

**CURE Webinar**  
**Targeted Treatment for the Genetic Epilepsies: Clinical cases**  
**(Transcript)**

- Brandon Laughlin: [00:05](#) Hello everyone, and welcome to today's webinar. My name is Brandon Laughlin with CURE, Citizens United for Research in Epilepsy, and I'd like to thank everyone for joining us for today's presentation which is brought to you by CURE and sponsored by Invitae.
- Brandon Laughlin: [00:22](#) CURE is proud to host this webinar 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, the leading private funder of epilepsy research in the world founded its signature program, the epileptic genetics initiative or EGI to help broaden our understanding of the genetic causes of epilepsy, which is leading us toward personalized medicine and bringing us one step closer to a cure.
- Brandon Laughlin: [00:54](#) The vision is to improve the ways we prevent, diagnose, and treat this devastating disease. EGI centralized database holds the genetic data of people with epilepsy and that data will be analyzed and then re-analyzed until the cause of a patient's epilepsy is found. Findings will then be reported to the patient's treating physician and the data will be made available to fund cutting edge research projects.
- Brandon Laughlin: [01:20](#) To date, EGI has enrolled over 700 epilepsy patients and their family from around the world, providing a novel genetic diagnosis in 10 of these families, as well as identifying a new gene that was not previously implicated with epilepsy. For more information on becoming an EGI enrollment site or referring a patient to the EGI project, please contact our team at [EGI@cureepilepsy.org](mailto:EGI@cureepilepsy.org) or 1-844-EGI-CURE.
- Brandon Laughlin: [01:48](#) Today, we have Katie Angione from Children's Hospital Colorado and Lacey Smith from Boston Children's Hospital here to discuss targeted treatments for the genetic epilepsy's clinical cases. Katie Angione is a certified genetic counselor in the neurology department at Children's Hospital Colorado. She provides genetic counseling services to patients and families with neurological disorders with a primary focus on syndromic and non-syndromic epilepsy disorders. She participates in the tuberous sclerosis and Rhatt syndrome multidisciplinary clinics as well as the diagnostic neurogenetics clinical at Children's Colorado.
- Brandon Laughlin: [02:28](#) In addition to her clinical work, Katie is involved in research studies with the goal of furthering the understanding of

epilepsy genetics. This currently includes participation in the epilepsy genetics initiative study based at Columbia University as well as multiple internal studies investigating the genetic etiology of doose syndrome. Katie is also a member of the EpiGC, a consortium of epigenetic counselors whose aim is to promote quality services to patients and families affected by epilepsy.

- Brandon Laughlin: [02:59](#) Lacey Smith is a licensed genetic counselor in the epilepsy genetics program at Boston Children's Hospital and she provides genetic counseling services to patients and families in the clinical consultation program. In addition to her clinical work, she develops and coordinates the PCDH19 patient registry at Boston Children's and is involved in a variety of research projects and collaborations that aim to better understand the genetic contributions to epilepsy.
- Brandon Laughlin: [03:28](#) Lacey is also a member of the EPIGC and is a co-author in the upcoming NSGC practice guideline for genetic testing in epilepsy.
- Brandon Laughlin: [03:39](#) Before we begin, I do have a couple housekeeping items that I'd like to mention. First, please go ahead and submit any questions you have anytime during the presentation by typing them into the questions pane of the GoToWebinar control panel and clicking send. Zara from Invitae will go ahead and read those aloud to our speakers during the Q&A portion of today's program.
- Brandon Laughlin: [04:01](#) Also, today's webinar will be recorded and be available for on-demand viewing on both the CURE and Invitae websites. Now, I'm going to go ahead and turn it over to Lacey Smith and then Katie Angione to follow. I'd like to thank everybody for joining us today.
- Dr. Lacey Smith: [04:24](#) Great. Thank you, Brandon, for that introduction and to the teams at CURE and Invitae for inviting us to speak with you guys today. I think I can speak on behalf of both Katie and myself in that we're delighted to have the opportunity to share some of our clinical experiences with you, particularly cases in which a genetic diagnosis has impacted epilepsy treatment.
- Dr. Lacey Smith: [04:46](#) We spend a lot of time talking with patients, families, and providers about the importance of genetic diagnosis, which have been discussed in previous webinars in this series and I'll highlight briefly today as well. But options for specific treatments is certainly one that comes up quite often.

- Dr. Lacey Smith: [05:02](#) Our objectives for today are to begin with an overview of what is currently available in regards to treatment considerations for the genetic epilepsies. From there, Katie and I will each go through some of our cases which we hope will highlighted how some of these considerations are incorporated into the clinic. Finally, we've planned our presentation to allow some time at the end for questions.
- Dr. Lacey Smith: [05:23](#) As some of you may know, there are a variety of causes of epilepsy, including trauma, stroke, infection, tumors among others. A large portion of otherwise unexplained epilepsy is presumed to have an underlying genetic etiology, either straightforward single gene genetic epilepsy to epilepsy caused by a more complex genetic architecture with modifiers at play.
- Dr. Lacey Smith: [05:58](#) Some of the benefits of having a genetic diagnosis we've listed here. A diagnosis can allow us to provide accurate information to patients and families regarding risk to other family members and recurrence risk. It can end what can at times be a long diagnostic odyssey for patients and families and provides them with an answer or an explanation for their epilepsy.
- Dr. Lacey Smith: [06:23](#) A diagnosis may reduce the number of other tests that need to be run either for diagnostic or management purposes and additionally it allows clinicians to give those younger patients the ability to prognosticate based on what is known about a particular underlying genetic etiology.
- Dr. Lacey Smith: [06:40](#) The focus of our talk today is going to be on the last point here and that is impact on clinical management, specifically in terms of medications.
- Dr. Lacey Smith: [06:51](#) Here's a list of current treatment considerations based on genetic etiology. I say considerations here because some of these are a little more well established than others and several treatments on this list are really in the early stages of implementation. For example, Pyridoxine for epilepsy caused by a pathogenic variance in ALDH7A1 and Pyridoxal 5-Phosphate in PNPO related epilepsy are some of the more well established treatments for the genetic epilepsies.
- Dr. Lacey Smith: [07:19](#) The ketogenic diet is particularly helpful in individuals of GLUT1 deficiency and Vigabatrin is often used for infantile spasms. Others are fairly new considerations so it should be approached with caution. For example, in patients who have a gain-of-function variant in their gene GRIN2A, one could consider a memantine which is an MDA receptor agonist.

- Dr. Lacey Smith: [07:47](#) There have been some discussion on the use of quinidine in gain-of-function variants in the gene KCNT1 but there's been some back and forth recently. I think that initial experiments were quite promising but later, some patients didn't quite respond as well. There have been discussions about length of time that patients were trialed and also considerations about the cardiac findings as well that are associated with quinidine.
- Dr. Lacey Smith: [08:13](#) Other treatments are more general guidelines, such as the use of sodium channel blockers in SCN2A and 8A and some KCNQ2 variants. In addition to identifying medications that could potentially be helpful in patients with certain genetic epilepsies, a genetic etiology could also suggest medications to avoid. The more well-known are to avoid sodium channel blockers in SCN1A related epilepsy and Dravet syndrome and also valproic acid in POLG related epilepsy, due to the possibility of liver toxicity.
- Dr. Lacey Smith: [08:48](#) Now that we've gone through some general background, I'm going to hand it over to Katie who's going to start with some clinical cases.
- Dr. Katie Angione: [08:58](#) Thank you, Lacey. I also want to echo Lacey in thanking Brandon and CURE and Invitae as well for asking us to participate in this webinar today. I'm going to start by going through some of the cases that we've seen here at our center that have illustrated how genetic diagnosis can be helpful in providing treatments targeted to that diagnosis.
- Dr. Katie Angione: [09:18](#) The first case was an eight week old baby boy who presented to the emergency department having spells concerning for seizures. An EEG was done and confirmed that seizure activity and then a lumbar puncture was done. We found on doing that testing that he had low CSS glucose levels which is suggestive of a diagnosis of GLUT1 deficiency syndrome. Genetic testing confirmed a pathogenic variant in the SLC2A1 gene.
- Dr. Katie Angione: [09:49](#) Glucose transfer to type one deficiency syndrome or GLUT1 is a disorder that is caused by the lack of transport of glucose into the brain. Glucose is the primary source of fuel for the brain and without this essential protein, glucose is not getting into the brain the way it's supposed to. So, patients with this disorder are not getting enough energy and that's what's resulting in the seizures, developmental issues and movement disorders caused by this disorder.
- Dr. Katie Angione: [10:19](#) The recommended diet, as Lacey mentioned, the recommended treatment for this disorder is the ketogenic diet and this diet

provides the brain with an alternate source of energy. Instead of getting most of the energy from glucose, the ketogenic diet uses carbohydrates or fats instead of carbohydrates so that the brain is getting an alternate source of energy.

Dr. Katie Angione: [10:41](#) The ketogenic diet was initiated in our patient at 11 weeks of life, which is pretty early for this disorder. Since that diet was started, he has not had any further seizures. Development has been age appropriate. It's been a really remarkable treatment for him.

Dr. Katie Angione: [10:59](#) Most of the time when we make this diagnosis, it's a little bit later in life and at that point, those children can have developmental issues that have already started and they also usually have acquired microcephaly. By starting the diet early on because of this diagnosis, we're able to prevent those things from happening.

Dr. Katie Angione: [11:20](#) Our second case is a five month old male who presented to dermatology with hypopigmented skin lesions. There was really nothing else going on at that time but there was a concern raised for tuberous sclerosis. So, a brain MRI was done and that revealed extensive tubers and subependymal nodules and then genetic testing was done, which confirmed a pathogenic variant in the TSC2 gene.

Dr. Katie Angione: [11:44](#) At seven months of life, the patient developed infantile spasms and hypsarrhythmia was noted on EEG. This is something that is seen in about 40% of children with TSC. It's a little bit more common in TSC2 than in TSC1 and if untreated, infantile spasms can result in a developmental plateau or regression or even intellectual disability.

Dr. Katie Angione: [12:08](#) Vigabatrin was started very early on and this was partly because we knew this diagnosis and were able to be looking out for the disorder for the infantile spasms. Vigabatrin has been shown to be very effective for controlling infantile spasms in about 73% of children with TS. Hypsarrhythmia in the patient had resolved by one month later and after about six months, they were weaned off of Vigabatrin and the spasms have not returned. They have not had any seizures, development is progressing and there's still no hypsarrhythmia or epileptiform discharges on the EEG.

Dr. Katie Angione: [12:46](#) The third case that I want to talk about is a four year old male who presented to neurology with new onset seizures and staring spells. His development at that point was pretty typical. He had some mild incoordination and toe walking, but otherwise cognitively was quite normal. Over the next year, his

seizures were intractable to all the medications that were trialed. He had language and motor regressions and began to have some behavioral issues and not quite seem to be acting like himself.

Dr. Katie Angione: [13:14](#) An epilepsy panel was done, mostly because there was not a specific gene in mind at that point and he was found to have compound heterozygous pathogenic variants in the TPP1 gene. Enzyme testing was done after that genetic testing and confirmed that there was significantly decreased TPP1 activity.

Dr. Katie Angione: [13:36](#) This is consistent with a diagnosis of neuronal ceroid lipofuscinosis or Batten disease, specifically CLN2 which is one type of Batten disease. This is a lysosomal storage disorder caused by deficiency of the tripeptidyl peptidase 1 enzyme. Reduction in this enzyme's activity causes accumulation of peptide in lysosomes, particularly in nerve cells and that leads to cell death.

Dr. Katie Angione: [14:00](#) This is a very devastating disorder, typically presents first off with epilepsy, followed by the developmental regression that we saw in our patient. That then goes on to visual impairment, dementia, and progressive cerebellar and cerebral atrophy. Unfortunately, the life expectancy in this disorder is only eight to twelve years.

Dr. Katie Angione: [14:23](#) There is actually a new treatment called Brineura. It's an enzyme replacement therapy which significantly slows the rate of progression of this disorder. Clinical trials have shown a lack of progression of the motor deterioration in 21 out of 22 of the patients that were studied over 96 weeks. That's compared to progression in about 50% of patients in the natural history study.

Dr. Katie Angione: [14:48](#) This is the first FDA approved therapy for neuronal ceroid lipofuscinosis. It's a very exciting drug. It seems to be extremely effective in this population. The drug has been available since this summer. Unfortunately, we have been unable at this point to obtain insurance coverage with Colorado Medicaid. I wanted to highlight this case because I think as more drugs are being developed for these rare disorders, this is something that a lot of us are going to run into in our practice.

Dr. Katie Angione: [15:16](#) It's been a very common obstacle for us not just with this drug but with Spinoraza, the drug for spinal muscular atrophy as also been challenging to get approval for. Unfortunately, our patient has continued to progress. As of this October, he's having daily seizures, slurring of speech, is no longer speaking in sentences.

He's not able to sit without support, has difficulty holding objects, trouble eating and drinking, and loss of bladder control.

- Dr. Katie Angione: [15:44](#) Again, this is something that I think we all need to be aware of as more drugs are developed. It can be very helpful to establish that diagnosis and know what type of treatment can help, but that's not the end of the road. I'm going to turn it back over to Lacey to go over a few cases that she's come across.
- Dr. Lacey Smith: [16:06](#) Okay, great. Thanks, Katie. I'm going to start with Christopher. Christopher first came to our clinic when he was 11 weeks old and he came for a second opinion. At the time, he had refractory tonic seizures that began his first day of life. In fact, mom first became concerned for abnormal movements just a few hours after birth. Seizures would typically last 30 seconds and occur anywhere from every 10 minutes at their worst to about every three hours at the time of his presentation. Every two weeks or so, he had clusters of increased frequency.
- Dr. Lacey Smith: [16:42](#) In regards to his development, he was smiling spontaneously but not yet responsively. He'd started a little bit of cooing and would bring his hands to his mouth but was not reaching. So, a little bit delayed at 11 weeks. He was primarily being fed through G-tube but was able to take small amounts by mouth. His EEG showed a burst suppression pattern as shown here and overall, his clinical picture was consistent with a diagnosis of Ohtahara syndrome.
- Dr. Lacey Smith: [17:08](#) Ohtahara syndrome is a neonatal development and epileptic encephalopathy. It's a clinical diagnosis and it's characterized by difficult to control epilepsy, often with burst suppression pattern on EEG and developmental delay. It can be caused by a pathogenic variant in one of a variety of genes and I've listed some of those here.
- Dr. Lacey Smith: [17:29](#) I also put a link to Aaron's Ohtahara which is a family organization to which patients and families can be referred for additional support and advocacy. Back to Christopher. In regards to his treatment, he was initially put on phenobarbital. The topiramate was added shortly after while he was still initially hospitalized. He was trialed on pyridoxine with no response and Levetriacetan, again with no response.
- Dr. Lacey Smith: [17:55](#) Soon after he saw us for his initial clinic visit, our epileptologist here recommended genetic testing and a long term EEG. While admitted for his EEG and while we were waiting for genetic test results, he was started on dilantin. Now, dilantin is a sodium channel blocker and he was started on this because there was a

high suspicion for a genetic epilepsy and specifically, a variant in either SCN2A or KCNQ2 which are genes that are known to be responsive to sodium channel blockers.

- Dr. Lacey Smith: [18:26](#) He showed fairly significant improvement once he started on the dilantin. Meanwhile, the genetic test results came back. We had sent a targeted rapid epilepsy panel because we had a very targeted differential and certainly, he had a likely pathogenic variant in KCNQ2.
- Dr. Lacey Smith: [18:46](#) KCNQ2 related epilepsy. KCNQ2 encodes a voltage gated potassium channel. It's autosomal dominant, in which most of the pathogenic variants result in a loss of function. Although, there have been a couple gain-of-function variants reported. Pathogenic variance in KCNQ2 can result in a phenotype that falls within a spectrum of severity.
- Dr. Lacey Smith: [19:09](#) On one end, individuals can have these benign early onset seizures. When I say benign, I mean that the seizures usually resolve on their own or patients grow out of them. On the other end of the spectrum is this early onset developmental and epileptic encephalopathy. Most often, the more severe phenotypes are the result of a denovo variant, in cases of the early onset encephalopathy. I've listed a couple of family organizations here to which patients and families can be referred to for additional support.
- Dr. Lacey Smith: [19:42](#) Fairly recently, a drug known as Retigabine, also known as ezogabine or by the brand name Potiga was found to directly interact with the KCNQ2 protein. Specifically, it acts by opening up the potassium channel and was found to actually lessen seizures in N1 models and in patients with loss of function variants in KCNQ2.
- Dr. Lacey Smith: [20:06](#) We took that information and started our patient on ezogabine and he responded quite nicely. We saw an improvement in seizure control and he continued to do relatively well. Unfortunately, this past summer, the pharmaceutical company that produced the drug decided to pull it from the market, essentially due to low sales and there really just weren't enough patients using it.
- Dr. Lacey Smith: [20:30](#) In anticipation of the future unavailability of the drug, we started to wean our patient off this medication. He immediately developed longer and more frequent seizures, so kind of almost in a panic, we put him back on his dose of ezogabine while we made another plan to figure out how to move forward.



- Dr. Lacey Smith: [20:50](#) Thankfully, and due in large part to the work of his parents, they were able to secure a sufficient quantity of ezogabine through pharmacies. So, we're able to keep Christopher on it. This turned out to be a happy ending for our patient but just to highlight some of the obstacles we face as Katie mentioned with insurance companies. Sometimes it's difficult to find... Once we do find a drug, to make that marketable and available to all patients.
- Dr. Lacey Smith: [21:20](#) This is a case where it's unfortunate for other patients who could potentially improve and benefit on this medication but won't really have the option or opportunity to do so. There's ongoing work now to try to develop a new potassium channel opener to help kids in the future.
- Dr. Lacey Smith: [21:41](#) My next case is Sammy. I met Sammy back in 2014 when he was 10 months old. He began having seizures within the first week of life and these were described as clusters of spasms that could last anywhere between 20 minutes to two hours.
- Dr. Lacey Smith: [22:01](#) Sammy's family history is significant for a brother who was similarly affected. Sammy's brother had also presented with these neonatal onset seizures that were also likely spasms, for which he was given prednisone and following the addition of prednisone, he subsequently developed pneumonia and he later passed away due to complications from pneumonia at around four months of age.
- Dr. Lacey Smith: [22:27](#) As one could imagine, the parents were initially reluctant to seek medical care for Sammy given their prior experience. For treatment, they initially tried some homeopathic remedies which were not really successful in controlling his spasms. They eventually sought medical care when he was about two months old. At that time, he was put on prednisone which helped somewhat initially in the really high doses, but when they started to bring him down, his spasms returned.
- Dr. Lacey Smith: [23:03](#) He was trialed on Levetiracetam which offered no change. They then tried Vigabatrin, given his history of spasms, which was also ineffective. After weaning the Vigabatrin, they started Sammy on Vitamin B6 or pyridoxine, after which his clusters of spasms actually stopped. They became very well controlled. However, he developed a new seizure type at that point. He started having these prolonged generalized tonic-clonic seizures in setting of illness.
- Dr. Lacey Smith: [23:41](#) While his daily seizures were controlled, he was still having these occasional really scary, really bad seizures. They were

hesitant to start... The family was hesitant to start a new medication. I remember his father saying to us, "Unless you have a specific mechanism for how this will treat the underlying cause of the seizures, we're not going to try it", which is understandable given their history.

- Dr. Lacey Smith: [24:06](#) But unfortunately, with epilepsy, without a genetic diagnosis specifically, which Sammy didn't have at the time, it's often trial and error with many of these medications. Give that his seizures were quite long in duration, the family did ultimately agree to start him on a new medication in addition to the pyridoxine.
- Dr. Lacey Smith: [24:27](#) From a diagnostic standpoint, we started with both a chromosome micro-ray and an epilepsy gene panel. The micro-ray isn't listed here. But as expected, given the [inaudible 00:24:38] of the family, the micro-ray showed multiple regions of homo zygoty but there are no copy number variants and it wasn't clearly... We really didn't have any place to go based on the micro ray.
- Dr. Lacey Smith: [24:51](#) The gene panel was non-diagnostic. We then went on to whole exome sequencing which was negative. At that point, the family... This is an international family. The family went home and were there for a little while. We saw them back a little over a year later at which time we had ordered a re-analysis of his clinical exome.
- Dr. Lacey Smith: [25:15](#) This time, it came back with a variant of uncertain clinical significance in just the candidate gene, PROSC. The function of this gene product actually wasn't known at the time. It was just reported that it was ubiquitously expressed in multiple tissue types. That was basically what we had on our report.
- Dr. Lacey Smith: [25:35](#) Again, with no real direction to go based on this information, the family ended up returning back home as they planned to and then just two months later, this paper came out. It not only suggested that PROSC is an epilepsy gene, but actually it's an epilepsy that is responsive to Vitamin B6.
- Dr. Lacey Smith: [26:02](#) We called our family back with these results. They're happy to have an explanation or a diagnosis and of course, we told them to stay on that B6. I have a couple takeaways from this case, but I think they really can be applied to all of our genetics cases. The first is that in some cases, having a genetic diagnosis can impact management. If such diagnoses are obtain, then treatment started early on in the child's life, then seizure control can be optimized earlier in the developmental stages.

- Dr. Lacey Smith: [26:35](#) With better seizure control, kids sleep better, they do better in school, and overall they can have a better chance of reaching their full potential in regards to development and learning. For Sammy's case, it was helpful for him to find a treatment early on that worked. For his brother who passed away, who knows what would've happened if he was put on the B6 right away? Even if we did genetic testing earlier on, this gene wasn't known and we wouldn't have been able to provide this information.
- Dr. Lacey Smith: [27:04](#) We can imagine in the future as our knowledge continues to expand, we can imagine how early genetic testing and diagnoses and treatment can be beneficial. From Sammy's case and others, this highlights that we're continuously learning about new gene-specific or mechanism specific treatments. Even if a genetic diagnosis is made now, for which there's no current treatment available, that really may change over time and the patient may be eligible for new clinical trials or be placed on a new treatment as they become available.
- Dr. Lacey Smith: [27:38](#) Lastly, this case highlights the importance of continuing to analyze and reanalyze genetic data over time. We did this... Often, labs will offer this once from a clinical perspective which we did and were able to find a diagnosis, but this is also done on the research basis as well. Brandon had mentioned the Epilepsy Genetics Initiative at the beginning, so that is something that would be helpful in doing this as well. If we had stopped after that initial negative exome with Sammy, we never would've reached this diagnosis.
- Dr. Lacey Smith: [28:14](#) I want to end by providing just some resources both for clinicians and for families. For families, there are gene specific advocacy groups for many of the genetic epilepsies. There are also many syndrome specific organizations that can be helpful as well. For clinicians, if there are questions along the genetic testing process, I encourage you to reach out to your genetics colleagues at your institution.
- Dr. Lacey Smith: [28:40](#) I've included information here on the National Society of Genetic Counselors, which provides resources for yourself and also that you can direct to families as well. Brandon mentioned that Katie and I both are members of the Epilepsy Genetics Initiative, so we're a group of genetic counselors who specialize in epilepsy and we have our own website. We're working on building content, so we hope that will be more helpful in the future, but we do have a way to contact genetic counselors there.

- Dr. Lacey Smith: [29:13](#) Also, many of the diagnostic labs have genetic counselors that are available to discuss variants in cases with you, should you have any questions about a particular report or next steps in terms of testing to help classify variants. With that, I guess we'll stop and open it up for questions.
- Brandon Laughlin: [29:35](#) Yes. Thank you very much, Katie and Lacey. We'll go ahead and begin the Q&A session of our meeting. Again, if you have any questions for our speakers, please just go ahead and submit them in the questions pane of the GoToWebinar control panel and just click send.
- Speaker 4: [29:53](#) Great, so we'll start with questions here. The first question I have here is: at what point in the diagnostic work up of patient with epilepsy would it be appropriate to order genetic testing? For instance, do you need to wait until the patient has failed at least two different anti-epileptic medications?
- Dr. Katie Angione: [30:10](#) I think in most cases, it's completely reasonable to order genetic testing pretty early on in the work up. Unless there's a very clear structural cause on a brain MRI, genetic testing is reasonably high yield, especially if it's very early onset, so infantile onset epilepsy. Because there's the potential for identifying a treatable condition, I think it should be an important part of the work up.
- Dr. Katie Angione: [30:35](#) As we kind of went over, a lot of the conditions, earlier you start treatment, the better the response and the better the developmental outcome. Then there's also the potential for helping with medication selection. I don't think that there's really a need to wait until they failed medication and put the patients unnecessarily through that trial and error, because genetic testing can potentially give us some evidence to support a particular medication.
- Dr. Lacey Smith: [30:59](#) I'll expand on that too and we talked a lot about treatment, but there are certainly other benefits for genetic testing and diagnosis outside of treatment, right? You don't necessarily need to fail two epilepsy medications in order to start pursuing genetic testing. If families are interested in recurrence risk or are thinking about having additional children and wanting to figure out what the likelihood of having another child with this condition is, it can be part of the work up. As I mentioned earlier, it could reduce the number of tests that are warranted.
- Dr. Lacey Smith: [31:32](#) If you have a SLC2A1 variant, you may not need to do an LP for that for a small child. It could certainly reduce the number of tests during the diagnostic workup.

- Speaker 4: [31:46](#) Right. The next question here is how do you know which epilepsy panel is best for your patients?
- Dr. Katie Angione: [31:56](#) I think it depends on the patient obviously, which is often our answer. Sometimes a very specific phenotype or maybe you've done some biochemical testing, that may be pointing you in the direction of a certain gene or a class of gene. I think in those cases, it might make sense to start with a smaller panel, maybe even a single gene and then reflex to something larger if that's negative.
- Dr. Katie Angione: [32:18](#) But for a lot of our patients, maybe even the majority, we don't really have enough evidence to point us in any particular direction. There is a lot of phenotypic overlap in genetic epilepsy disorders. I think doing a slightly more comprehensive panel is, in most cases, going to be the best bang for your buck.
- Dr. Katie Angione: [32:41](#) That way, you're not extending the time it takes to reach that diagnosis. I would also say as far as which panel is best, which panel to order, there is a lot of options out there and that's always changing. Labs are always expanding their panels, adding new panels, different options for rapid options. So, there's really a lot to navigate. I think some of the important things to keep in mind are how big is the panel, what genes are included. If you do a bigger panel, maybe you're increasing the chances of getting variants of uncertain significance which can be hard to navigate.
- Dr. Katie Angione: [33:17](#) But you're going to be better at catching more rare disorders and maybe newer disorders, especially if the lab is kind of continually updating their panels as new genes are discovered. Then I think you also want to think about what is the coverage of the panel? What's the minimum depth of coverage and the average depth of coverage? Because that's telling you what's the quality of that test? Are you going to miss something? Is there any chance of detecting higher level mosaicism?
- Dr. Katie Angione: [33:46](#) Then the parental testing policies I think are something to be aware of as well because that's going to help to resolve any variance. It might help to see if there is a recurrence risk, if it's a recessive disorder, and then just overall how comfortable you are with the lab. Is there good communication? Is there a report that you're able interpret well and feel comfortable sharing with families?
- Dr. Katie Angione: [34:09](#) A lot of things to take into account and I think it definitely depends on your specific institution and the patient population you're seeing, but I think it's something to look into and make

sure you're evaluating the panels that you're ordering and asking questions of the lab, working with the lab to make sure you're getting the best testing for yourself and for your patients.

- Speaker 4: [34:35](#) Great. Next questions is: is deletion, duplication, and copy number detection important for genetic epilepsies or should that be left as a secondary option after sequencing?
- Dr. Lacey Smith: [34:48](#) I think it's important to include deletion duplication at the onset. We typically order panels that include both sequencing and deletion duplication. I think that if you're really doing a sequencing only panel, you're missing the potential for a diagnosis there and just by doing it sequentially, you're just expanding the time to a diagnosis for these patients.
- Dr. Katie Angione: [35:12](#) I think I've definitely heard people kind of maybe arguing against deletion duplication and saying, "We don't see a lot of evidence of deletion or duplications in a lot of these genes," but I think honestly, we don't really have enough data at this point to say that it's not an important thing to do, especially for some of the more recently discovered genes.
- Dr. Katie Angione: [35:34](#) Maybe we've only seen sequencing changes so far, but that doesn't mean that there's not the potential for deletion or duplication. As Lacey said, it would kind of be a shame to miss that by just doing sequencing and then have to go back just to make sure that you're not missing anything.
- Dr. Lacey Smith: [35:53](#) Right.
- Speaker 4: [35:54](#) The next question here is for Sammy's case. Was the exome resequenced in order to find the PROSC gene? What changed in the analysis?
- Dr. Lacey Smith: [36:03](#) Mm-hmm (affirmative). Sammy's DNA wasn't resequenced, but rather the lab just re-analyzed the sequencing data that was already available. I think it was a combination of factors. I think that the lab, in the time between the initial exome and the time that we got our re-analysis done, they may have changed their policy on reporting out candidate genes. Some labs are more proficient at reporting out candidate genes, so genes that really may not have been associated with any particular disease or disorder, but maybe it's expressed in the brain, for example, and it's a neurological phenotype.
- Dr. Lacey Smith: [36:55](#) They may report those out with the caveat that it is a candidate gene and we know nothing about this, but just to keep this on

your radar. As you saw shortly thereafter, we had the publication that came out. That's helpful.

- Speaker 4: [37:11](#) Great.
- Dr. Lacey Smith: [37:14](#) Doing a re-analysis of exome either on a clinical or research basis, the data's there. It's just our understanding of the genes. We have so many genes that we just don't know what they do and what their involvement is in the human body, so our understanding changes over time. It's not a change in technology, per se, in most cases. It's really just our ability to interpret it and draw conclusions from that.
- Speaker 4: [37:41](#) Right. The next question here is what can we do to keep drugs like ezogabine on the market so they're available for patients? Is it a regulatory issue or an insurance coverage issue?
- Dr. Lacey Smith: [37:54](#) I think it's different for different drugs that are available. Sometimes, for ezogabine, I think it was more of a financial issue. Ezogabine does have some side effects. Physicians were pretty reluctant to prescribe it, unless there was a pretty difficult to control epilepsy. I think for ezogabine, it was a situation where just not enough patients were on it for it to be marketable by the company, which is unfortunate but a reality.
- Dr. Lacey Smith: [38:29](#) I think that really it's been the families I've seen who have put in a lot of effort and advocacy and putting the information out there on how important this is and some labs and others are starting to catch on.
- Speaker 4: [38:49](#) Great. The next question is are there foundations or patient groups that can help pay for enzyme replacement therapy?
- Dr. Katie Angione: [39:00](#) I think there's definitely a lot of advocacy groups out there. As far as how powerful they can be, that's kind of another story. There's so many rare diseases out there and all of these families are advocating for their children, their families, and there's a lot to be overcome, I think.
- Dr. Katie Angione: [39:25](#) I think it's definitely a great thing to do to get involved with those programs. Honestly, the more people that do get involved, especially those that I think are in healthcare and are connected in a different way than the families, it's certainly really helpful. Honestly, I don't know the specifics but it goes a long way, just getting involved and even reaching out to advocacy groups, writing letters to politicians. Those things, they sound like they don't make a big difference for something

so rare, but you put enough doctors, enough families together doing those things and that's our hope is that we can get to the point that we don't have to deny a life-saving treatment because of insurance coverage.

- Speaker 4: [40:15](#) Awesome. The next question here is would specific EEG patterns, apart from hypsarrhythmia, give you an idea of which genetic etiology could be causing a person's seizures?
- Dr. Lacey Smith: [40:29](#) There have been some cases that neurologists have come forward with a specific EEG pattern that's directed very targeted treatments, so hypsarrhythmia as Katie mentioned, there's the burst suppression in Ohtahara that I mentioned.
- Dr. Lacey Smith: [40:54](#) We recently had a case, I don't remember the exact EEG pattern but it was really suggestive of a POLG related epilepsy so they were looking for that and there was a hit on POLG. So I think that there are some patterns but even when you do have a specific EEG pattern, so if you have hypsarrhythmia and you have spasms, there are a variety of underlying genetic causes of infantile spasms.
- Dr. Lacey Smith: [41:20](#) That may help the clinical diagnosis and give a general direction for genetic testing. There's still, as Katie mentioned, so much overlap with the genes and the phenotypes for epilepsy.
- Dr. Katie Angione: [41:32](#) Yeah, very true. CDKL5, ARX can cause infantile spasms. I think there's a list of maybe 15 or 20 different genes, so genetic testing definitely still is an important part of that work up, even if the EEG maybe points you in a certain direction.
- Speaker 4: [41:52](#) Great, and I think we have one more question here if no more questions come in. The question is, do you have studies on isodicentric 15Q?
- Dr. Lacey Smith: [42:04](#) I'm not aware of any off the top of my head, but that doesn't mean that there aren't available.
- Dr. Katie Angione: [42:14](#) I would say clinicaltrials.gov is usually my go-to for specific disorder targeted studies. Beyond that, I would say maybe one of the patient advocacy or support groups would be a good place to go. Honestly, Facebook groups a lot of the time can get you in touch with new research studies. Families are definitely very good at staying up to date on what's going on and what studies are available.



- Speaker 4: [42:48](#) Great. Okay, so I think that's the end of our Q&A period, so at this point, I'll pass it back over to Brandon to wrap up.
- Brandon Laughlin: [42:57](#) All right, great. Thank you. Now that we've come to end of our webinar, I would like to thank all of the attendees for their participation. Also, I'd like to extend a special thank you to Katie Angione and Lacey Smith for sharing this valuable information with all of us. Again, this webinar was recorded and it will be available to watch on both the CURE and the Invitae websites. You will receive an email notification of this in the upcoming days.
- Brandon Laughlin: [43:24](#) To close, we do want to wish everyone a happy and safe holiday season. This webinar series will go ahead and resume again in the new year, so please be on the lookout for an email with more details on the topics, the speakers, and the dates for our upcoming webinars. Want to thank everybody again and have a great day. Bye-bye.