Playing the Genetic Lottery: Understanding Rare Diseases

Shaun: Everything with this, it's so rare that no one can ever give me an answer for anything. Even when he was first diagnosed, his pediatrician was like, "This is something we learn about when we're going through med school, and we never actually see." He's like, "I've treated over 200,000 kids, and this is my first case."

~CTOR Tag~

Introduction

N1: Thanks for tuning in to another episode of Carry the One Radio! My name is Iris Chin.

N2: And I'm Marilyn Steyert.

N1: Today, February 28th, 2021, is Rare Disease Day: a day dedicated to diseases that you might not have heard of before. Even though they're not very common, they deserve just as much attention as more common disorders!

N2: There are lots of different people affected by rare diseases, and it goes beyond individual patients. To sample some of the many perspectives out there, we spoke to a patient, a caregiver, a genetic counselor, and a researcher dedicated to studying rare diseases.

N1: In this first section of the podcast, we'll learn about what classifies something as a rare disease, and hear about one family's story of getting a diagnosis. Then, later in the episode, we'll hear from experts who work with rare diseases, in both the clinic and the laboratory.

What is a rare disease?

N1: First, here's Dr. William Gahl.

William Gahl: My name is William Gahl. I'm a Senior Investigator at the National Human Genome Research Institute, which is one of the NIH institutes. I'm also the Director of the NIH Undiagnosed Diseases Program, which is part of the Undiagnosed Diseases Network, which is a group of centers around the country that pursues the investigation of undiagnosed diseases.

N1: Dr. Gahl is one of the country's leading investigators studying the biology of rare and undiagnosed diseases. That begs the question--what exactly *is* a rare disease?

William Gahl: In the United States, it's one that has fewer than 200,000 individuals affected. In Europe, one definition that I just read was a frequency of 1 in 2,000.

N1: So, the definition of a rare disease is one that's... well... rare! It turns out that rare diseases can be quite severe, and they often stem from some basic biochemical processes going haywire.

William Gahl: Maybe there's a good way to look at it too and that is, what is the incidence of some of the rare diseases that we're familiar with? And incidences are determined best, probably, by newborn screening.

William Gahl: The classic inborn error of metabolism would be phenylketonuria, which has a frequency of about 1 in 14,000.

N2: What's an inborn error of metabolism?

William Gahl: Well, an inborn error of metabolism is roughly the same as a biochemical disease. In other words, an interference with a pathway where the function of the pathway is impaired. And that causes either too much build-up of something or not enough production of something. There are classic inborn errors of metabolism that have to do with enzyme deficiencies. Most of the enzyme deficiencies that result in disease have to do with the break-down of products.

N1: Phenylketonuria, or PKU, is an example of one of these diseases caused by a defective enzyme–in patients with PKU, a protein in the body that's supposed to help break down the amino acid phenylalanine, is broken.

William Gahl: It really is biochemical pathways that have gone awry because of a genetic defect.

N1: We were curious to hear more about newborn screening. Here's Linda Manwaring, an awesome genetic counselor, to explain what it's all about, and why it's important. By the way-I'd like to give a big thanks to my genetics professor from undergrad at WashU, Dr. Ian Duncan, for connecting us with Linda!

Linda: Hi, my name is Linda Manwaring. I am a genetic counselor at Washington University School of Medicine and St. Louis Children's Hospital. I have been at Wash U since 1996, so a long time working in the department of pediatrics. And I got my master's degree in genetic counseling from the University of Pittsburgh.

Linda: So newborn screening historically had always been metabolic disorders for which there was a diet treatment available and it has expanded from that. So we are testing for Gaucher and Fabry, Pompe, MPS1 - also known as Hurler syndrome [00:19:30] and Krabbe's disease.

N2: What types of complications do you see with metabolic disorders?

Linda: It's a pretty broad spectrum in terms of what you can see with those conditions. Individuals with Fabry disease might have complications with their heart function and kidney function over time because it's an accumulation of a particular substance within their cells that can lead to long-term complications of that. Whereas individuals who have MPS I might need a bone marrow transplant.

Linda: So there's quite the spectrum in terms of what you can see, but the reason that they're all on the newborn screen is because there is treatment available. And so wanting to identify those kiddos who may need treatment, and not all of them are going to need treatment right away, but to identify the kids who are potentially at risk and who may benefit from treatment and get them hooked up with that treatment, as soon as possible.

N1: Thanks to newborn screening and the miracle of modern medicine, some patients avoid having to experience the worst symptoms associated with their disorders! PKU, for example, is included on the screening panel, because if patients know that they have it, it can be managed largely through diet. PKU

patients need to avoid consuming protein-rich foods, like milk, eggs, and meat, which have high levels of phenylalanine.

Shaun and Aiden's story

N1: We thought it was important to learn about what it's like to be personally affected by a rare disorder, so we asked Linda if she could connect us with one of her patients. Thanks to her help, we had the pleasure of meeting Shaun and Aiden!

Shaun: Hi, I'm Shaun, and this is my son, Aiden. Aiden, say hi.

Aiden: Hi.

Shaun: We're here to talk about our experience with Aiden having type 1 Gaucher disease.

N1: Aiden is a typical kid.

N2: What's your favorite thing to do for fun?
Aiden: Play video games.

N1: He also loves being active and playing soccer.

Aiden: I play soccer in the soccer season ...
Shaun: He's in first grade, it's more so they call it huddle ball because they don't stay in their positions.
Aiden: One time, I was actually at the first!
Shaun: First goal last year?
Aiden: Yeah.
Aiden: My first goal was actually an assist though. I just saw a kid not running right by the other team, so I was like, I had the greatest opportunity. I kicked it right to him, and he kicked it in the goal.

N1: Teamwork makes the dream work, right? It's funny, that'll be a theme that comes up later in the episode, too!

N1: Aiden's family is just like any other, and if you didn't ask, you would have no idea that they're affected by a rare disorder. Type 1 Gaucher's Disease is a metabolic disorder with a frequency of about 1 in 40,000 births. Getting Aiden's diagnosis, and all of the uncertainty surrounding it, was an emotional experience.

N2: How did Aiden get his diagnosis?

Shaun: Missouri was actually going through a trial from a company called Baebies, and their SEEKER, which was seeking out four different genetic diseases.

N1: SEEKER, a newborn screening platform developed by Baebies, is used to screen newborn kids for lysosomal storage disorders, including Gaucher's disease. It measures the activity of enzymes in newborn heel-stick blood samples. Shaun actually played a role in helping it become the first FDA-authorized screening platform of its kind for these particular lysosomal storage disorders! We'll hear more about that story later.

Shaun: It was probably about a week after he was born, we get a phone call from St. Louis Children's Hospital that his test came back that he may possibly have Gaucher disease, so they want us to come in, do additional blood tests, and it was sent out to the Mayo Clinic so they can do gene sequencing to figure out if he did and what type of mutation he had. He came back with the N370S mutation.

N1: Gaucher Disease is one of those “inborn errors of metabolism” that Dr Gahl was explaining earlier. It’s caused by a deficiency in an enzyme called GCase, which breaks down certain fatty compounds in the body called lipids. The N370S mutation refers to a specific change in the protein that makes it less active.

Shaun: It was extremely hard. My wife got the phone call actually, and I was at work. It was hard for me, because I couldn't react, because she was devastated. We knew nothing about the disease and what it entailed, so we didn't know what to expect. I had the privilege of after finding out--since we both work in the medical field, but I more so work in a hospital–to ask physicians about what it would be.

Shaun: They were just like, "It probably won't be too bad if he comes back with type 1, and just trust in St. Louis Children's Hospital." The worst part was waiting for the gene sequencing, because actually something happened with the test and there was an even longer delay, which it would normally take two weeks, it took six weeks, so this whole time we're thinking the worst, that it could've been type 2 or 3.

N1: There are 3 types of Gaucher disease. Patients with Type 1, like Aiden, can have symptoms including enlarged liver and spleen, anemia, bleeding problems and bone problems. Despite all of these symptoms, it’s actually the least severe of the 3, because it doesn’t affect brain development or produce any neurological symptoms. Type 2 and Type 3 both have central nervous system involvement. Type 2 is tragically often fatal within a few years after birth, while Type 3 has a more gradual onset of symptoms, which can include seizures.

Shaun: Then, going through my mind is, we're losing this time, especially if he had the worst case scenario where he could possibly die before he was three or four years old. Until we got back the diagnosis from type 1, it was nail biting and nerve wracking. It was really, really difficult.

N2: So at that time, were there any treatments available for Type 2 or Type 3?

Shaun: No, none at all. It was pretty much just comfort measures as he progressed, because his condition right now is non-neuronopathic, whereas the others one are, so he'd eventually need to be vented, get a G tube, things like that, and it's just wait it out until it happens. We had to have the conversation with my wife where I was like, I will make the decision if it comes down to it, because she wouldn't have been able to do it.

N2: That must have been incredibly stressful.

Shaun: Yeah, it was, but as his geneticist says, when it comes to genetic disease, we got lucky and we hit the genetic disease lottery, because he has one of the few that is treatable, that since being treatable will minimally affect his life.

N1: Getting his diagnosis at birth has allowed Aiden to live a pretty normal life. Other people, even with the same condition, may not have that experience. Some can live in pain for years without even realizing that they have a disease.

Shaun: As far as symptoms, we haven't had to experience any because we knew before he developed the symptoms, but Shire Pharmaceuticals who we get his medicine from, VPRIV, they would hold once a year a dinner, and they'd have Gaucher patients come in and talk about their experiences.

Shaun: The big thing is a lot of them develop avascular necrosis, and they often try to rule out leukemia first, so he gets to skip all of that, so no bone marrow biopsies, no lab tests, no trying to figure everything out until they're like, "Maybe we should check for a genetic disease."

N1: Avascular necrosis is the death of bone tissue. It's tricky to use as a diagnostic for Gaucher Disease, because it's also a hallmark for leukemia, or blood and bone cancer. Leukemia, with 300,000 new cases every year, is a lot more common than Gaucher's, with fewer than 200,000 people affected in total.

N1: It's the classic case of the saying doctors are taught in med school: "when you hear hoofbeats, think horses, not zebras". Only in the case of Gaucher's, it's one of those rare times when it actually is a zebra! Patients who don't know that they have the genetic variants associated with Gaucher's may have to go through a lot more invasive testing before arriving at a diagnosis.

Shaun: He actually seems, to me, get to skip the worst part, and we get to skip...It was scary for us waiting for the sequencing, but worrying if your son has cancer and such things like that, so it was good for him, good for the tests that he found out and gets treatment. We've just got to look out when he's older if he starts complaining about knee pain or hip pain, things like that, because high impact things, even playing soccer, anything that's hard on the joints, they typically can develop an avascular necrosis, so we've just got to look out for that. Anytime he starts complaining of any pain in his legs, we're just like, "Oh god, is this it?" Fortunately, there's never been anything, it's normally just a kid bumping his knee.

N1: Kids are pretty damage-prone in general, but having his diagnosis means that Aiden's parents know to be on the lookout for pain which could be an indicator of something more serious.

Learning about the disorder

N1: When you learn that you or your loved one is affected by a disease that you know nothing about, it can be a pretty scary experience. The first step that many people take in gaining some control over the situation is learning everything they can about the condition.

N2: You mentioned that after the diagnosis you'd learned a lot about the disease. Did a lot of that come from talking to doctors and genetic counselors, or was a lot of it Googling on your own?

Shaun: It was both. I was constantly speaking, when we first found out, I was speaking to our radiologist, and he was the one who reassured me and went over some of the things that could possibly go wrong. We immediately were in contact with the genetics department. They brought us in, and they explained to us what the disease was, but they didn't tell us about 2 and 3, because 95% of cases I believe are type

1, so 2 and 3 they really kind of dismissed it. Of course, then we go and do our own research, and we start freaking out. And then a lot of it came from actually going to those dinners that Shire would hold, and listen to the Gaucher patients. So Shire actually gave us the numbers, and actually gave us probably the most education as far as raw data.

N1: Connecting with other patients going through the same experience can be an important source of support and information.

N2: Aiden, what do you know about your disease?
Aiden: That I have to go to the hospital every two weeks. I get an infusion.

Shaun: Yeah, he goes every two weeks and he gets an infusion of VPRIV. It takes about an hour and a half, but the whole process takes about three hours for the pharmacy to mix the meds, send it up. They don't start the IV until we're there and it's mixed, because it's so expensive.

Shaun: And then, there's a waiting period afterwards. He actually started to, after about almost two years of treatments, developed a reaction to it. He was sitting in his chair and he started complaining he couldn't breathe, so they had to intervene with steroids and antihistamines, so now he takes an antihistamine before it and everything's been okay.

N2: Wow, that must have been terrifying.

Shaun: Yeah, especially when you have two years of everything being normal, then all of a sudden out of nowhere he develops a reaction.

N1: Gaucher Disease is a recessive genetic disorder. This means that a person needs to get one mutated copy of the gene from their dad, and one from their mom, in order to have any symptoms of the disorder. A person can also be a carrier, which means that they inherited just one mutated copy of the gene, and they don’t have any symptoms. Aiden has an older sister, so we were curious to hear a little bit about her.

Shaun: She’s 12, and she's actually a carrier. The only thing we tell her is if you get older and you may want to have your husband genetically tested if he's from ... I think it's really prevalent with an Ashkenazi Jewish population, so if he's Ashkenazi, you may want to have genetic testing done to see if he's a carrier.

N2: Yeah, that must be a tough thing to process as a 12 year old.

Shaun: Yeah, but she understands it well because we're always openly honest with them. Any question they ask, we tell them straightforward what it is, and they actually understand it very well.

N2: Do they have any friends who are also affected by a rare disorder, who they can talk to?

Shaun [13:05]: We don't know any other parents with a child with Gaucher disease. So far as we know, he was the only one in Missouri found with the newborn screening, but Linda always reaches out to us when there may be a case of a positive to ask if maybe we can speak to a parent if they do come back positive for it.

N1: As a reminder, Linda, who explained newborn screening to us at the top of the episode, is Aiden's genetic counselor. We'll hear more from her soon!

Shaun: And we've never had to speak with anybody, so as far as we know, he's the only one who's been treated for it at St. Louis Children's Hospital, and we haven't really had contact with any other children. Everyone we know who's had it has been an adult.

N2: Growing up is tough enough, even when you're not the only kid you know with a unique genetic condition! It's really impressive how mature they are about this.

N1: It was so great to hear about Shaun and Aiden's experience with a rare disorder. Gaucher disease is just one of over 6000 identified rare diseases out there. Put together, it's been estimated that rare diseases have a prevalence of between 3.5-5.9% in the global population--this amounts to 236-446 million people. When you think about it like that, "rare" diseases don't actually seem all that rare anymore.

N2: After the break, we'll hear more from Linda about what it's like to work with people affected by these conditions. Then, we'll hear from Dr. Gahl about the clinical research side of advancing care for these rare disorders.

Section 2: Genetic counselor, research and financials

GC perspective

N1: Linda has been a genetic counselor for over 20 years. We talked with her to find out...

N2: What do you do as a genetic counselor?

Linda: So we know when the initial diagnosis is made, it is a lot of what I would consider typical genetic counseling and helping the family understand the diagnosis. But at least in our role at Washington University, we will also help the physicians in the ongoing care. So sometimes going in and just when we see a patient back, going into the room and finding out how they've been doing; Are there any new issues or concerns that have come up to help the physician with that patient and helping to answer any questions that come up. So it's something that we do, follow the patients long-term, not from a traditional genetic counseling role, but more in regard to just kind of helping with their overall medical care.

N2: How did you decide to become a genetic counselor?

Linda: So my story goes back to middle school, actually. Cornelia de Lange syndrome is a genetic disorder and they were having their annual conference. And they asked my girl scout troop to babysit while the parents were attending the educational sessions. So we babysat not only for the kids who had Cornelia de Lange syndrome, but also for their unaffected siblings. And we were invited back for several years to provide babysitting. And it just really developed in me a heart for these families. I mean, you couldn't help but meet these kids and their families and fall in love with them.

And when I then went on to pursue my undergraduate degree, I had an amazing genetics professor who knew about the field of genetic counseling, but I was a little bit stubborn and didn't heed her advice. And I decided to go and work for a couple of years and pursue a master's degree in epidemiology at Johns Hopkins. And so I worked there for two years where I was doing research testing for a hereditary form of colon cancer. And when the principal investigator of the study would come and she would find out the results of the different people, and it was always just interesting to me, hearing the family's side of things. And at some point I decided I would much rather be talking with the families than the ones looking at the test tubes and the blood samples. So from there I decided to make it real and go back and get my master's degree in genetic counseling.

N1: It's clear that Linda is passionate about her work as a genetic counselor, and she really cares deeply about the patients and their families. But it's not all smiles on the job...

N2: It must be really scary for parents who get an abnormal result in a genetic test. How is it from your perspective? Do you have a sense for how parents might be feeling?

Linda: It's hard. And I will say, when Missouri first started doing this, I will never forget the first person I called out with a true positive abnormal result. I hung up the phone after telling them that their child had this condition that left untreated, their child could die. And I hung up the phone and cried, because here I am telling this family who thinks they have this beautiful newborn baby who, for all intents and purposes, looks completely healthy. And I'm telling them that they need to bring them in pretty urgently, run a battery of different tests, and we're going to be starting them on treatment as soon as possible because of the diagnosis that we've made in their child. And that's a hard thing to do. You feel like you're squashing a bit of hope. I've gotten better at it, but it's still hard.

You never like to be the, I don't want to say dream squasher, but it's hard when you're changing the direction that a family had envisioned for their child, because when your child is born, you envision the world for them. And when you're suddenly saying that your child has a medical diagnosis and it's going to need a lot of follow-up, that's hard for families to kind of assimilate when moms are postpartum and dealing with a lot of changes and not enough sleep and really trying to provide information and support for those families as much as possible.

N2: So, what's your favorite part about being a genetic counselor? What is it that brings you back to the office every day?

Linda: So for me, it's a real privilege to get to talk to families and work with them because for a lot of them, it's a really hard time in their lives and so it is a real privilege for me to work alongside them, and help provide them information to help with their care. And so bringing things down to something that depending upon their education level, they can understand, which is really important to help empower families.

And I enjoy where it's just something I've never seen before, so something that challenges my genetic thinking beyond some of the traditional things that we see a lot of. So it's a bit of a mix. I have definitely families who I've known for years, who I adore the opportunity to just even socially catch up on. They've seen me pregnant, they ask about my kids, and so those relationships that you develop with the families. But also the cases where the genetics is a bit more complex and trying to understand the genetic mechanism and understand that and how it relates to the clinical care that this individual is getting.

N1: As the term “genetic counselor” implies, to do well in the profession you need to have skills not only in the hard science of genetics, but also interpersonal communication.

N2: Do you feel like genetic counseling training programs provide enough guidance in the interpersonal and psychosocial skills required for your job?

Linda: Somewhat. And I will say that's something that is awkward as a student and as a new graduate of that emotional side of things. And I think that, that's something you become better at as you gain more experience of just learning to be comfortable with some of the awkward silences; learning to be comfortable with tears. Tears are awkward, we don't like to see people cry. But recognizing that that's a normal part of the family's grieving process as you're talking about a diagnosis. And sometimes families will start to cry for no reason. And being able to pause and say, "What is it that I've said that has upset you?"

Because what I perceive as upsetting might be something different to them. And sometimes it might be just that they've misinterpreted something that I've said. And so being able to clarify something for them. But the emotional part is something that I think you grow into and become a bit more comfortable with over time.

N2: It seems like we could all benefit from learning how to exercise that kind of understanding and empathy.

N1: So in addition to communicating the diagnosis to the families, the role of the genetic counselor is also coordinating treatment and even teaching the families about what the diagnosis means for them. We’ll circle back to the teaching aspect as it pertains to the intersection of these rare genetic disorders and socioeconomics later in the episode.

N1: Up next, we’ll hear about what got Dr. Gahl started in the field and what drives him in his career.

Researcher perspective

N1: Researchers studying the biology behind rare genetic conditions, like Dr. Gahl, care about being able to affect the patients and their families for the better. But as we found out, what really got Dr. Gahl involved was a deep fascination with the science underlying the conditions.

N2: How did you become interested in studying rare and undiagnosed diseases?

William Gahl: Maybe it started in high school when my father gave me a book called The Cell by Loewy and Siekevitz. I was intrigued by all the different organelles within the cell and their function. Then I went to MIT and in my second year, I was doing work in biochemistry and I realized that all of the pathways that we were learning were actually extant and functional in humans. I sort of wanted to be a physician, so then I recognized that this is probably the area of medicine that I wanted to pursue.

N1: Much like Linda, Dr. Gahl is driven by the positive impact his work can have on the patients and their families.

William Gahl: Well, this is an incredibly satisfying field, because of the relationship with the individuals that we care for. Because people who have rare diseases are to a certain extent abandoned, and they need a champion, they need someone to look into their disorder to make a diagnosis. And that's hard to come by when they're really rare diseases. So it's very satisfying, because people appreciate you. So I mean, that's that's one issue. The other issue is that of, discovery is a very satisfying thing for human beings. So, satisfaction on both scores.

Science/UDP story

N1: Dr. Gahl, in his quest to study inborn errors of metabolism and help the people affected by them, worked to build the Undiagnosed Diseases Program at the NIH. We were curious to learn more about the conception of the group.

N2: What's the story behind the Undiagnosed Diseases Program?

William Gahl: Yeah, in a way, it's a story that I don't tell too often because people don't ask, they just want to have their diseases taken care of. But I would say that, first of all, implanted in my mind has always been an interest in making discoveries about new biochemical pathways and it's hard to do that! In 2007 there were a couple of things that came together.

William Gahl: One was that the NIH as a whole, on this intramural campus, was interested in promoting the Clinical Center, which is our research hospital. And there was a committee of a whole bunch of Institute directors who drew up some long term plans and some short term plans.

N1: One of those plans was to create clinics specifically dedicated to studying rare disorders.

William Gahl: I got myself on the committee, I actually wasn't invited, but I invited myself.

William Gahl: The second thing that happened was that I had really close associations with Steve Croft, who was the head of the Office of Rare Diseases in the Office of the Director of the NIH. And Steve called me up and said, "We have a hotline or correspondence from people who are supposed to have rare diseases and asked us for help, and 6% of the people who call have some rare disease, but they don't know what it is, they're undiagnosed." And what's being done for these people? There is no outlet for them. There's no source of information.

William Gahl: So those two things conspired.

N1: Now, he was armed with a practical mission and the permission to do something about it. Returning to the committee, he said...

William Gahl: I'm going to hire two nurse practitioners and a scheduler and use the clinical research protocol that I have.

N1: A clinical research protocol allows for a researcher/physician to test out new treatments and try to advance the way we care for patients.

William Gahl: That allowed me to see the patients I wanted to see who had no diagnosis. So we put together the protocol, and then the committee said, "Okay, well, let's see what you do, and so we won't get in your way for now."

N1: A few months later, the Undiagnosed Diseases Program was revealed to the world.

William Gahl: Elias Zerhouni was the director of the NIH at the time, and he calls a press conference, And there were 26 news organizations, 90 advocacy groups--a whole bunch of people there. And he introduces this program to the country. And I said a few words or so and pretty soon, within a few weeks, I'm sitting there with charts, like this big.

N1: From here the idea grew and grew, headed in large part by Dr. Gahl himself.

N2: How do patients get their conditions studied through the Undiagnosed Diseases Program?

William Gahl: So a patient, first of all finds out about the existence of the Undiagnosed Diseases Network. And they will register online through the coordinating center at Harvard. And they send in some, let's say, a letter from their physician, and some modicum of medical records.

William Gahl: And then based on geography, the coordinating center assigns that to one of the 12 sites around the country. So the medical records now are in the hands of one of these sites, and each site looks it over, asks their experts to review it and they decide either to accept for an inpatient or an outpatient admission, or else to reject and sometimes they'll give recommendations on what to pursue.

William Gahl: And then for us, we see the patients generally as inpatients for five days here, get a lot of studies done and pretty much everything we want.

N1: Research is an expensive endeavour. The UDP has a congressionally-approved budget allocated from the NIH of **millions of dollars** each year. . For now, the UDP stands strong. Advances made in the lab from studying patients with rare disorders lead directly to new, better treatment methods for patients with a variety of conditions.

Financials

Insurance (Linda, Shaun, Gahl)

N1: Not only is research expensive, but for the families affected by rare genetic disorders, the therapies and all the visits to specialists really add up.

Shaun: The cost is expensive, it's about... I mean, we're lucky insurance pays for it, but it's about $20000 per treatment now, he gets them every two weeks, so it's undoubtedly expensive. Over $300000 a year. Shire has a program called OnePath that helps out deductibles, so we really don't have to pay much out of pocket except for the specialist visits, and those co-pays.

N1: And we asked Linda what the most challenging part of her job was. WIthout hesitation, she said:

Linda: Insurance. It can just be incredibly difficult to get approval for certain genetic tests, depending upon the patient and depending upon what their insurance is. So our physicians sometimes will make

recommendations for a particular test and the insurance denies it. And so trying to then figure out, is there a way that we could maybe get part of that test done instead, since the insurance has declined the larger panel of genes that we had wanted to test for? But insurance has really just become very difficult with us.

Linda: I know that our dieticians have done a tremendous amount of advocacy work with newborn screening, trying to get some approval for formulas. Formulas are not always covered for the metabolic patients. And so trying to work on the government level to advocate for the inclusion with insurances to be covered in mandated coverage for formulas.

N2: It seems like it should be fairly obvious to insurance companies that genetic tests and specific baby formulas are really critical for these patients. Do you have any thoughts on why it's so difficult for insurance to go through?

Linda: I mean, I understand that they're a business in their own right. So they are wanting to make sure that we're not just ordering the biggest and most expensive test possible when there might be something cheaper available. But it's hard. I get that they want to save money, but it's just really very difficult sometimes with the insurance companies.

N1: I mentioned earlier that we would come back to education, specifically as it pertains to socioeconomics. Shaun explained to us that he and his family were really lucky on this front when they got Aiden's diagnosis.

Shaun: I'm a CT technologist, and my wife is actually a pediatric nurse also. It actually came in handy when he was first diagnosed and we were meeting with a geneticist, because they normally do MRI imaging to determine the volumes of the liver, because with his disease they get enlarged liver and spleen since they can't break down the lipids, so it deposits in the bone marrow, the liver, the spleen.

Shaun: But since he was so young, they didn't want to start sedating him for MRIs, so we actually developed a plan to where we would just do yearly ultrasounds, even though it wouldn't be a true volumetric study, it would still give us a generalized idea as to if his liver and spleen are normal sizes.

N1: Having a background in medicine allowed Aiden's parents to learn information about Gaucher's and develop a treatment plan for their son.

N2: Linda, from your experience, do folks who don't work in healthcare or science, and don't have ready access to those types of resources, know to seek out specialists?

Linda: I don't specifically have an answer to that. Certainly the more educated families are the ones who are doing their internet searches and who are pursuing all the different diagnoses, as opposed to the families who have less means to be able to be doing those searches and figuring out who they need to see, as well as just the means to get into where they need to see someone. Because if they're more rural, they're not going to have access to some of the broader specialties that are available in the metropolitan areas.

N1: Patient groups and communities can be a really important source of information. In addition to the corporate events like Shaun has mentioned, there are also social media pages and patient groups for

some of these conditions, which makes it possible to find and connect with other patients around the world.

Linda: And now I will say that that's something that's been a real shift since I started. I mean, when I first started, we were the ones who were providing families with the names and numbers of advocacy groups. And we had a file cabinet of pamphlets for different advocacy groups. And families now come to us a lot of times already having been plugged into the different groups for their specific disorders, which is really amazing that families are connecting either through websites or through Facebook groups or what have you, to provide them a sense of being able to relate to one another. And that's wonderful.

N1: So education and accessible healthcare are really important for being able to properly treat these rare diseases. That sounds like a concept that could be applied to promoting health and wellbeing for those without rare disorders, too. Just some food for thought!

Section 3: Collaboratioin + Hopes for the Future

Collaborative process

N1: While clinicians and basic biomedical scientists may have different approaches to tackling scientific problems, the future of rare diseases depends heavily on the successful collaboration between the two. In this third section, we'll learn a bit about how it all fits together and talk about how the treatment of rare diseases could look in the future.

N2: As a genetic counselor who interacts directly with patients, are you ever in communication with researchers at your institution who study the molecular mechanisms of disease?

Linda: Oh, for certain. There's so many opportunities to network with people and to get plugged in with people if you have a patient who has a condition. And there's been countless times where there is someone who is doing research within our own institution. And so being able to contact them and touch base with them about what they're doing on the benchtop side of things to provide some information to families.

N1: Academic programs that uncover the new biology thrive upon inter-institutional collaborations. Dr. Gahl discussed several collaborative efforts between research universities within the UDN. It just so happens that WashU is one of the 12 sites nationwide.

N2: So, what is the extent of the interactions between different institutions in the UDN?

William Gahl: Well, first of all, there's a common protocol, and that protocol has a consent that allows for the sharing of identifiable information to the database within the network, and de-identifiable information more broadly, with investigators around the world. So that database is available to the members of the consortium of the Undiagnosed Diseases Network.

N1: The database shared within the UDN contains information about patient genome sequences and symptoms, which is an invaluable resource for researchers. As I mentioned earlier, there are over 6000 different known rare diseases, but because they each affect so few people, it can be difficult to come by

a large enough collection of biological information about each one. That's why a centralized patient database is critical for biomedical research about these disorders.

William Gahl: And there's a rather large amount of collaboration that comes out of the model organisms core, because when there are variants that need a model organism, it goes to the core at Baylor, and there's now a core at St. Louis as well. And they do research into the pathogenicity of variants, and then seek other collaborators, including other patients within the network and around the world.

N1: This is it! This is the point I was talking about way at the top of the episode--teamwork makes the dream work!

~fanfare noise~

N1: We all know that working together leads to great ideas, because when we're exposed to different perspectives, we can approach problems from innovative, new angles. Hopefully, some of these collaborative efforts will lead to new strides in diagnosing, understanding and treating rare diseases.

Promoting newborn screening

N1: One advancement in the treatment of rare diseases has been in the area of newborn screening. As our understanding of the biology behind some of these disorders has improved, people have worked to expand the breadth of tests available, as well as improve utilization of these tests.

Linda: One of the main groups that I'm involved with is just newborn screening in general. And so there has been a tremendous push to increase awareness about newborn screening and as states increase the number of disorders that they're doing. And there are families who lobby on Capitol Hill and do various things in terms of promoting education. So that's something that I feel like there is ever-growing awareness and still need for awareness in terms of what is happening on the front lines with newborn screening.

N2: Are there any newborn screening advocacy organizations in particular that you're working with?

Linda: It's more just working with our state newborn screening programs that we're working with families and trying to raise awareness a lot with pediatricians as well in regard to these disorders.

N1: It's important that pediatricians know what types of tests are available, and know to recommend them for their patients. For a more personal perspective, we also talked to Shaun.

Shaun: The newborn screening is every newborn here, they draw blood from them from the heel-stick, and we didn't know they were doing it. They just sent it out, so there was no charge. We had no idea they were looking for genetic diseases.

Shaun: Even before that when she was pregnant with him, we did ... I guess it wasn't as invasive or as complete as we thought it was, but we did the genetic screening, but it was just the blood and the finger smear. It came back with nothing, so when we got that news we were like, "Wait, I thought we did something like this?" It was an experience that we realized we didn't, and we know a lot more now. We've become greatly educated in the matter.

N1: Because of his personal experience with the benefits of neonatal testing, Linda recruited Shaun to speak in front of an FDA panel review for the SEEKER test that provided an indication about Aiden's disorder.

N2: Could you tell us a little bit about the time when you went to speak in DC?

Shaun: We just got a call from Linda that Baebies, who is the company who was doing the trial and developed the test to test for the disease, would ask if we would speak in front of a FDA panel review.

Shaun: It was honestly terrifying, because I didn't know what to expect either. I was like, "Is there anything I need to prepare for?" They were like, "No, you're just going to come, tell your story." But it was really interesting, because I didn't know the process of how drugs and tests get approved. It was really enlightening to see, because the amount of research and what they have to remember, because they just spitfire questions, and there is no delay. They know all the data, and it was astonishing what they could do. I actually have much more respect for the pharmaceutical and research fields who are trying to get these things approved.

N1: The test was indeed approved by the FDA, and is now available for use nationwide. There was a tangible payoff for Shaun's, and the researchers who developed the test's efforts–now, families across the US can use that neonatal test for lysosomal storage disorders like Gaucher's.

What are your hopes for the future?

N1: Researchers, caregivers, and patients alike all have hopes for the future of rare diseases.

William Gahl: I hope that we're able to continue to have undiagnosed disease programs around the country with some input in terms of financial support from the NIH, to coordinate things, and to provide enough prestige that medical centers want to be involved in this. And then to continue to take these really rare cases for the benefit of the patient, but also for the benefit of the medical profession, and in advancing our armamentarium in terms of diagnosis and eventually treatment. One other thing too, and that is that when you get a diagnosis, you have the opportunity to join a community of people who have that diagnosis as well. And patients really, really appreciate that, because otherwise, they're islands.

Shaun: Probably what I'm most hopeful for, that they'll develop a gene therapy treatment to where it could hopefully correct this. That there will be advancements in gene therapy that he won't have to get these infusions for the rest of his life.

Linda: I think what I would love to see is not only treatment, but also some compassion for families. I recently was participating in a lecture where a family member was part of the panel. And the family member was saying how their partner was just sad that their child was going to be labeled as being different and having a genetic disorder. And the parent speaking said, "But aren't we all different in some way?" And the parent was saying that diversity is being promoted so much more now than when they were kids. That hopefully, this push for diversity would not only include different races and socioeconomic statuses, but also spread the gamut to include just the diversity of health issues that different individuals have and are faced with, and the diversity of genetic disorders, that people are more accepting of kids who have learning concerns, or who just look different because of whatever genetic disorder they have.

N1: Shaun and Aiden agree with this sentiment.

N2: Aiden, do your friends know that you have Gaucher disease?

Aiden: I think not.

Shaun: Yeah, we really haven't had to ... He really hasn't had to tell anybody because he doesn't miss much. He doesn't miss schooling much, especially now that they have virtual schooling.

Shaun: Now, he just takes his laptop with him, he does his classes while he's in the hospital getting his infusion. That's also the reason why we haven't had a port put in him yet, because as he gets older, we want that to be his decision. When it comes to gym classes and playing other sports, we don't have to worry about the port getting hit and broken.

Shaun: Then, if kids seeing it ... it's up to him if wants, because kids can be cruel, so we have to worry about that too. I'm pretty sure as he gets older, they'll start to notice and then he'll probably have to explain it more.

Shaun: Yeah, that's our biggest thing is when he gets older, having to explain it to people and how they react to it, or when he gets older and he meets somebody and has to explain to them, hopefully they accept it and they realize that it may not affect them at all, that they accept it and it's just part of their life.

N1: Hopefully with developments in treatment and growing awareness, he, and all of the other people diagnosed with rare diseases, can live normal lives and fulfil their dreams.

N2: Hey Aiden--what do you want to be when you grow up?

Aiden: A baker.

N2: A baker? Cool!

Aiden: Yeah, I bake with mommy.

Aiden: My favorite thing to bake is maybe brownies.

Aiden: I like to put ice cream on top of my brownies.

N2: That’s a good combination.

N1: There’s a huge variety of rare and undiagnosed genetic diseases in the world. While treatments exist for many of them, others are still complete medical mysteries. Well-studied or not, it’s really hard to hear from a genetic counselor that your child is sick. Fortunately, there is government funding going towards advancing our understanding of these rare diseases.

N2: Hopefully, this research will produce some new therapies to treat some of the conditions and give us some insight into human health in general. In the meantime, we can all do our part by putting our trust in the scientific process, and showing compassion and acceptance for human diversity in all its forms.

N1: For more information about what we've covered today, please visit the Rare Disease Day page (https://www.rarediseaseday.org/). The link will be in our show notes. We'll also include a link to the Undiagnosed Diseases Network (https://undiagnosed.hms.harvard.edu/) .

Credits

N1: This episode was written and produced by Marilyn Steyert, Devika Nair, and me, Iris Chin, with help from the rest of the team at Carry the One Radio. A big thanks to Dr. William Gahl, Linda Manwaring, and Shaun and Aiden for sharing their stories with us.

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~post-credits~

Iris: Do you make them from scratch, or do you use the box?

Aiden: Use the box.

Shaun: I know, I'm always saying, "Make them from scratch, teach him!" But, the box is just so much faster, and they taste the same every time!