arrived at the local hospital, Noel was his usual self and seemed totally fine. Over the next two days, though, his odd movements started happening again – and more often. Patrick and Taylor took Noel to another hospital.

Patrick: So we drove to the bigger city. To another emergency room. Then I almost got shrugged off again, but luckily. We were videotaping him the whole time, and he did it. So we caught it on video. And then we showed one of the pediatricians that on staff there, and they seemed to know what it was right away.

Hannah: Noel was admitted on the spot and stayed for a few days for testing. He was diagnosed with Infantile Spasms, a severe form of epilepsy. Epilepsy is an umbrella term that describes any brain disorder causing recurring seizures. There are many kinds and many causes, but more than half of patients will have a genetic basis. There's also a wide range of treatments and medications, which might work for one form of epilepsy, but not for another.

For Noel, none of the drugs seemed to work, and Patrick and Taylor could only watch as the spasms got worse and more frequent. To really help Noel, it wasn't enough to know that he has epilepsy. But more importantly, *why* he had it. Here's Noel's mom, Taylor.

Taylor: After we got the diagnosis we were connected with the Infantile Spasms Clinic at SickKids. From there, we had appointments and EEGs. We had done…

Patrick: A CT scan.

Taylor: Yeah, and an MRI. Nothing had come back with any answers for us. And the SickKids team said, you know, we have this program, Gene-STEPS. We could do the testing for you at SickKids, you would get results within a couple of weeks. And it would be covered under Noel's SickKids care. So, for us, we jumped on that right away. We wanted to know. We wanted answers.

Hannah: 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 Unexplained Seizures.

Hannah: Gene-STEPS is an international research study that began in 2021. The immediate goal is to find a genetic diagnosis for unexplained epilepsy in babies using whole-genome sequencing. And to do it quickly – within weeks, not months. More on genome sequencing later.

Greg: Knowing that someone has epilepsy doesn't tell you immediately why they have epilepsy. The goal of our genetic testing is to see if we can identify or pinpoint a precise explanation at the DNA level for why does this person have epilepsy, and not perhaps a sibling or parent or classmate or neighbor. By some accounts, there are about a thousand different genes that, if not working properly in a given individual, can cause epilepsy. And so there are a thousand different genetic diagnoses that we could potentially make to explain someone's epilepsy.

Hannah: That's Dr. Greg Costain, a medical geneticist and scientist at SickKids. He studies and treats rare genetic diseases. And he's part of the large Gene-STEPS research team at SickKids. Though epilepsy isn't considered a rare disease, there are many rare forms of it. Some, like Noel's diagnosis, are quite severe and can hugely impact a child's cognitive development.

Greg: Unfortunately, the motivation for doing Gene-STEPS was largely that many babies who begin to have epilepsy go on to have epilepsy that's very difficult to control with standard medications, and epilepsy that either directly interferes with their development, or seems to go hand in hand with major problems with development. Such that as these children grow up. They have additional significant needs for care that might be lifelong. We chose to focus on epilepsy also because understanding the specific genetic cause can give us useful insights right away, in some instances, into which medications are most likely to be effective. Or which medication should be avoided.

Hannah: For Noel's disorder, treating spasms early is critical. The longer they go unchecked, the more they can affect a child's ability to think and learn. When Noel got his initial diagnosis in the summer, he was immediately started on a few standard anti-seizure drugs. But the process of trial and error was slow and frustrating. Here's Noel's mom again.

Taylor: And one thing I found about the epilepsy medications was you can start one, but you have to kind of slowly work your way up to the highest dose. And then when you're at the highest dose, it's sometimes a couple of weeks before you start seeing results. And I think for us that was frustrating because when they're having seizures, we noticed with Noel, but like right away, he kind of stopped progressing, stopped learning new skills. It was, you know, scary knowing like, okay, we have to try different medications, but it takes a long time. And then if they're not working, it's a couple of weeks, if not months to get him off of it. So, for us, like just kind of navigating the different medications and then also him not developing was really, really tough. We were realizing that his seizures or his spasms were very drug resistant. And it was very frustrating because we didn't know why.

Hannah: Standard genetic testing for epilepsy usually takes about two to three months. An eternity for parents who are desperate for answers. The analysis focuses only on specific genes, where there are known variants associated with epilepsy. How and when this genetic testing is employed varies from place to place. Depending on the hospital or the country, some babies might get tested right away. Others may first cycle through several medications. Or get tested only when major developmental problems arise.

Gene-STEPS eliminates this lag by doing genetic analysis as soon as a baby is diagnosed with epilepsy. And not just on the known genes. The team analyzes the entire genome – more than 20,000 genes and billions of nucleotides that make up human DNA. It's called whole-genome sequencing, the most comprehensive genetic test out there.

Greg: DNA is like a recipe book. Each gene is its own recipe. Anyone's genome or recipe book contains thousands of lettering differences compared to another person's genome. The majority of those changes don't seem to cause in isolation a severe genetic condition. The challenge is identifying the metaphorical needle in the haystack – or a given lettering change that could actually be a diagnosis or an explanation for an issue that someone is showing us. Genome sequencing has been a game changer in that it changes the paradigm away from always needing to be knowing exactly where to look, to being able to look in a more comprehensive fashion.

Hannah: The Gene-STEPs study aims to return results of whole-genome sequencing to families within three weeks. This is a huge clinical feat, considering the immensity and complexity of these results. The goal is to do this for 600 families, and not just at SickKids. Gene-STEPs involves three other major paediatric hospitals: Boston Children's, Great Ormond Street in London, England, and Royal Children's in Melbourne, Australia. Together, they make up IPCHiP – the International Precision Child Health Partnership. It was launched in 2021 to pool data and expertise to study the benefits of broad genomic testing for rare diseases, starting with epilepsy. Gene-STEPs is their first project. And it doesn't end with a diagnosis.

Greg: Our plan is to follow all the children participating in Gene-STEPS until they're at least two and a half years old. Ours is one of the first studies to both perform rapid genome sequencing in a baby, and to follow those children over time. The reason we chose to design our study in that way is that we need to better understand what the consequences were of that early genetic testing intervention in their lives.

Hannah: In other words, will rapid whole-genome sequencing result in better outcomes for babies with epilepsy, like Noel? And if so, what could that mean for other genetic diseases?

Hannah: For Patrick, Taylor and Noel, participating in Gene-STEPs involved a simple blood draw for their genetic analysis. Analyzing the genomes of biological parents is a unique aspect of the study and allows the team to crosscheck any variants to see if they were inherited. Noel also had some developmental testing to see where he was at with his milestones. In the meantime, his spasms were getting worse.

Taylor: He was having multiple clusters a day, and I want to say six, seven episodes. And those clusters could be anywhere from like 30 to sometimes even 50 spasms. And they would just be horrible to watch. He would be so just exhausted after and sleep for hours during the day. And we were going through times where he had insomnia at night. So me and Patrick were up at night.

Hannah: When a baby is having a seizure or a spasm, caregivers can only provide safety and comfort.

Taylor: We would kind of just lay him down, make sure he's safe and just, you know, talk to him and let him fall asleep on us and feel safe after it was all said and done.

Patrick: Yeah. It's pretty heartbreaking. There's really not much you can do. Just hold their hand and hug him and, yeah, wait for it to be over.

Hannah: Being part of Gene-STEPs meant that Patrick and Taylor wouldn't have to wait long to get to the bottom of Noel's seizures. As soon as the genetic results are ready, they're received by two genome analysts who are standing by. These specialists evaluate hundreds or thousands of rare differences in DNA. And they weigh them alongside other genetic and clinical factors to determine if the variants are important. Do they explain why the baby is having seizures?

Greg: Those genome analysts for Gene-STEPS are two people, both of whom volunteer their evenings and weekends to look at this data as soon as it comes off the machine and is available. These people choose to spend their time on weekends looking at this information right away, such that there's almost no delay between when the data are available for analysis, and when we have a general sense of: do we think there's an explanation here.

Hannah: The final report is ready in a matter of days, and families are notified as soon as possible. Lyndsey McCrae is a nurse practitioner with the Infantile Spasms Clinic at SickKids. She helps identify families eligible for Gene-STEPs. And because she's a familiar presence to families, she's often in the room with the medical team when they reveal the results. She talks about what that's like, particularly watching Greg deliver complex and daunting news.

Lyndsey: Explaining genetics results is not easy. And he is able to also break it down in a way that, is very digestible to a family. And translates it into more everyday language, that, you know, families then leave their appointment, feeling like they have a good understanding of what this means, for their child and potentially for themselves. He strikes quite a wonderful balance between being realistic, but being very hope-filled as well. And also reassuring families that we will be the genetics doctor for your child until they're 18, and we will keep looking for how we can get more answers.

Hannah: Sometimes, genetic testing comes back negative. This, along with other reassuring clinical results, often means that the child's seizures will respond well to treatments and stop altogether.

Lyndsey: Sometimes we don't find anything and we actually love that too. If we don't find a cause for the seizures, the prognosis is much better in terms of continuing to be seizure free, minimal risks to development, if any. So, part of our workup is also hoping to find nothing.

Hannah: Patrick and Taylor desperately hoped for nothing. But Noel's analysis revealed a genetic diagnosis called CDKL5. It's a rare and severe form of epilepsy known to be extremely drug resistant and associated with cognitive delays. Noel's genetic difference was found to be unique to him, rather than inherited by one of his parents. For them, finally knowing the cause of Noel's seizures was, yes,

upsetting and scary. But at least they knew what they were up against. There was a clearer path forward.

Taylor: One of the first things they told us was, you know, we have an answer to why Noel's seizures have been so drug resistant. And they did tell us, you know, you're going to go home and read a bunch of stuff about his condition, and it's going to be really scary. But that might not be Noel. There's a spectrum, and, you know, there are some, some kids who experience a whole range of the symptoms on the spectrum. And some kids do not. And it would be up to Noel to show us what he can do and what he can't do or what he needs help with. You know, hearing that, that was kind of, you know, it's scary, but it was also reassuring to know.

Hannah: As a clinician, Lyndsey also feels empowered by the diagnosis, because it allows her to provide the right care for that patient right away.

Lyndsey: I feel quite honored to be a part of this study. And just grateful because it makes me feel that I'm offering also the best possible care option to families, and through participating hopefully can allay some fears. Or the big thing, too, is also minimizing that wait time for results. Because you know, that sitting in that sort of in-limbo is emotionally taxing for families.

Hannah: If Patrick and Taylor had chosen not to enroll in Gene-STEPs, they would be getting the standard, clinical-grade genetic results as we speak, several months later. They might still be cycling through medications. They wouldn't yet be part of the CDKL5 community, where they gather support and updates about new drug developments. And Noel probably wouldn't be doing as well as he is now.

Hannah: Results from the first 100 patients enrolled in Gene-STEPs at all four hospitals were recently published in a major journal. Remarkably, 43% of these patients received a genetic diagnosis. And for more than half of these participants, the diagnosis informed treatments that improved their seizures, in some cases stopping them outright.

Since receiving his genetic diagnosis, Noel is a different kid. He was taken off some of his medications and was immediately prescribed a strict ketogenic diet. This is a high-fat, low-carbohydrate diet shown to help reduce seizures for certain types of epilepsy, like Noel's. And it seems to be helping. Noel went from having up to 100 spasms a day to just a few or, some days, none at all.

Taylor: He's started to sleep through the night again for us. He's making some really great developmental gains. He's just recently started to pull himself up on furniture and cruise around and crawl, so he's keeping us on our toes. We're having to chase after him all day long. He's done really, really well with the ketogenic diet. He does have developmental delays and, but with his diagnosis, we've been able to fast track getting therapies for him. He gets physio, OT and speech weekly. And he seems to be responding pretty well to the therapies and making some great gains.

Hannah: By compiling and publishing these tangible results, the research team aims to build a compelling case for rapid whole-genome sequencing as a standard clinical test. Right now, it's used largely for research. And it isn't covered for clinical use by most governments and insurance plans. As a test case, Gene-STEPs hopes to change that, for epilepsy, and eventually for other disorders. Here's Greg Costain again.

Greg: The goals of IPCHiP, and specifically of this Gene-STEPs study, have coalesced around trying to improve access to timely, accurate genetic diagnosis for rare disease. To try to develop an evidence base for new genetic technologies that would convince payers in these different countries that they should become part of our public healthcare systems. And to begin to expand our knowledge of the underlying cause, to the point that we can start to think much more about using those diagnoses to inform precision therapies.

Hannah: Knowing that Noel has CDKL5 means the family's medical team will be on the lookout for drug trials and new therapies in development. One is a potential gene therapy, a drug that would target Noel's precise genetic variant. Here's Noel's dad, Patrick.

Patrick: It gives us hope that one day there will be a gene therapy that could help. And I guess if we didn't know the diagnosis, you know, we just wouldn't have that sort of hope. We'd always just be trying medications and hoping something changes. But at least, you know, we know the root cause. There are companies that are trying to figure out the solution and hopefully one day they do.

Hannah: And beyond the impact of a diagnosis, the genetic data is a powerful resource – the rich soil from which to unearth new disease-genes and expand our understanding of other genetic disorders.

Greg: In time our hope is that by performing the test on more individuals, we learn more about how to read the DNA and understand it. This creates a positive feedback loop. The more that we sequence or read the DNA of individuals on this planet and are able to connect that information with something about their health status, and ideally able to share that information in a safe way with other people around the world, the more we all benefit.

Hannah: From SickKids Foundation, I'm Hannah Bank. Thanks for listening. To support breakthrough research and care at SickKids, please visit SickKidsFoundation.com/podcast. And if you liked this episode, subscribe and rate us wherever you listen to podcasts.

SickKids VS is produced by me, Hannah Bank, Jasmine Budak, Liz Surani, Emily Holland, Deanna Cheng, and our showrunner Neil Parmar. This episode was written by Jasmine Budak. Sound Design and Editing by Quill. Check out our show notes for helpful links and resources. Until next time.

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For more information about IPCHiP and Gene-STEPs, visit here:

About IPCHiP: Four leading children's hospitals announce IPCHiP, a collaborative to develop new treatments for paediatric diseases (sickkids.ca)

About Gene-STEPS: Global genomic collaboration provides diagnoses and informs care for infants with epilepsy (sickkids.ca)

Early results from Gene-STEPs: Evaluation of the feasibility, diagnostic yield, and clinical utility of rapid genome sequencing in infantile epilepsy (Gene-STEPS): an international, multicentre, pilot cohort study - The Lancet Neurology