

## Seizing Life, episode 30 Hot Topics in Epilepsy Research

- Kelly Cervantes: [00:00](#) Hello. I'm Kelly Cervantes, and this is Seizing Life, a biweekly podcast produced by CURE, Citizens United for Research in Epilepsy. Last month, we had the opportunity to take our Seizing Life podcast on the road to the seventh annual Epilepsy Awareness Day at Disneyland. This amazing event showcases the epilepsy community, spreading awareness about this complicated condition, while also offering educational courses and resources for patients and caregivers.
- Kelly Cervantes: [00:39](#) This event is a two day expo featuring vendors, clinicians, and researchers from around the world, culminating in an inspiring day at Disneyland Park, where families proudly display their purple shirts in support of epilepsy awareness. This year, CURE highlighted promising advancements in epilepsy research, including information on clinical trials and emerging epilepsy therapies.
- Kelly Cervantes: [01:03](#) While there, we spoke with some of the top experts from around the U.S. on a variety of different topics. Today, we bring you some of the highlights from those conversations. It's only appropriate that we begin with the man who started this amazing event, Brad Levy, the founder of Epilepsy Awareness Day at Disneyland and father to Sophie, his teenage daughter living with epilepsy.
- Kelly Cervantes: [01:26](#) I am beyond thrilled to be able to sit across from someone who has become such a dear friend of mine, Mr. Brad Levy, who actually is the reason that we are all here today at Epilepsy Awareness Day at Disneyland. Brad, thank you so, so much for creating this, for hosting us, for giving us all this platform and the ability to educate and raise awareness. What you have created here is really phenomenal.
- Brad Levy: [01:56](#) Thank you so much.
- Kelly Cervantes: [01:56](#) So, tell us a little bit about your journey into epilepsy. Your daughter, Sophie, has epilepsy, and so tell us a little bit about her and your inspiration.
- Brad Levy: [02:06](#) So, starting at five, Sophie started having seizures. We kind of chased our tails for a few years looking for the answer. We were very fortunate to land at UCLA, who diagnosed her with a lesion on her left temporal that was causing all the seizures. It was a major decision for the family to go through brain surgery. It was pretty simple for the doctor to sell us on it, but it was hard to go through with. And fortunately, from the day of the surgery, she is seizure-free, almost a little over 10 years now.

- Kelly Cervantes: [02:39](#) Which is, it's just an amazing thing, and I think you have built something really remarkable and your passion just speaks volumes.
- Brad Levy: [02:46](#) This is going to move on. This is my legacy. This event is going to be the legacy. Will go on forever. We need cures, we need better results, we need better surgical outcomes, we need more meds, we need to stop epilepsy. This is ... Every disability and medical ailment has major fundraising efforts, major organizations funding research and science and looking for cures, and in epilepsy, we seem to be struggling.
- Brad Levy: [03:14](#) Until CURE came along and decided that they were going to really focus on a focused agenda to find a cure, and now we have somebody to work with. But until then, it was all these support groups were out there on their own, independently trying to wage war against epilepsy while helping families get to where they need to be. And that old slogan, united we stand, divided we have nothing.
- Brad Levy: [03:43](#) So we are really all about uniting the entire epilepsy community. Everybody working hard, all these grassroots support groups are working hard with each other, sharing data, sharing families, sharing resources, and that's really why we do it.
- Kelly Cervantes: [04:04](#) Dr. Heather Mefford, an attending physician at Seattle Children's Hospital, spoke with us about genetics. Can you sort of give us a very brief overview of the genetic tests that are currently available that patients could request from their doctor?
- Heather Mefford: [04:20](#) Sure. So, the tests that I usually recommend for patients depend a little bit on exactly how they present with epilepsy, but the tests that are available would include a chromosome test that looks for kind of missing and extra pieces of DNA. So what we call deletions, or duplications. Those look like they're responsible for about five to 10% of kids who have really severe early onset pediatric epilepsies.
- Heather Mefford: [04:50](#) And those are the ones where testing has really been successful. The second test that's available is what we call a gene panel. So this is a test that looks at the spelling, or the sequence, of the DNA, for genes that we know if you have a genetic change can cause epilepsy. And those tests, sometimes, will look at 10 genes at once, a hundred genes at once, or even a thousand genes at once.

Kelly Cervantes: [05:19](#) Oh, wow.

Heather Mefford: [05:20](#) There's a lot of variability. So it's really good to talk to your genetics provider or your epilepsy provider or both about what the right test is.

Kelly Cervantes: [05:28](#) I didn't realize that, when doctors are talking about an epilepsy panel, that there were that many different, I guess, brands of panels is what you're dealing with there, so that ... Oh, that's really interesting to know.

Heather Mefford: [05:41](#) Right. So I always tell providers, you have to know your test, because you can't find what you're not looking for. So if you suspect a certain genetic diagnosis, and you send a gene panel, and the gene you think is causative is not on that panel, you'll never find it. Right? Luckily, today, many of the panels are pretty expansive and inclusive of lots of genes.

Heather Mefford: [06:03](#) But the most inclusive test would be an exome, and an exome is a fancy word for, let's look at all 20,000 genes that humans have and look for changes. So there, you'll get, obviously, all the genes that we know are associated with epilepsy, but a lot of other stuff as well. So there are caveats to doing that test, too.

Kelly Cervantes: [06:25](#) What is the difference between whole exome and whole genome sequencing?

Heather Mefford: [06:29](#) So, whole exome sequencing, and for kind of the suite of tests that I talked about, can give us a diagnosis maybe up to 50% of the time in if you choose your patients carefully. But that does leave half the patients without a diagnosis. So whole genome sequencing is looking at every single base, or letter, in our genome. So looking at all of the DNA and the spelling therein.

Heather Mefford: [06:58](#) Well, exome sequencing, which I mentioned looks at 20,000 genes, those make up only about 1% of our DNA. So despite the fact that those 20,000 genes provide the primary instructions, right, for building our body, for ourselves communicating properly, it's only 1% of our DNA. So the genome sequencing, which is 100% approximately, offers a lot of promise.

Heather Mefford: [07:28](#) One of the difficulties with genome sequencing is that we don't know as much about if you make a change in a piece of DNA that's not a gene, what does that mean, and what's the effect? So we're learning a lot, but we're not able to interpret it as quickly as we can for the exome.

- Kelly Cervantes: [07:50](#) I've often heard, specifically within the scientific community, encouraging patients to go back and have their whole exome sequencing or genomes redone. What is the value in going back and having that genetic material retested?
- Heather Mefford: [08:08](#) I would say that in the past five years, the number of genes associated with epilepsy has just grown. So if you had an exome five years ago, they may have found a change, but it was in a gene that we didn't know anything about. And if you went back and looked at that today, they might say, "Oh, we see this change, and now there are three reports in the literature of patients with epilepsy who have changes in this gene."
- Heather Mefford: [08:33](#) So we think now that this is important. We just didn't know enough five years ago, or three years ago, or even, sometimes, a year ago. So it is important to do that and to continue to see genetics even if you don't yet have a genetic diagnosis.
- Kelly Cervantes: [08:48](#) What's some of the exciting research that we're seeing in genetics? What comes after you do whole genome sequencing and you still have no answers? What's going to be next?
- Heather Mefford: [08:59](#) Where do we go next is kind of exactly what my lab is working on right now. So we have all these patients without a diagnosis. We say, "What is it that we're missing?" And even the technology that we have to sequence the whole genome, there are things that we miss. There are different types of changes, so changes that don't necessarily change the sequence or the spelling of the DNA, but maybe the attachments to the DNA, or the shape of the DNA.
- Heather Mefford: [09:28](#) And so those are things we can start to explore and say, "Maybe there's something about the DNA that turns off that gene, but it's not a sequence change, for example." Or maybe there are other types of changes where there are lots of repetitive letters in the DNA, and those are actually hard to read with regular sequencing.
- Heather Mefford: [09:50](#) So sometimes we have to look for them in different ways, and those types of changes can alter how a gene functions, or whether it's on or off. So there's a lot of work right now, to say, "Okay, what are we missing, and how do we go about finding it?" So those are the directions that we're going.
- Kelly Cervantes: [10:08](#) We were fortunate to speak with one of the premier epilepsy researchers, Dr. Robert Fisher, professor and director of the Stanford Epilepsy Center. I think we're all in this community

grasping at straws, to try, and specifically for the 30% of folks who remain resistant to available treatments, whatever we can get our hands on is helpful. To that end, is there anything coming down the pike in terms of devices that it looks promising or exciting to you?

- Robert Fisher: [10:41](#) Sure. So, the neurostimulation devices we have now are not curative. They're palliative. We'd love to have methods to make them applicable to a much larger group of people and to completely stop seizures. We're going to try and better identify who are the best candidates, what are the best targets. We've only tried a very few targets in the brain. I think there are many more that are probably even likely to be more effective than the ones we've done so far.
- Robert Fisher: [11:15](#) In terms of different devices, it would be nice if it could be noninvasive, if you didn't have to drill through skull or put machinery in the chest. And several of us, me included, are working on attempting to develop noninvasive devices that use either magnetic pulses from a helmet or electrical stimulation through the scalp that may have effects that would be similar to the implanted stimulators, but something that would be entirely noninvasive, and maybe even something that could be done at home with some people.
- Robert Fisher: [11:56](#) And then there's a new technology that's come out. It's really very old technology, but new in neuromodulation, called focused ultrasound, that I think has some promise in this area, as well. Everybody in medicine knows about ultrasound, for example, looking in the womb during a pregnancy.
- Kelly Cervantes: [12:20](#) Yeah, I was going to say pregnancy. Yeah. Obvious. Yeah.
- Robert Fisher: [12:20](#) And it's super safe, but there's use of ultrasound as well as a surgical tool right now, basically burning a very small, well-localized hole in a brain as a surgeon would do if a surgeon went in and removed it. It can be done externally, so it's approved, for example, for reducing severe tremor in people by burning out a very small area of brain that causes tremor.
- Robert Fisher: [12:46](#) Now, between this super safe low dose that you can use on a pregnant woman and the high dose that will burn the piece of the brain out, there's a whole middle ground which does not destroy brain tissue, but may modulate its effects, and ultrasound has the beauty of being able to focus very precisely on any part of the brain we want by directing the beam.

- Robert Fisher: [13:11](#) So if we can make it, make the brain less excitable at the place that we shine it by engineering that effect, then that also would be a very exciting thing to do noninvasive. And I'll mention one other technology that is revolutionizing neuroscience, and I think may someday come to the clinic, and that is called optogenetics.
- Robert Fisher: [13:38](#) This is a technology that was invented by a Stanford researcher, Karl Deisseroth, and it injects genes in brain. This is only done in animals so far, not in humans, but it would potentially be applicable to humans, that make the nerve tissue sensitive to light, to different wavelengths of light.
- Robert Fisher: [14:04](#) And, for example, a yellow light might have one effect on the tissue to excite or inhibit it, and an orange light might have the opposite effect. So you can literally turn on and off regions of brain with fiber optics shining different colors of light on that part of the brain. And that is a degree of control that we've not had before.
- Robert Fisher: [14:31](#) That's not available in humans yet. The technologies from magnetic and electrical stimulation or ultrasound modulation are not clinically available or clinically proven. So they're in a different category from the three I mentioned before that are approved. But there's just a tremendous amount of work here.
- Robert Fisher: [14:53](#) We will continue to get better drugs. They're coming out all the time. But you're right, that 30% who don't respond to the medicines is the same 30% that existed 30 years ago. So it is time to look in some other directions to supplement the drugs.
- Kelly Cervantes: [15:13](#) Dr. Joffre Olaya, board certified pediatric neurosurgeon at Children's Hospital of Orange County, spoke with us about surgical approaches to epilepsy and the ROSA robot. What makes someone a candidate for surgery?
- Joffre Olaya: [15:26](#) So, as you know, there's a big workup that's done to determine if somebody is an epilepsy surgery candidate or not. First, someone with epilepsy would be worked up by an epileptologist, and the epileptologist would order a imaging study, they would get an MRI to make sure there's no underlying brain lesion that could tend to be causing the seizures.
- Joffre Olaya: [15:46](#) They would get an EEG, or a longterm EEG, or VTM, [inaudible 00:15:49], to see if they could lateralize or localize what part of the brain the seizures are coming from. In addition to that, we

may get some additional studies such as a PET scan, a SPECT, a MEG, and these are all other studies that can be used to help localize where the seizures are coming from.

- Joffre Olaya: [16:07](#) And then at that point, and patients would also get a nurse psychiatric testing. And that helps us to localize any sort of deficits. And sometimes, it can help lateralize seizures, as well. And so all that information is then taken together, and typically, we would meet as a group with a surgeon, the epileptologist, the neuropsychologist, the radiologist, go over all the studies and then determine if someone is a candidate or not.
- Kelly Cervantes: [16:29](#) It sounds like, in order to be a candidate, you really have to be able to zero in on exactly where those, what part of the brain those seizures are originating from.
- Joffre Olaya: [16:38](#) Ideally. But once we have the information, we come up with a hypothesis of where we think the seizures may come from, and there may be multiple different areas. And so, to gather more information then, we can place electrodes directly into the brain, or around the brain, either on one side or bilaterally, depending on the hypothesis, to then try to capture a seizure and see where that electrical activity is coming from.
- Kelly Cervantes: [17:02](#) And what kind of surgical procedures can be done in that case?
- Joffre Olaya: [17:07](#) Classically, we would do what's called a craniotomy. We make an incision, we elevate the bone, we open up the dura, or the covering over the brain, and then we place electrodes directly on the brain, and particularly, the areas of the brain that we're concerned with the seizures are coming from. But we can also place electrodes directly in their brain. So instead of doing a large craniotomy through a small, a few millimeter upper holder opening, we place an electrode, a direct stereotactically, so using a special neuro-navigation software directly into particular parts of the brain.
- Joffre Olaya: [17:38](#) And this is much, much better tolerated. There's less blood loss, less pain, and then we can still gather a lot of important information to help, again, try to pinpoint where the seizures are coming from. And so, in order to do this, at our institution, for example, and historically, people would use frames, and they're special frames, and you have to calculate exactly where you put the electrode in.
- Joffre Olaya: [17:58](#) But now, we use a robotic arm, which is a tool that we use, is the ROSA robot. And so I, prior to surgery, I can plan exactly

where I want the electrodes to go, and then the day of the surgery, I basically make the small opening, I put a little bolt in the bone, and then pass the electrode down to the target. I try to avoid any important structure, any vascular structures, to prevent any bleeding or causing any damage to the brain.

Kelly Cervantes: [18:24](#) And so is the ROSA robot that you work with, is that for diagnostic, or are you actually removing part of the brain using that robot?

Joffre Olaya: [18:32](#) That's a great question. So, as I was describing it, and then in this particular case, it would be diagnostic. So it's to gather more information and figure out where the seizures are coming from. But once we figure out where the seizures were coming from, then we remove the electrodes, and then we have another conversation as to what the next step in treatment would be.

Joffre Olaya: [18:50](#) And so, potentially, if it's an area that can be resected, we would remove it. If it's a place that can be ablated, we could put a laser ablation probe and burn the tissue. It would give us a similar effect.

Joffre Olaya: [19:03](#) Or, if it's in an eloquent part of the brain, some part of the brain that helps us with language, with movement, and we decide we can't take that part of the brain out, then sometimes, we can put electrodes directly on or over the brain that are there, permanent electrodes that are then connected to a generator, which is called the RNS, and that basically detects the electrical activity on the brain, and then when there's a seizure, it'll send a signal to help stop the seizures, as well.

Joffre Olaya: [19:28](#) And so the ROSA can actually be used for implanting the electrodes, initially. It could also be used to help target and place the ablation probe, or it can be used actually to place the depth probe if we're doing an RNS. So it can be used for a lot of different steps in the surgery.

Kelly Cervantes: [19:43](#) What is it about it that sets it apart from what we had before?

Joffre Olaya: [19:47](#) Sure. Well, again, in terms of invasive monitoring, it gives us our ability to place lots of electrodes throughout the brain in a much more efficient manner. So again, as I mentioned before, previously, we would use frames, and then it just took a lot more time to be able to manually adjust the frame to get to all the different targets that you wanted to get to.



Kelly Cervantes: [20:09](#) Significantly more invasive.

Joffre Olaya: [20:11](#) Exactly. Yeah. Well, not necessarily. It's still making smaller openings, but it just takes a lot more time to do all the planning and placement of the electrodes. So the ROSA is much more efficient for that. And so we can do a lot of that planning ahead of time, and so on the day of the surgery, the electrics can be placed much more quickly.

Kelly Cervantes: [20:31](#) We had a conversation with Dr. Scott Perry, medical director of neurology at Cook Children's, about new treatments for Dravet syndrome. Sort of on a top level, what is Dravet?

Scott Perry: [20:44](#) Dravet syndrome, it's a rare genetic epilepsy. One in about 15,000 people will have an abnormality most commonly in a gene called SCN1A that impacts a sodium channel in their brain and it causes this epilepsy. The epilepsy begins in the first year of life with seizures, often in the setting of fever. Many times, they're very long seizures.

Scott Perry: [21:07](#) And then, as they get older, after age one, they develop other types of seizures, myoclonic seizures, absence seizures, tonic-clonic seizures, that are often very difficult to control with medications. The seizures are often associated as well with other problems, so delays in development, behavior problems, sleep problems, sometimes GI problems, problems with eating, feeding. Autism can be more common. So a lot goes in to make the whole picture of Dravet syndrome.

Kelly Cervantes: [21:38](#) And is genetic testing the main way of diagnosis at this point? Are there other genes associated other than the SCN1A?

Scott Perry: [21:47](#) Yeah, so genetic testing is definitely the best way to kind of get a confirmatory diagnosis. So the history is most important. It has a very kind of particular way it presents, but doing the gene testing and finding SCN1A is going to be the gene that is involved in about 85% of the cases.

Scott Perry: [22:05](#) The other 15% may be from other genes. There are some other genes that rarely are associated with a very similar presentation, and then some, maybe we don't know yet. Maybe there's genes we're not aware of yet we're still looking for.

Kelly Cervantes: [22:17](#) What promising leads are out there for treating Dravet?

Scott Perry: [22:24](#) So, we could talk for over an hour about all the things that are available, or are soon to be available right now. Years ago, there

wasn't much to talk about. It was expert opinion, and a few drugs that people were used to using. In the last two years, we've had several drugs approved. Stiripentol was approved earlier this year. Epidiolex, which is a CBD, was approved last year.

- Scott Perry: [22:49](#) There's a new drug called fenfluramine that's likely going to be approved in the early part of next year. There's an ongoing study of a drug called OV935 that is looking at Dravet syndrome as a population. And then there are a variety of gene-based treatments that are coming up that are quite exciting.
- Kelly Cervantes: [23:10](#) Why is it that, in a lot of the clinical studies, that for the new drugs, I know it was certainly that case with Epidiolex, and I've seen it with fenfluramine as well. Why is it that they often do these studies with patients with Dravet, that that is the population that they do these clinical studies with?
- Scott Perry: [23:29](#) Oh, there's a couple of reasons. One is, when you do a clinical trial for a drug, and you need to show it works, it's superior to a placebo, you have to have a certain number of patients to show that. And what you want is people who very similar. So they all have a very similar disorder, which Dravet is something that's very clear. It is one entity.
- Scott Perry: [23:52](#) And then you want a group of people that has a lot of seizures, because you don't want a trial that's going to last years to collect enough seizures to see there's a difference. So with something like Dravet syndrome, similar to Lennox–Gastaut syndrome, you have children who have a lot of seizures, so in a short period of time, 12 to 14 weeks, you can show that there's a difference with the drug and not drag it out for so long.
- Kelly Cervantes: [24:14](#) What is coming in the future? Where would you like to see research focused moving forward? Where do you find there to be the most promise?
- Scott Perry: [24:23](#) Well, the future, to me, is now. So what's going on right now is that all these drugs we kind of talked about at the beginning are drugs that treat epilepsy. They treat seizures, but that's a symptom of the epilepsy. That's not the whole problem. Right? And while these drugs might get approved in Dravet syndrome, they're approved that way because that's who we studied it in.
- Scott Perry: [24:44](#) Does it mean that drug couldn't possibly work for Lennox–Gastaut or any other epilepsy? My point is that the drugs are not necessarily special to Dravet. What we want to do is you

want to get at the problem in Dravet, which in this case, is a gene that we know, we know what it does, we know what the gene is, right?

- Scott Perry: [25:02](#) So the treatments that are coming down that are very exciting are genetic-based treatments that look to basically change the way the good version of the gene works, so that it produces more of good SCN1A, so that these kids are not deficient in that protein, and they end up hopefully not only having seizure control, but maybe not developing some of the other things that we see.
- Scott Perry: [25:26](#) If we treat them early enough, can we make this disease just go away altogether and actually cure an epilepsy?
- Kelly Cervantes: [25:32](#) A real cure.
- Scott Perry: [25:32](#) Like a real cure, not a take a part of your brain out cure, or not a part of keep you on medicines for the rest of your life cure. A truly fix the problem that caused the epilepsy and get rid of it. And if it works for SCN1A, there are a variety of other genetic-based epilepsies that it makes perfectly good sense, we could just extrapolate it to more and more epilepsy. So it's a lot closer than people think.
- Kelly Cervantes: [25:58](#) Than we think. Yeah, that's amazing to hear, and I think it's a lot of families hope, which is what we are all scratching for, so.
- Scott Perry: [26:06](#) It gives their doctors hope, too, that we can actually, we have some real cures coming, I think.
- Kelly Cervantes: [26:15](#) I want to thank everyone who took the time to speak with us at Epilepsy Awareness Day at Disneyland. The event is truly inspirational, and provides all of us who have been touched by epilepsy with another reminder that we are not alone. There are 65 million people worldwide, and 3.4 million Americans affected by this devastating disease.
- Kelly Cervantes: [26:35](#) We are a community of patients, families, physicians and researchers, desperately seeking an end to epilepsy. CURE knows the only way to achieve that goal is through research. Please consider supporting CURE's mission by donating at [cureepilepsy.org/donate](http://cureepilepsy.org/donate). Thank you.
- Speaker 7: [26:59](#) The opinions expressed in this podcast do not necessarily reflect the views of CURE. The information contained herein is provided for general information only, and does not offer

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Speaker 7:

[27:17](#)

CURE strongly recommends that care and treatment decisions related to epilepsy and any other medical condition be made in consultation with a patient's physician or other qualified healthcare professionals who are familiar with the individual specific health situation.