CURE Webinar
A Diagnostic Odyssey: Early Genetic Testing in Epilepsy
(Transcript)

Brandon Laughlin:	00:09	Hello, everyone. I want to welcome you to today's webinar. My name is Brandon Laughlin with Citizens United for Research in Epilepsy, or CURE. I'd like to thank everyone for joining us for today's presentation that's brought to you by CURE and sponsored by Invitae. CURE is proud to host this webinar today on the importance of early and accurate genetic testing in epilepsy. Many people don't know the cause of their epilepsy, but genetic research is starting to change that. CURE, which is the leading private funder of epilepsy research in the world founded its signature program, the Epilepsy Genetics Initiative, or EGI, to help broaden our understanding of the genetic causes of epilepsy, leading us more towards personalized medicine and bringing us one step closer to a cure. The vision of EGI is to improve the ways that we prevent, diagnose, and then ultimately, treats this devastating disease.
Brandon Laughlin:	01:10	EGI's centralized database holds the genetic data of people with epilepsy, and that data will then be analyzed and reanalyzed until the cause of the patient's epilepsy is found. Findings will then be reported to the patient's treating physician, and the data will be made available to advanced cutting edge research projects. To date, EGI has enrolled over 700 epilepsy patients and their family members from around the world, providing a novel genetic diagnosis in 10 of these families as well as identifying a new gene not previously implicated with epilepsy.
Brandon Laughlin:	01:45	For more information on becoming an EGI enrollment site or referring a patient to EGI, you can contact our team at egi@cureepilepsy.org, or one 1-844-EGI-CURE. Today, we have Dr. Brenda Porter from Stanford University, and Kimberly Nye from the TESS Research Foundation. And they're here to discuss a diagnostic odyssey, why early and accurate genetic testing in epilepsy is so important. Dr. Brenda Porter is an associate professor of neurology at Stanford University. She received her MD and PhD from Washington University in St. Louis.
Brandon Laughlin:	02:26	Dr. Porter also developed an interest in difficult to treat epilepsy, with a special focus on children with neurodevelopmental disorders, leading to epilepsy, such as tuberous sclerosis, and focal cortical dysplasia. Her clinical research focuses on improving outcomes in epilepsy surgery and increasing parental understanding of epilepsy and the role epilepsy surgery plays in treatment. Currently, she sits on the NIH Neuroscience Training Study Section and has helped CURE and the TS Alliance with their grant reviews.

Brandon Laughlin:	03:03	Kim Nye is the president and founder of the TESS Research Foundation, a nonprofit organization that aims to find better treatment options for SLC13A5 deficiency. Kim holds a BA from Princeton University. She lives with her husband, Zach and their four children, Tessa, Lily, Maggie and Colton. Both Tessa and Colton have SLC13A5 deficiency. Kim was a graduate student at Oxford University when she gave birth to her first daughter, Tessa. When Tessa began having unrelenting seizures shortly after birth, Kim began searching for the underlying cause.
Brandon Laughlin:	03:40	This was the start of a 10-year diagnostic odyssey. In addition to her work at the TESS Research Foundation, Kim serves as a lay viewer for CURE and is on the steering committee for the Rare Epilepsy Network. Before we begin, I have a couple of housekeeping items to mention. First, please submit your questions anytime during the presentation by typing them into the questions' pane of the GoToWebinar control panel and clicking sent. Zahra from Invitae will go ahead and read them out loud to Dr. Porter and Ms. Nye during the Q&A portion of today's program.
Brandon Laughlin:	04:19	Also, today's webinar will be recorded and will be available for on demand viewing on both the CURE and Invitae websites. Now, I'll go ahead and turn it over to Dr. Brenda Porter, and Kim and I will follow. Thank you very much for joining us today.
Dr. Brenda Porter:	04:39	Thank you, Brandon. I'm going to talk a little bit about why I think genetic testing is so important, and hopefully, by the end of the session, you'll have a good idea of why I find it very helpful to take care of my patients. When we think about epilepsy, we think about treating the seizures, but we also try to identify the underlying cause. It turns out that genetic disorders, especially in children, is the leading cause of epilepsy, and children with genetic epilepsies often do not have other dysmorphic features that you might think of when you think of a genetic disease. They may have things like nonspecific MRI abnormalities, but you're not able often to identify them in the clinic just based on how they appear or how their MRI appears.
Dr. Brenda Porter:	05:31	More than 100 genes have been identified as directly causing epilepsy, and many more are probably out there waiting to be identified. Many of the genes that we've to date realize cause epilepsy are important in brain development, or they affect the way neurons communicate such that they influence ion channels or synaptic function. Many of the genetic epilepsies that we think about, begin in the first few years of life. They cause a very severe form of epilepsy called early infantile epileptic encephalopathies. Patients may have epilepsy with

many seizures per day, although others may have infrequent seizures, and no one seizure type is predictive of a genetic cause.

Dr. Brenda Porter: 06:21 They'll have a mixture of seizure types, and they'll often have intellectual disabilities. I'm going to give several examples of why I think genetic testing is so important. The first is rather straightforward from a genetic perspective, which is that there are reproductive implications for the family. Mrs. Nye will give a very clear cut example of that in a few minutes. But the very first EIEE described, which is due to a mutation in ARX, which causes an abnormal development of inhibitory interneurons results in severe seizures, often infantile spasms, and it frequently occurs in males.

Dr. Brenda Porter: 07:03 They can have a smooth brain, lissencephaly, and lack of normal genitalia, but several of my patients that have had this over the years have appeared normal. The MRI is pure normal and there's no obvious syndromic features. But in the patients, on rare occasions, but sometimes ARX can have a maternal transmission, meaning that the mother can have a mutation that causes a mild phenotype in her, but a severe phenotype in her children. If you don't identify that, she could go on to have future children with the ARX mutation.

Dr. Brenda Porter: 07:42 Another reason to do genetic testing is there are some therapeutic implications. I'm going to talk about one of the more common genetics epilepsy syndromes, EIEE-6 or 52, and those are due to mutations in sodium channels. They often are associated with Dravet syndrome, and there is loss of sodium channel activity in the inhibitory interneurons. This causes a wide variety of seizure type, but most often, it's associated with prolonged seizures during fever, and there's clear-cut implications as to what medication seems to be more effective and which medication seems to exacerbate the patient's seizures.

Dr. Brenda Porter: 08:27 For example, some sodium channel drugs such as carbamazepine, oxcarbazepine, and lamotrigine are often associated with a worsening in the patient's seizures. Then other studies have suggested that there's benefit from certain medications, such as valproic acid, clobazam, topiramate, and the ketogenic diet, and most recently, a study with CBD. Better seizure control has also been implicated in better neurologic outcome. The children will do better, both from a seizure standpoint, but also from a developmental standpoint, if the correct medications are identified. Finally, I personally have

done epilepsy surgery on a few kids with Dravet syndrome 10, 15 years ago.

Dr. Brenda Porter: 09:13 There are several reports saying that surgery is not a therapeutic option in children with Dravet. So, not only can we make good choices for the patient, but we can also make bad choices if we don't identify the correct genetic diagnosis. There are some disorders that have a very strong therapeutic implication. I think the one that comes to mind is the glucose transporter deficiency. This is due to a mutation in the glucose transport into the nervous system. SLC2A1 is the gene that the mutation is found in. These children are not dysmorphic. They have mixed seizure types.

Dr. Brenda Porter: 09:57 They often have pretty significant ataxia, and developmental delay and behavior problems. If you can identify this genetic epilepsy treatment with the ketogenic diet is highly effective. It provides improved seizure control. In my patients, some of them have gone from being developmentally delayed to cognitively normal, being able to join regular classes and have much improved behavioral and cognitive outcomes. They actually are able to come off many of their other seizure medications. This one in particular is something that I think is a real tragedy if we miss it, so another reason to do genetic testing.

Dr. Brenda Porter: 10:42 What do you say to families about genetic testing if you don't think there's likely to be a therapeutic treatment? Well, what I found is that parents feel that they can better predict the future. They can also find comradery, mostly online, because some of these are relatively rare, but they can learn from other families that have the same diagnosis. They're also able now to enroll in clinical trials, but also in the future, I think many trials will be based on genetic diagnoses. They can share their clinical information with other researchers and other families. They discover treatments that have worked and not worked as they become available.

Dr. Brenda Porter: 11:21 It really does help the family and some of the diagnostic odyssey. There's less testing that needs to go on in the future and they don't have to keep searching for other etiologies, so their child's diagnosis. I'm going to briefly describe this, but Mrs. Nye is going to go into much more detail, about EIEE-25, which is due to SLC13A5. It's a citrate transporter disorder. Seizures usually begin within the first day of life. The children have lifelong epilepsy, a movement disorder, dystonia, motor delay, and it's due to an autosomal recessive mutation leading to the loss of citrate transport in the nervous system.

Dr. Brenda Porter:	12:05	It's a rare disorder, but due to Mrs. Nye's diligence, approximately 50 families have been identified around the world, and research is already ongoing trying to improve therapies and to understand the cause of this neurologic disorder. I'm going to pass this on to Mrs. Nye, who will give you more of an update on SLC13A5.
Kim Nye:	12:34	Great. Good morning, everyone. I'm just going to share my family's personal journey with genetic epilepsy, and I'm hoping that my family is a case study in the importance of early and accurate genetic testing. For me, it all starts with being a really lucky kid. I'm one of seven kids, in a fun blended family. You can see me down there at the bottom. My husband is also from a big family. He's one of four kids. This is a little more recent picture. We have no significant history of any major childhood illnesses in our family tree.
Kim Nye:	13:15	My husband and I went to high school together and then to college together, and when we realized we couldn't seem to escape each other, we decided to get married. We moved to England where we split our time between my graduate school at Oxford University, and Zach's at London Business School. Life was pretty darn perfect. After being married for a couple of years, we decided it was time to have a baby. 41 weeks into an uneventful pregnancy, I was induced, and 24 hours after being induced, my doctor decided things were not progressing. So, sweet Tessa was born by C-section on December 22nd, 2003.
Kim Nye:	13:52	The same year that the human genome project was completed. Tessa seemed to be perfectly healthy, but we couldn't get Tessa to eat, and she turned really blue during her first bath. On Christmas Eve, a doctor walked into my hospital room. He told me Tessa was having fits, and that she had most likely had a stroke. We would know more after an MRI. I had no idea what a fit was. It turns out it's a British word for seizures. I don't think I really even knew what a stroke was, and I was definitely in shock.
Kim Nye:	14:23	I remember delivering the news to my husband, my big strong husband dropped to his knees and wept. We were 23 years old. After a couple of weeks, we were able to control Tessa's seizures with phenobarbital and phenytoin. Her MRI was normal, and as the months went on, she looked like a healthy little six month old. She received a diagnosis of benign idiopathic neonatal seizures. We thought we had escaped unscathed from a close call. We took Tessa off her seizure medications. On the day of what was supposed to be her last

dose of phenobarbital, she had a seizure. We were never able to control her seizures again.

Kim Nye: 15:03 Tessa spent the next few years in and out of the hospital. She had dozens of hospital stays under her belt by the time she entered preschool. We knew our ambulance crews by name. Tessa tried dozens of medications in different combinations to no effect. We traveled across the country to see the best neurologist. We attacked the seizures logically. We tried standard antiepileptic medications, we tried steroids, and later IVIG in case it was an autoimmune problem. We tried paradox and other supplements in case it was a metabolic problem.

Kim Nye: 15:37 We had more MRIs and PET scans and EEGs to see if she was a surgical candidate. We implanted a vagal nerve stimulator and separate through the ketogenic diet several times. We had every gene test available. We sought out researchers who could do exome and genome sequencing, which was not yet available clinically. We threw hail Mary pass after hail Mary pass. Tessa's diagnosis shifted to catastrophic epilepsy. We weren't sure she would survive until kindergarten. We still could not find a cause for Tessa's seizures. The one thing that we took solace in was that none of the doctors we saw thought that Tessa had an inherited genetic condition.

Kim Nye: 16:17 We were told to be fruitful and multiply. We complied. Lily and Maggie were born uneventfully. They're wonderfully healthy and normal. In 2012, we received news that Tessa had an ATP1A3 mutation alternating hemiplegia of childhood. My husband and I were tested. We were both negative. AHC is almost always a de novo mutation. We celebrated, and a year later, we decided to have another baby. When I was seven months pregnant, we found out that an error had been made in the lab.

Kim Nye: 16:49 Tessa's sample had been switched with another child's. Tessa did not have alternating hemiplegia of childhood. We were back at square one, but we were still hopeful that our fourth child would be healthy. On August 26, 2013, I gave birth to a seemingly healthy baby boy named Colton. My husband and I knew our family was complete, and we were confident that we were the luckiest people on the planet. At around 2:00 in the morning, Colton started having trouble feeding. He started looking blue. I remember calling in the nurse and telling her something was wrong.

Kim Nye: 17:22 She reassured me that Colton was fine. I knew that he was having seizures. Doctors agreed to transfer him to the NICU for

observation. At around 5:00 in the morning, I emailed Dr. Porter. I had only met her twice before, but despite the early hour, she responded to my email within minutes. She had a neurology team in place almost immediately. Colton was indeed having seizures. I went from dreaming of future college tours and picking out football pads to knowing that my son would likely never talk or live independently.

Kim Nye: 17:54 Dr. Porter put Colton on the medications that had been the most successful for my daughter, Tessa. It took us four years to find out that diamox helped Tessa. Dr. Porter started Colton on diamox when he was three days old. Whereas Tessa was in and out of the hospital for years, Colton came home from the hospital at two weeks old and he has never been hospitalized since. We immediately reached out to every researcher and geneticist that Tessa had ever seen. We sent samples of Colton's blood to the NIH Undiagnosed Diseases Program, to Baylor, even to the doctor who had misdiagnosed Tessa with alternating hemiplegia of childhood. None of them could find a genetic marker.

Kim Nye: 18:34 When Colton was three months old, a friend introduced me to Matthew Bainbridge. Matthew is now at Rady Children's Hospital, but he was a genetics researcher at Baylor at the time. We talked for quite a while about the kids and our family history. When I hung up the phone, I remember wondering if I would ever hear from him again, but a few months later, I got a call from Matthew. He said, I think I found the gene and I think there's something to do about it. Matthew had found compound heterozygous SLC13A5 mutations in Tessa and Colton, a citrate transporter disorder. I introduced Matthew to Dr. Porter. We tried potassium citrate to no effect.

Kim Nye: 19:14 We measured citrate levels in blood and urine and CSF. We tried various supplements. Matthew and Brenda reached out to a drug company that was developing a medication called triheptanoin. An agonizing year later, we had FDA hospital and drug company approval for a triheptanoin trial. I flew with my kids to Baylor to start the miracle oil. My kids gagged it down for months. No miracles occurred. We started hearing about more and more children diagnosed with SLC13A5 mutations. They all have the same symptoms. Intractable mixed epilepsy beginning shortly after birth for no apparent reason.

Kim Nye: 19:53 Tessa continues to have many seizures daily. Most of them are short, but she likes to throw longer seizures at us as well. She is globally delayed, has minimal language and she staggers when she walks. I wish I could say that Colton is perfectly fine. He is

not. Although we have controlled his seizures, he is now four years old with minimal language and he is just starting to take independent steps. But I do feel confident that he benefited from having a big sister who had spent a decade trying different treatment options. Having an early and accurate genetic diagnosis is like giving every child a big sister.

Kim Nye: 20:30 It lets families and doctors know that they're dealing with the serious epilepsy. Early and accurate genetic diagnosis also helps families avoid a diagnostic odyssey, and it gives them a sense of community. I spent a decade hearing other families' epilepsy stories and feeling like they were so different from my family's journey. It was a lonely and isolating experience. Perhaps most importantly, an accurate genetic diagnosis has allowed for targeted research that will someday lead to better treatment options.

Kim Nye: 21:01 We set up a website, a Facebook page and added a link to our website to the SLC13A5 Wikipedia gene page. We started connecting with SLC13A families around the world. We didn't know if there was a treatment that helped consistently, so Dr. Porter created a questionnaire for the families that asked about what they had tried in the past and what seemed successful or unsuccessful. It became clear that we needed a more formal way to organize our disease community and to collect funds for research, so we formed TESS Research Foundation. This chart highlights some of the research breakthroughs that have been made possible by an accurate genetic diagnosis.

Kim Nye: 21:41 If you look sort of at that first row, those are the things that we've achieved already, among the highlights are that we've been able to establish that the known pathogenic mutations result in a loss of function. We've also been able to create animal and cellular models of SLC13A5. We announced a formal peer reviewed grant cycle, and we were lucky enough to receive a dozen applications from researchers around the world from both academia and industry. That middle rung of the chart that says, in progress, is the research that we have underway as a result of that grant cycle. It includes things like repurposing drug screens, better mammalian models, and a better understanding of the underlying mechanism of the disease.

Kim Nye: 22:30 We're cooking up plans from 2018, which you can see in the bottom row of the chart from increased biobanks to gene therapy and patient derived IPSCs and better expression studies. We're excited about what the future holds, and it really is made possible by identifying the gene responsible for my kids' epilepsy. So, I'm going to hand it back over to Dr. Porter, but I

hope that my family's journey helps highlight the importance of early and accurate genetic testing in epilepsy.

Dr. Brenda Porter: 23:04 Thank you, Mrs. Nye. I'm just going to have a few summary slides here. One of the things I want to point out is I am a pediatric epileptologist, but I have many colleagues in the adult epilepsy world, and they often come to me for help with their patients that they think have genetic epilepsies. I think it's really important to remember that 10, 15 years ago, when some of these patients were my patients, but are now on adult epilepsy physicians, patients, there wasn't a very good genetic testing. I wasn't able to test those patients at that time, but they are still having epilepsy, and they need genetic testing.

Dr. Brenda Porter: 23:49 Older patients with genetic epilepsies would not have been diagnosed as children, but they still would benefit from these diagnosis and specific therapies based on their genetic diagnoses. I just want to encourage all the adult epileptologists to think about their patients from a genetic epilepsy standpoint and consider testing. They're very common, more common than any other cause of epilepsy, and they begin during early childhood, but they do persist into adulthood. Testing for genetic epilepsies is readily available now. If you're really not sure how to order genetic testing or you're unsure what tests to send, you can certainly ask a genetics colleague to see the patients, or I would say now, many pediatric epilepsy specialists have quite a bit of genetic testing under their belt and could be helpful.

Dr. Brenda Porter: 24:44 Genetic diagnoses impact treatment, their eligibility for clinical trials and family and caregiver engagement with other families. It really does. Mrs. Nye gives a very clear cut example of how success in genetic testing can really help with the diagnostic Odyssey and make families feel that they have some control over what is going on with their children or family members.

Brandon Laughlin: 25:12 All right. Thank you, Dr. Porter and Ms. Nye. We will go ahead and begin the Q&A portion of our meeting. Again, if you have any questions for our speakers, go ahead and please submit them in the questions' pane of the GoToWebinar control panel, and then go ahead and click send.

Zahra: 25:47 Great. Okay. So I will read the questions aloud, and then Dr. Porter or Ms. Nye will answer them depending on how appropriate they are for each of the speakers. We had one question that says, I am 66 and I've had epilepsy since I was 13. Is genetic testing important at my age? I have children age 31 and 28 who do not have epilepsy.

Dr. Brenda Porter:	26:14	Yeah. I think there's a lot of detail that would have, to be fair, to have to determine if genetic testing would be helpful in this situation. I guess I don't really feel confident in coming out strongly one way or the other, but I will say that genetic epilepsies are complicated. Mrs. Nye had the situation where her husband and her both have mutations in this particular gene and they're completely healthy, and it was only when they came together that they had a child who had mutations in both copies of the gene. There's other situations where a single mutation is new de novo in the child, and that won't be passed on necessarily to the next child from the parents. I don't feel very comfortable in saying that, but it's something you can certainly talk to your epileptologist about.
Zahra:	27:18	Great. Another question. What does Dr. Porter see as the major barriers to genetic testing in epilepsy?
Dr. Brenda Porter:	27:29	Well, that's a good question. Sometimes cost is as an issue. We have sometimes difficulty getting insurance to cover it or to cover all the testing costs, but many of the companies, including Invitae, but other ones as well are making the testing quite reasonable, meaning that there are programs for patients that are on Medicaid to help them fund the testing. Some of the companies have like a cutoff where you can't be required to pay more than a certain amount for testing. That's number one. I would say number two is sometimes interpreting the results. There, I'm very lucky cause I have a lot of genetics colleagues. I have a genetic counselor for just this situation, but we do come down to sometimes being not absolutely sure that the differences in the genetic testing are really causal.
Dr. Brenda Porter:	28:42	I don't think that that should deter you from testing because I think, as time goes on, it'll become more clear whether differences are in fact causal, but costs and interpretation, I think, are still two issues that we face. The final thing though, is that there are patients that I know, I absolutely, in my heart, know have genetic epilepsy and we still cannot find a mutation. That's why the EGI program is in existence, because if your exome sequencing, meaning the parts of the gene that make proteins don't have a finding in them, the data can be uploaded to EGI, and it will continually be investigated.
Dr. Brenda Porter:	29:30	I think in the future, some changes in certain genes that we don't know right now cause epilepsy will be identified as causing epilepsy. So, it's important to not think of this as a static question. Your gene testing is negative. Well, it's negative at this moment. It doesn't mean it's going to be negative in a year or two.

Zahra:	29:54	Next question. Are there any consensus statements or practice guidelines that can be used to help support the need for early genetic testing in epilepsy when working with insurance or institutional send out labs?
Dr. Brenda Porter:	30:08	Yes. I don't know who sent that, but if you want to send me an email, I can send you a generic version of a letter that we use. I think the Lennox-Gastaut Syndrome also has some generic wording on some letters. I will not say that they're always successful, but I think it's a worthy cause, so it's worth trying to do that. Feel free to just send me an email and I'll give you our generic a letter. But again, some of the companies now have very low copays, or even an amount that you don't have to pay over if the insurance refuses to pay for it. I think there's ways to work around the insurance companies, to some extent, but I do have some generic letters I could send you.
Zahra:	31:17	Next question. If I don't have many genetic colleagues at my institution, can I ask for guidance and testing and interpretation from the genetic testing lab?
Dr. Brenda Porter:	31:28	Yes. They all have genetic counselors, at least when you say that. I'm almost positive they all have genetic counselors, at least in my experience they do. They can walk you through some of the interpretations. If that's not fruitful, I think referring to some of the epilepsy genetics clinics that have been kind of springing up around the country, or to somebody that has more expertise in epilepsy genetics would be another reasonable option, even if it's not at your institution. Sometimes families are willing to travel for something so important.
Zahra:	32:13	Next question. Do you recommend biochemical testing for metabolic disorders prior to genetic testing for epilepsy or should these be done simultaneously?
Dr. Brenda Porter:	32:25	Yeah. We've spent a lot of time working up a protocol that we're instituting here on how to work up a child, in this case, with suspected genetic epilepsy, including metabolic epilepsies. We have decided to kind of take a multi-pronged approach. So, we do metabolic testing, often simultaneous with the genetic testing. I would say there are certain circumstances where we might vary that slightly. It also depends a little bit on the patient's situation. So, if it's a very severe catastrophic epilepsy and they have features that make us highly suspect metabolic diseases, then we would definitely push for that more strongly. If the epilepsy seems to not be as severe or we think, it's much more likely, it falls into a certain genetic syndrome, then we

might skip the metabolic testing. But right now, our pathway is to do them simultaneously.

Zahra: 33:49 Next question. Can we get copies of the slides?

Dr. Brenda Porter: 33:55 I don't know. Somebody who's in charge of the slide presentation. That's fine with me.

Zahra: 34:02 I think the answer to that is that we are recording this webinar and it will be available for viewing after the fact, and you'll get a notification on that. So, you'll be able to review this entire webinar from start to finish. Next question is, how do you broach the topic of genetic testing with a patient given that their diagnostic odyssey might already be expensive?

Dr. Brenda Porter: 34:36 I am not totally sure I understand the question, but at our institution, MRIs are extremely expensive, especially if there's a need for sedation. I think we just need to get our head around the fact that we don't ... I don't blink too much at the expense for that MRI, and our genetic testing is about a 10th of that. So, I agree medicine's very expensive, but the yield from genetic testing is quite a bit higher frequently than an MRI, and I don't really worry about the 10,000, $20,000 MRI. So, doing an exome sequencing seems like a bargain to me.

Zahra: 35:31 Next question. How early is too early for genetic testing in epilepsy.

Dr. Brenda Porter: 35:45 I guess, Mrs. Nye might have a different opinion, but if they were going to go forth and multiply again, I would guess maybe they would do testing in utero, now that they know what they're looking for. If you don't have a clear cut epilepsy gene that you're looking for in a pregnancy, I don't know that I would test the baby. That's probably not reasonable in utero. We send genetic testing on neonates a couple of days old if we think they have a neonatal epilepsy.

Zahra: 36:39 Next question. Do you think it makes more sense to start with an epilepsy panel or whole exome sequencing?

Dr. Brenda Porter: 36:44 That's a very good question. So we still use epilepsy panels before we do exome. I don't know when the tipping point is going to come when we stop doing epilepsy panels and we flip over to just doing exome, or then, now some of my patients get a whole genome if the exome has been negative. I guess for right now, anyway, I usually start with a panel because the yield is pretty high in many of my patients. But some of them that are

negative, we do go on to do exome, or as I said, rarely now we're doing whole genome.

Zahra: 37:39 We have a question for Ms. Nye. How did you know which steps to take, to establish your foundation and work towards discovering treatment for your children's condition?

Kim Nye: 37:51 Well, I was really lucky to have friends that I had met along the way who also were dealing with rare diseases or had started foundations of their own. I was actually hesitant to do it. We tried triheptanoin first. We thought there was a treatment out there, and so we've tried the treatment before we started the foundation. It was only when it became clear that the gut instincts of treatments weren't working that we decided to take a step back and formalize and organize everything. We continue to be close partners with other organizations. There's a lot work to do. We certainly still work with CURE and other organizations that are also fighting the epilepsy battle.

Kim Nye: 38:38 But I think it does just depend if you have enough patients and if there seems to be enough information to gather and enough work to do.

Dr. Brenda Porter: 38:46 This is Brenda. I would just say that, of my families that I give them a diagnosis, I tell them to go out there and look. There's almost always a Facebook page or some other group that they can meet with and start to talk about what their children have or how they've dealt with certain situations. So, getting together with other families that are sharing all the things that you're going through is really important. Mrs. Nye is amazing, because she has taken it an extra step and raised money to really work on epilepsy that her children have, but even just getting together with other families is so helpful. It's helpful to me sometimes in taking care of the kids, because the parents will say, "Oh, we talked to this family in Brazil and they tried this and it seemed to help their child. Can we talk about that?" That's something I might not have known had they not been in contact with another family?

Zahra: 40:10 Next question. How do you know which epilepsy center is the best, and how do you find the best neurologist for your child near your home?

Dr. Brenda Porter: 40:24 Mrs. Nye, you've seen probably some of the world's best epileptologists. How did you come to seek out epileptologists around the world?

Kim Nye:	40:37	I guess we tried to find the neurologist that had maybe seen something similar to what we thought we were dealing with. It might not be the same doctor or the same place for every family, but I tried to get an idea of what neurologists or epileptologists or geneticists might have seen something like this before.
Dr. Brenda Porter:	41:00	Yeah, I think seeing large numbers of patients with epilepsy and genetic epilepsies is very helpful. You start to see patterns. I can almost always pick up a kid now. Well, I shouldn't say this, but usually I can pick up a kid with a glucose transporter, because I've seen enough of them over the years, fairly successfully. I think it's a little bit just seen a lot of kids with genetic epilepsies that allows you to see patterns. People who specialize in epilepsy as opposed to some general neurologist who see some epilepsy, but maybe specialize in headache, they may not be the right person to take care of a child with really complicated epilepsy.
Kim Nye:	41:57	We would see a great doctor, that doctor would maybe have three or four ideas. We would try those three or four ideas, and then maybe it was time to seek out another opinion to see if anybody else had the next three or four ideas. As a parent, you don't really have the option of giving up, so you just keep going and keep talking and trying to find a doctor who has an idea that hopefully moves the child's health in the right direction.
Dr. Brenda Porter:	42:25	I think also the idea that in some places there may not be a lot of specialists, but if your physician is willing to work with somebody else that's more at a distance, that that's always very reassuring. I certainly have people that I think of as colleagues around California, for example, or Hawaii I talk to about patients. They'll send me some information and I'll try to assist them as best I can. Even if your local physician may not be the world's expert in X disease, they can certainly reach out to someone who is, and it is a collaborative environment for the most part.
Zahra:	43:15	Next question. How do you find support from other families if you don't know your child's genetic diagnosis?
Kim Nye:	43:26	I guess I would say that there are both broad and specific diagnoses. While we went on a 10 year odyssey to find the genetic marker for the type of epilepsy that the two of my kids have, we had other diagnoses along the way. Epilepsy, in and of itself, is something of a diagnosis. So, there are certainly support groups for other families dealing with epilepsy. We seem to collect different labels. As the years went on, things like

CP or ataxia or apraxia, or just developmental delay. There are support groups for all of those more clinical descriptions of what's going on. I think families do find some comfort in those groups as well.

Dr. Brenda Porter: 44:12 Yeah. I would definitely agree with that. There are, that I know of, support groups for infantile spasms, Lennox-Gastaut Syndrome. These are all seizure types, or seizure syndromes, and all of those organizations have networks. The Lennox-Gastaut Syndrome foundation is having a meeting in Orlando next month that I'm going to. If you find the type of seizure your child has, often they'll be a group. Then locally, the epilepsy foundation of America has local chapters all over. For instance, the one in Northern California has a very ... well, I think most of them around the country have the very nice camp for kids that gives them a sense of inclusion. They have a parent support groups they help with as well.

Zahra: 45:14 Next question. If there's a family history of a genetic epilepsy and another child is born with the same genetic condition, would you start antiepileptic medication before seizures begin, or do you need to wait for symptoms to become apparent?

Dr. Brenda Porter: 45:32 That's a very good question. We do not have epilepsy prevention therapies. I work on a trial right now trying to look at that in tuberous sclerosis, whether we can actually prevent the development of epilepsy and autism in children with tuberous sclerosis, treating them before they develop seizures. But for the most part, right now, we don't have therapies focused on the prevention of epilepsy. I personally, if I know that a child is at high risk for epilepsy, I often use EEG to try to make sure I'm not missing any seizures that are subtle, or just present on the EEG, but that is a conversation you would need to have with your physician to determine whether your child would benefit from frequent EEGs.

Dr. Brenda Porter: 46:27 This is also important to note that some genetic predisposition to epilepsy does not absolutely say that child will have epilepsy. There are certain mutations that it's highly likely they will have epilepsy, and there are certain mutations where some small percentage of patients have epilepsy and others don't. So, it really depends on the specific situation.

Zahra: 46:52 I think we have time for a couple more questions. Do you think that technologies such as antisense oligonucleotide therapies and gene therapy using the new vectors provide hope for various types of genetic epilepsies, or will these type of advances take many more years?

Dr. Brenda Porter:	47:16	They definitely provide hope. I think that the timing of when these kind of therapies will be available is much more challenging. The neuromuscular field is obviously ahead of us as far as getting across the finish line with antisense or vector-based approaches for gene therapy. I don't think epilepsy is that far behind, but it is a little bit more complicated in some situations about how to get the protein and all the cells in the brain, how to get it early enough. There are a lot of challenges, I think it's coming and it probably isn't fast enough for anybody that's on the phone with a child with epilepsy, but I don't know when, but just take heart that it's coming. I just don't know when.
Zahra:	48:22	I think we have one more question. This is for Ms. Nye. What would you say to a mom who's just beginning the diagnostic odyssey for their child with epilepsy?
Kim Nye:	48:37	I would say that there's going to be some good days and an awful lot of bad days where you want to just give up, but I just take a step back, take a deep breath, and then when I'm ready to go at it again, you just keep trying. I think that you can't just make the diagnostic odyssey the whole goal. A diagnosis helps certain parts, but it doesn't actually change your child. Your child is the same child the day before you receive a diagnosis, as he or she is the day after. Even though continuing this research and finding a diagnosis are really important to me, and I think they are to a lot of parents and families, the majority of my time is still spent doing physical therapies and occupational therapies and figuring out IEPs at schools, and just trying to make sure my kids have hobbies that give them something to look forward to.
Kim Nye:	49:36	I think the diagnostic odyssey or a diagnosis in general is like a piece of the puzzle, but it's not the whole puzzle. So, try not to just completely go down that rabbit hole, and try to have fun with your kid because you don't get these days back.
Zahra:	49:59	Pardon me. I think we have one more question. What is the yield for a multi-gene panel and for exome sequencing for a patient with epilepsy? What would the yields be if the patient has additional features?
Dr. Brenda Porter:	50:20	I've seen papers trying to address this question, and I think it's extremely challenging because it all comes down to the denominator like what kind of patients you include in that group. I've seen 30% for a panel. Again, though, it really depends on the denominator. When did the patient develop epilepsy? What kind of epilepsy do they have? Do they have some other syndrome features? Syndromic features, meaning

		their ears are set differently, their eyes are set differently, their MRI has an abnormality on it that's frequently associated with a certain genetic disease.
Dr. Brenda Porter:	51:08	I don't know the specific answer, but I think it's not 1%, and it's probably not 100% percent. It's probably somewhere less than 50%, but in the 10s to 20s to 30%, so good we're doing, I think.
Zahra:	51:32	I think that's all ... oh go ahead.
Dr. Brenda Porter:	51:34	I just wanted to say that I liked Mrs. Nye's description of ending on this that, understanding your child's epilepsy is so important, but having fun with your child and doing things that you and your child both can enjoy is so important. The families that I see in clinic that really take that to heart and do things with their kids that their kids can enjoy, and that they can enjoy watching their kids enjoy is so important. Maybe your child's not going to be able to play regular soccer. I had a patient last week that is playing in the special Olympics soccer team, and he absolutely loves it. He's so happy with it, and his parents were really enjoying it too. That is so important, to taking care of a child with special needs, is finding out what they like to do and helping them do that. It just is a nice way to end, I think.
Brandon Laughlin:	52:47	Now that we are nearing the end of our hour, I would like to thank all of the attendees for their participation. Also, extend a special thank you to Dr. Brenda Porter, and also for Kim Nye for sharing this valuable information with all of us. Again, this webinar was recorded. As Zahra mentioned to you earlier, it will be available to watch on both the CURE and Invitae websites. You will receive an email notification of this in the next coming days. To close, we did want to share an interesting fact about epilepsy testing from Invitae, the molecular diagnostic rate from the Invitae epilepsy panel for infants less than a year old is as high as 30%, and the overall rate ranges from 16% to 25%.
Brandon Laughlin:	53:41	Our next webinar, in this webinar series, will cover this topic in a little bit more detail, and this is titled, panels and exomes, diagnostic yield and detection of childhood epilepsy. This is with Dr. Swaroop Aradhya from Invitae, and also Dr. Joseph Sullivan from the University of California, San Francisco. This will be on Monday, November 13th. You will receive an email in the coming week inviting you to register for this webinar as well. I want to thank you all very much and have a great day.
Dr. Brenda Porter:	54:14	Thank you.