Seizing Life, episode 82
Guest: Lacey Smith
Genetic Testing & Counseling for Epilepsy
From Genome to Exome and More
(Transcript)

Kelly Cervantes:	00:00	Hi, I'm Kelly Cervantes, and this is Seizing Life, a biweekly podcast produced by CURE Epilepsy.
Kelly Cervantes:	00:17	Today on Seizing Life, we focus on one of the most promising areas of epilepsy research and future treatment options, genetics. I'm happy to welcome Lacey Smith to the podcast to speak about genetic testing and counseling, what it is, how it works, what it can provide for patients and families, and what it may promise for the future of epilepsy knowledge and care.
Kelly Cervantes:	00:39	Lacey is a genetic counselor at Boston Children's Hospital, where she provides guidance to families seen in the hospital's Genetics Clinical Consultation program. In addition to her clinical work, Lacey is involved in a number of collaborative research efforts that aim to better understand epilepsy genetics.
Kelly Cervantes:	00:57	Lacey, thank you so much for joining us today. I have to say, I have been fascinated by genetics ever since I first learned about them in my eighth-grade science classroom. I'm so excited to have this conversation with you today. I think to begin, if you can just on a broad scope explain genetics and exactly what a genetic counselor does.
Lacey Smith:	01:21	Of course. Thank you, Kelly, for having me. I'm so excited to be here.
Lacey Smith:	01:26	Just in a general broad scope, the National Society of Genetic Counselors describes genetic counseling or genetic counselors as the process of helping families understand and adapt to the medical, psychological, and familial implications of a genetic diagnosis. Genetic counselors can help individuals navigate the genetic testing process and understand what a genetic diagnosis means to their family.
Kelly Cervantes:	02:00	Okay. What is the difference between a counselor and a geneticist?
Lacey Smith:	02:05	A geneticist is somebody who has a medical degree and can evaluate a patient on the medical side and make diagnoses, whereas a genetic counselor is somebody who is trained in a master's program and can talk and meet with families and talk about more of the counseling side, the consenting side, and can

		help families navigate the testing process and understanding the results.
Kelly Cervantes:	02:38	Okay. Within the epilepsy community, who should be getting genetic testing?
Lacey Smith:	02:45	Mm-hmm (affirmative). We know that there are a number of different things that can cause epilepsy. We know that head injuries can cause epilepsy, infections can cause epilepsy, but for a number of individuals there's no apparent cause. For individuals that we deemed otherwise unexplained, those individuals should be referred for genetic testing because we consider them to have at least some sort of genetic contribution to their seizures.
Kelly Cervantes:	03:21	Okay, that totally makes sense. Should adults do genetic testing as well, or is this something that really should just be focused on children?
Lacey Smith:	03:30	Absolutely. Genetic testing is warranted for any individual with unexplained epilepsy, regardless of their age. We know that there are a number of genetic epilepsies that can onset later in life. Adults that either had seizures that started earlier that just haven't had genetic testing yet, or even adults that might have had seizures that started later should also be referred to get genetic testing done.
Kelly Cervantes:	03:59	So anyone and everyone. You have seizures that are unexplained by MRI, injury, viral, whatever, go get tested. Genetic testing is a broad term, there are various different types of genetic tests that can be ordered. Explain those genetic tests to us.
Lacey Smith:	04:23	Genetic tests differ by the technology used and how they look at the DNA and also how much of the DNA they look at, at any given time. If we think about our genes as a long string of letters, each one is a long string of letters and each gene is strung together like popcorn on a string. We can look at DNA by looking for pieces of genetic material that are missing, so pieces of popcorn that are deleted. You can be missing an entire gene, for example, so we have genetic tests that look for missing pieces of DNA. We also have genetic tests that can run through and basically do a spell check of the genes, so each individual gene and run through and make sure that those genes are spelled correctly. With a little bit at a variation, genes need to be spelled correctly in order for them to work properly, because if you have a misspelling, then that could increase the likelihood of developing seizures or other conditions.

Kelly Cervantes:	05:32	What are the names of these various tests?
Lacey Smith:	05:35	Some of the tests you might have heard of, for example, a chromosome microarray is the test that looks for pieces of DNA that are extra or missing, so the popcorn on the string, the piece of popcorn that might be gone. The other tests are the spell checker types of tests. They differ in how much of the genetic material they're looking at, at once. The multi-gene panels, those are looking at a targeted gene list. Oftentimes those are a handful of genes that we might know more about or more of the well-known epilepsy genes. Whole exome sequencing, that's a test that is looking at the important or coding parts of all 20,000 genes. That's a more extensive clinical test.
Lacey Smith:	06:27	Then we have something called whole genome sequencing. The whole genome sequencing is a test that is much more expansive. It's looking at basically all of the DNA, all the genetic material that we have. It's looking at genes that we know to be associated with epilepsy, and it also looks at other genetic material that might not code for genes. If we're thinking about our gene as being ... This is what I tell families. If a gene is like a light bulb, looking at the genome is looking at the light bulb, but also looking at the light switch that controls the light bulb, the circuit breaker that also might control the light bulb. It's not necessarily the information that you're looking at directly, but all of the regulations. It's really tough to interpret right now, but we're still learning about it.
Kelly Cervantes:	07:26	I talk to families and to patients within the epilepsy community and there is a perception that genetic testing is not necessarily accessible. Now, it may be that they looked into it for five years ago, 10 years ago, and so much progress has been made here, but for a long-time insurance wasn't covering genetic testing or it was difficult to get into a provider who would order these tests. Knowing that so much progress has been made, as you were just saying, how accessible is genetic testing today?
Lacey Smith:	08:04	Yeah, that's a great question. I think genetic testing is much more accessible now than it probably was years ago, and I think that's true on many different levels. If we think about it on a cost and coverage side, the cost of genetic testing has gone down and insurance payer coverage has gone up. I think insurance companies have started to appreciate the value of genetic testing and we've noticed that it's gotten a little bit easier to get insurance companies to cover genetic testing. We've been able to get genetic testing done for nearly all of our families who've come to us seeking genetic testing, so that certainly has changed.

Kelly Cervantes:	08:50	Now, is that something if their insurance company doesn't cover it, are there other programs out there that will help get them genetic testing, and how should a patient or family go about finding those programs?
Lacey Smith:	09:05	Yeah. There are a couple different options available. If out-of-pocket costs are high based on insurance, some of the clinical genetic at testing labs have either self-pay options or financial assistance programs that are available to families as one option. For some individuals with certain types of epilepsy syndromes, there are certain sponsored testing programs that are available. As another resource, if costs of genetic testing are still prohibitive, there are other things, such as research studies that do genetic testing on a research basis, that has the opportunity to provide any clinically diagnostic or significant results back to families.
Kelly Cervantes:	10:00	Who orders a genetic test?
Lacey Smith:	10:06	Genetic tests can be ordered through a number of providers. Genetic tests can be ordered through neurologists or epileptologists. They can be ordered through a general genetics clinic. Neurologists can refer to general genetics to help facilitate the ordering of genetic tests. Also, genetic tests can be ordered with the help of, of course, genetic counselors who are either embedded in the neurology clinic or in the genetics clinic as well.
Brandon:	10:39	Hi, this is Brandon from CURE Epilepsy. Did you know that one in 26 Americans will develop epilepsy in their lifetime? For more than 20 years, CURE Epilepsy has funded cutting-edge, patient-focused research. Learn more about our mission to end epilepsy at cureepilepsy.org. Now back to Seizing Life.
Kelly Cervantes:	10:59	How do you determine which test is right for you, and then what does that test look like? Is it saliva? Is it blood?
Lacey Smith:	11:10	Yeah. The type of genetic test is largely determined based on the clinical symptoms in each individual. It might depend on the type of seizure or epilepsy. Are there any other symptoms? Is it seizures plus learning and developmental challenges? Is it seizures plus autism? Is it seizures plus heart problems, kidney problems, other symptoms in other parts of the body? Would that direct specific genes that we're thinking about? If that's the case, it might dictate a targeted gene panel. If it's really uncertain, we might go for an exome to look at more genes. The type of symptoms would really dictate the type of genetic tests that we would recommend for a family.

Lacey Smith:	12:02	Also, the bigger test, the more information you might uncover. Depending on what type of information a family would want, that would also dictate that conversation with the family. Do you want to look for something more targeted or would you want to expand and look a little bit further? That dictates the type of tests we'd want to order.
Lacey Smith:	12:23	How we actually collect the sample, most genetic tests could be either a blood sample or a cheek swab saliva sample, which has been great with the remote world we live in now. Families can just do a quick cheek swab, drop it into the mail and send it in.
Kelly Cervantes:	12:42	How long can sometimes these tests take to get results back?
Lacey Smith:	12:46	You are looking at a lot of information, and the turnaround time for some of these tests sometimes are lengthy because of the analysis part. The technology is getting so good that you can sequence the DNA and spell check it, but it's actually interpreting. Some of the tests can vary. The chromosome microarray, the multi-gene panels can take about a month or so. Usually four weeks is what most of the labs are saying. The exome sequencing usually takes about two to three months, depending. The genome would probably take a little bit longer than that to come back.
Kelly Cervantes:	13:28	Then you get these results back, you talk about the spell check process actually is a little quicker, it's the analyzing of those results, what are these scientists looking for? How many genes are known to cause or affect epilepsy?
Lacey Smith:	13:47	There are lots now. We have, right now, over a thousand genes that are in some way associated with epilepsy and these have different roles in the body. These are genes that can be involved in how baby's brain develops or involved in how brain cells communicate with each other or involved in just disrupting that delicate balance between too much excitation and not enough inhibition in the brain, so lots of different roles and these genes have lots of different functions in the body. That's just something that came relatively recently. With the increase in technology within the past few years, there's been this explosion in gene discovery and epilepsy. In the early 2000s we had a handful and now we are up to over a thousand, so there's certainly been this explosion in gene discovery in the epilepsy in recent years.
Kelly Cervantes:	14:49	It is really exciting to see science push forward in that way. All right, so the genetics test has been ordered. What should the patient and their family expect?

Lacey Smith:	15:03	When I meet with a family, I like to go through a pre-test genetic counseling session just to give families a heads up of the types of results that could be expected, just so there's no surprises on the other end. But after a genetic test is sent, or either just before, we do like to get a prior authorization from insurance just to make sure that insurance piece is taken care of. Then the genetic test is sent, we wait the four weeks or the two to three months, depending on which test we ordered, we get the result back. For our clinic, we do like to bring families in, by in of course now I mean either in person or over Zoom in the world we live in now, for that face-to-face discussion with the results, because genetic test results can be complex and it can have different implications.
Kelly Cervantes:	16:03	What happens when something is found? What do you do as a genetic counselor, and what does that provide or mean to the families?
Lacey Smith:	16:15	We, as genetic counselors, we are able to, at least in our clinic, work very closely with our epileptologists and we like to return those results to families together. Whenever we do get a genetic diagnosis, that's really helpful for families in a number of different ways, and not all of them are immediately obvious. It's really important to talk about what some of those reasons are.
Lacey Smith:	16:45	First and foremost, there are a handful of genes for which there is a targeted treatment available or perhaps a class of antiseizure medications to either lean towards or avoid based on a genetic diagnosis, so we'd want to talk about those. A genetic diagnosis could help guide management in other ways, so maybe a referral to another specialty. Maybe the gene causes epilepsy, but maybe could also cause cardiac problems or other problems and we'd want to refer to other specialties. It may guide decisions to continue anti-seizure medications or ween anti-seizure medications if that was a question.
Lacey Smith:	17:30	Genetic diagnosis can aid in prognosis. Genes can be associated with a wide spectrum of symptoms and severity. Particularly for families of young children, we're able to help guide prognosis. We can say, "Okay, this gene is associated with this spectrum," and evaluate where their child is, for example, and look at their trajectory.
Lacey Smith:	18:01	Other ways a genetic diagnosis is helpful in what we talk to families about is the chances for recurrence, either for that individual or for other family members, and talk about potential

testing if they want to use that information in reproductive management.

Lacey Smith: 18:21 Finally, it provides an answer for families who may have been asking why this happened for that or for their child, and it provides a way for families to connect with other families who have the same diagnosis. In the same way that Cure provides an avenue for advocacy in research for all individuals with epilepsy, gene-specific advocacy organizations can provide that for families with each individual genetic diagnosis so they have both avenues for support.

Kelly Cervantes: 19:00 I think that it's so important for all of the reasons that you just said, providing that community, having this idea of a prognosis, being able to utilize precision medicine for that genetic issue, should that be available.

Kelly Cervantes: 19:18 Going back now to if there are no results, because this was not something that I was expecting, I assumed there was something clearly not okay with my daughter. Her MRI was clear, every other test was coming back fine, clearly the genetic test was going to come back with something. Microarray came back clear, the gene panel came back clear, whole exome, and then even we had a couple maybe hits on the genome. That was pretty frustrating to hear as a parent, as you go through all this and then you go through all of the waiting. What does that mean when you get these results back and there isn't an answer?

Lacey Smith: 20:04 When there's a negative genetic test results, it doesn't necessarily mean it's not genetic. There's so much in the DNA we don't know or understand. In fact, we're only diagnosing about, I would say, 30 to 50% of the individuals we test, and that's those with presumed genetic epilepsy. There's a lot we still don't know, there's a lot we've discovered. That's 30 to 50% more than we were diagnosing before, so we're finding answers for a lot of families, but there's still a lot of families that we're not finding those answers for.

Lacey Smith: 20:40 Just because we get a negative genetic test, despite doing all of these tests, it doesn't necessarily mean it's not genetic so we encourage families to continue to look. That's not necessarily doing additional tests, but revisiting and reanalyzing the tests that they've already had done. That could be a negative exome or a negative genome, to go back, a year down the line, two years down the line, just saying, "Hey, let's take another look at this negative test. Let's just take another look at it to see if there's anything there that maybe wasn't necessarily significant

back when we did it, but maybe there was a change in a gene that we didn't know what that gene did three years ago, but all this research has taken place, all this gene discovery has taken place, maybe now we appreciate that that gene is actually associated with epilepsy." We do encourage families and clinicians to work together to get this information reanalyzed over time.

Kelly Cervantes: 21:41 This is actually something that your epilepsy had gotten involved in with our Epilepsy Genetics Initiative, in trying to get those negative epilepsy panels retested. I know that you were a part of that program, and Boston Children's was one of our sites. Can you talk to us about what that program entailed and, and your part that you played in it?

Lacey Smith: 22:03 Yeah. The EGI was a study that and involved multiple institutions. It was throughout the US, and actually throughout the world, in which anybody who had a negative clinical exome, that was that big test that looked at all the important coding parts of the genome, anybody who had a negative clinical exome could enroll in this research study and consent to have their genetic information transferred from the clinical testing lab that did the test over to a centralized location, and at the time it was Columbia University, and researchers would analyze and continue to analyze the exome data over time. What they would do is they would try to discover new genes associated with epilepsy and compile all the patients' data together. By doing that, they would also increase the number of patients that they could analyze. If at any point along the way they found an answer or a diagnosis for any individual involved in the study, they could go back to the referring clinician and they could facilitate returning that result to each family that enrolled, so we're able to provide diagnoses back to families.

Kelly Cervantes: 23:25 It was a really remarkable program. Even though it ended in 2019, that data lives on for researchers, de-identified, so that they are able to use it for various research studies and to continue to help push that science forward. Totally understanding that there are confidentiality issues here, but how, generally, did the EGI program affect patients and families at Boston Children's?

Lacey Smith: 23:55 In general, we found that families were eager to participate and to get involved. It provided to continued hope that they would find an answer for their child and that we weren't at the end of the road, so to speak, at least from a genetics perspective. For us, for families who got a result back from the EGI, just generally speaking, it families who either initially had a

		completely negative exome who got back a result, a fresh new result, that provided a diagnosis, or it was a family who had a questionable result, a candidate gene finding, so maybe it was a newly discovered gene, a gene that maybe was important for the brain or not associated with epilepsy yet, so it reclassified a finding that happened before, that had been discovered before.
Lacey Smith:	24:58	At least for one of our patients that was relatively young, it was a diagnosis that came early on in their journey, but for others who had been on this long journey looking for an answer, we were able to provide a couple of families with answers who had been looking for a long time. It was a nice opportunity for them to be involved and to find answers for them.
Kelly Cervantes:	25:25	It sure is complex and complicated, but we're excited and grateful to have practitioners like you who are helping and guiding us along the way. Lacey, thank you so much for joining us today. This was such an enlightening conversation and I hope will really help families navigate these important decisions around genetic testing. Thank you so much for sharing your knowledge with us today.
Lacey Smith:	25:50	Thank you so much for having me. This has been great.
Kelly Cervantes:	25:56	Thank you, Lacey, for helping us understand genetic testing and counseling and for sharing your insights about its potential impact on research and care.
Kelly Cervantes:	26:05	For families and patients searching for the cause of an epilepsy diagnosis, genetics offers the promise of both an explanation and improved treatment options. As you heard during the podcast, over a thousand epilepsy genes have been identified through research. In labs around the world, work continues every day to identify new genes, provide families with answers, and most importantly, develop new therapies. CURE Epilepsy believes in the promise of this research. To date, we've raised over $78 million to fund epilepsy research like the Epilepsy Genetics Initiative. Please support our efforts by visiting cureepilepsy.org/donate. Through research there is hope. Your support and generosity are greatly appreciated. Thank you.
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recommends that care and treatment decisions related to epilepsy and any other medical conditions be made in consultation with a patient's physician or other qualified healthcare professionals who are familiar with the individual's specific health situation.