Genetic Testing in Epilepsy: Criteria for Adults and the Promise of New Treatments
2024 CURE Epilepsy Webinar
(Transcript)

Dr. Laura Lubbers: CURE Epilepsy provides grants that support novel research projects that advance the search for cures in more effective treatments. We're excited to bring to you our third webinar as a part of our 2024 CURE Epilepsy webinar series, where we highlight some of the critical research that's being done on epilepsy.

Today's webinar is entitled Genetic Testing in Epilepsy: Criteria for Adults and The Promise of New Treatments. This is the second of two webinars this month that address CURE Epilepsy's ongoing focus on epilepsy genetics and research into the rare epilepsies. If you weren't able to attend that first webinar earlier this month, more details will be shared at the end of today's webinar on how you can watch that recording.

Genetic testing has largely been seen by medical professionals as necessary only for epilepsy patients who are children, but it's becoming increasingly apparent that genetic testing in certain adults with epilepsy can be really beneficial. Our last webinar, participants learned that genetic testing can shorten a patient's diagnostic odyssey, help tailor specific treatment options to their type of epilepsy, and aid in family risk and planning decisions. Many of these benefits are also relevant to adults with epilepsy, including those who developed epilepsy as a child and at a time when genetic testing wasn't as widely available.

Today, you'll learn how to identify even if an adult with epilepsy would benefit from clinical testing, you'll understand the types of clinical genetic tests available and how to interpret them, and distinguish between clinical and research genetic testing and the value of being involved in research studies. In addition, attendees will get to hear from Maggie Loesch, a college senior who underwent two types of genetic testing as an adult. She'll share more about her experience and motivation behind her desire to undergo testing, and why her results have proven that she is truly one of a kind.

Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE Epilepsy website. You can also download transcripts of all of our webinars for reading. This webinar is being presented by Doctors Gemma Carvill and Elizabeth Gerard. Both are professors of neurology at Northwestern University right down the street in Chicago, Illinois. Dr. Carvill's research lab uses genomic technologies, machine learning and high throughput functional assays to define the molecular basis of epilepsy, including examining coding and non-coding genetic variants. Her research group also uses patient derived stem cell models to study how rare variants and genes cause epilepsy. Dr. Carvill co-directs the adult epilepsy genetics program at Northwestern with the goal of expanding neurogenetics research and facilitating genetic for patients.

Dr. Gerard is an adult epileptologist with clinical and research interest in the care of women with epilepsy and genetic diagnosis of adult patients with epilepsy. She directs the Women with Epilepsy program at Northwestern

Medicine, as well as the Adult Genetics Clinic. Her research interests include gene discovery and variant interpretation of adults with epilepsy. She also studies pregnancy and contraception in women with epilepsy and is the site principal investigator of what is known as the MONEAD Study that focuses on maternal outcomes and neurodevelopmental effects of anti-epileptic drugs.

The Adult Epilepsy Genetics Clinic at Northwestern is one of the few clinics in the country that offer both genetic testing and counseling to adults living with epilepsy. Dr. Gerard's clinic works closely with the Carvill Lab, and together, their primary goal is to use gene discovery and molecular biology approaches to identify new treatment options for epilepsy.

Before I turn it over to our two doctors, I'd like to encourage everyone to ask questions. We'll address the questions during the Q&A portion of the webinar. Keep in mind, you can submit your questions anytime during the presentation by typing them into the Q&A or chat tab located at your WebEx panel and click send. We'll do our very best to get through as many questions as we can. We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you try to make your questions general and not specific to a loved one's epilepsy. So with that, I'll turn it over to today's experts, Dr. Gerard.

Dr. Gerard: Thank you so much, Laura and Brandon, for this invitation. It's really nice to be here and to talk about something that Dr. Carvill and I are so passionate about and enjoy working together on. And I just want to acknowledge that all the work we do together we do as a team, and we couldn't do it without our genetic counselor, Lisa Kinsley and our research coordinator, Irena Bellinski, as well as many staff who support us in the clinic and an additional epilepsy, genetic-minded specialists who work with us as well. So, I'll go to the first slide.

The first concept I want to get across is that we tend to talk about epilepsy as one condition, but really it's many, many, many, many thousands of conditions. And so we're really in a paradigm shift where we're starting to think about epilepsy not as one condition, but as one of many epilepsies. And I think a goal for me as a physician and for many of my patients is to understand why they have epilepsy and what's their specific underlying cause, not just which has symptoms of seizures.

And so this is an oversimplification, but there are a lot of different categories that we're now recognizing as possible contributions to epilepsy, with at least 20% of all epilepsies either being known to be genetic or being presumed to be genetic. There's another 37% that are contributed to structural abnormalities, which means that there is something structurally different about how the brain formed or an acquired change to the brain. This includes a variety of different causes, but many of these, if you go next, Gemma, many of these also have genetic causes as well.

Finally, a big chunk of our epilepsies are still unknown as to the cause, and many of those will turn out to be genetic. I think what you've been hearing over this month, and will continue to hear, is that there's been an explosion in gene discovery and epilepsy in the last 15 years since the next generation sequencing era. And there are now over 900 genes that are associated with single gene disorders that cause epilepsy, which are known as monogenetic [inaudible 00:06:57] disorders.

As an example, for the developmental and epileptic encephalopathies, which are rare disorders that start in infancy or young childhood and are associated with developmental delay, over 50% have known genetic causes, and these are the highest yield patients when you go for genetic testing. But that doesn't mean that other epilepsies can't be diagnosed or it's not worth trying to find them, even if the yield is slightly lower. Next slide.

So why do genetic testing? I have to say, I think Laura summarized this better than I'm going to, but she had the same concepts there. I think for many patients that answer of, "Why do I have epilepsy?", is so important because it's very frustrating to deal with seizures, to deal with a new diagnosis, but to not know why if you can't see it on MRI or anything can be very frustrating. And giving that closure can be extremely important. And as Laura mentioned, it can also limit the need for repeated and other testing over time once you have an answer.

Another really powerful thing about making a diagnosis of your specific epilepsy type is the ability to connect with similar individuals. And it's amazing how patient groups have started to organize around particular genetic disorders, connect with each other, fund research, push the field forward, and I think that's extremely powerful part of getting a genetic diagnosis.

There is also the potential to understand the risk to other family members, based on the inheritance patterns of your genetic condition. And we talked a little bit, Laura talked a little bit about the potential to direct treatment. So there is the hope of precision medicine, where particular genetic diagnoses linked to very particular cures or treatments that are currently available. I do tell patients it exists, but it's not common. So in adult patients, this is something that might come less than 5% in the papers that have been published of the time. And so while this is a reason to do testing, it's not the only reason to do testing.

But the other thing about directing treatment that I've found very powerful is, again, through connecting with others and other Facebook groups, patient groups, patients within my own clinic or those that my colleagues know, we can see the experience they've had with different treatments for their disorder and their epilepsy and their seizures. And so by comparing and contrasting other people's experience, that sometimes helps us carve out the treatment that is best for a particular individual.

Another really important thing in this generation is to be ready for clinical trials. So we have more and more clinical trials that are being developed for specific genetic diagnoses. And so if you know your genotype, if you know your genetic diagnosis, you're going to be eligible for that clinical trial and that's important. And then at the end, Dr. Carvill's going to talk about how knowing your genetic diagnosis and knowing genetic diagnoses in general and participating in genetic research can help us all develop better treatments for specific epilepsies and epilepsy in general.

Next slide please. So who should consider neurogenetic testing? So I'm going to start with some of the patient groups that we started testing and have the highest yield. So if you have a strong family history of epilepsy, if several members of your family, particularly first degree relatives or a parent have epilepsy as well, the chances of making a genetic diagnosis go up. And so these patients definitely have good reason to consider genetic testing.

Another group are patients we consider to have epilepsy plus, which means that the seizures and the epilepsy are part of a condition that affects other systems and other parts of the body. So when epilepsy is seen in concert with developmental delay or learning differences, there is a high chance of making a genetic diagnosis. Same for autism or autism spectrum disorder, disorders of movement including gait or tremors, and involvement of other parts of the body. Malformations of cortical development, which are an increasingly important cause of epilepsy that we recognize more and more as our radiology improves, these often can have genetic determinants for different reasons, and Dr. Carvill will talk about some.

There are also specific syndromes, that as adult epileptologists, we're starting to recognize, really should trigger us to think about genetic testing. So one in particular is a syndrome called sleep-related hypermotor epilepsy. So patients may particularly have seizures in their sleep, not exclusively, but largely in their sleep, and seizures that cause them to have a lot of movements in their sleep and potentially even jump out of bed. This syndrome has been associated with a set of genes and at least in 5 to 10% of them we can make a genetic diagnosis. So, we recognize that as a syndrome with or without a family history that should dictate consideration of genetic testing. And more and more I think that epilepsy specialists and geneticists are starting to recognize that really we should be considering neurogenetic testing for any unexplained epilepsy, particularly if it's refractory to seizure medications and is not found at treatment.

Next slide. So I want to review some of the myths that I've heard about genetic testing in adults. One is, "I had genetic testing as a child and they didn't find anything, so it wouldn't be helpful to do it again." So as Laura mentioned, actually, because of the explosion in advancings in genetic testing, both the methodology to do genetic testing and the bioinformatics and interpretation of genetic testing, it's very helpful to repeat genetic testing or analysis periodically. We're even saying as frequently as six months to a year. So if you have a

condition that has a high chance of being genetic and you were tested as a child, it is high time to repeat the genetic testing in my opinion. Next.

So I also hear a lot, "No one in my family has epilepsy, so my epilepsy is probably not genetic," but for a variety of reasons that's not true. Oftentimes, the genetic epilepsy is the individual being diagnosed is the first in their family to be diagnosed, and so don't discount genetic testing just because it's not in your family. Next.

And then we also hear sometimes that someone did genetic testing with another type of doctor or a company, some of the online companies that offer genetic testing for different reasons. And it's important to know that when you order a genetic test, even though it's your DNA going through the test, the test is different and the way it's looked at is different. So for example, testing that's done for prenatal testing or prenatal screening for recessive disorders is very different from what we do in neurogenetic testing. And so it may be possible that patient needs both, depending on what question that they're asking, but if your question is about why do I have epilepsy, it should be done through the lens of neurogenetic testing. Next slide.

So I do want to encourage anybody thinking about genetic testing to kind of do a mental checklist about whether it's the right time and whether they're ready for it. So, you do want to have seen an epilepsy specialist who can confirm the diagnosis of epilepsy and characterize the diagnosis of epilepsy, and/or a geneticist who's skilled in genetic interpretation. All genetic testing really should be done with the assistance of a genetic counselor. In my clinic, I'm very fortunate that myself as an epileptologist, we get to work with a genetic counselor and we do this together.

One difference between testing as adults and testing as children is that it's important to get cost estimate, because insurance companies are not yet completely on the same page as we are about the importance of genetic testing in adults. It is usually more affordable and more covered than you might presume, but it really varies by state and by insurance, and so it's important to understand what the cost estimate is for your genetic testing. And for pediatrics, we have some free programs which we don't have available in adults.

It's also important to check in with other family members about what you're looking for in genetic testing and your intention to do this. We don't like to cause family conflict by doing genetic testing. And we've learned that in families, particularly when the patient is the adult, there are a lot of other people in their orbit that may have differing opinions of genetic testing.

And so I think it's important, because genetics do affect other family members, it's important that people know what you're doing. Of course, it's ultimately your choice. And we do encourage you to bring that family member to the visit with you, both because it may have downstream effects on them, but also

because they can provide family history. It's also a good habit to review your family history before a genetic visit. Okay, next slide.

So, we actually did not go through the types of testing in detail. We can in the questions, just because of time, but I think it's important to acknowledge the different types of results that can come back from genetic testing. So one is a positive result. We either usually coded as pathogenic or likely pathogenic variance. And these are changes in genes that affect the way the gene functions and may offer an explanation for your condition, does depend on the inheritance pattern. Next.

You can have a negative result, which may seem disappointing and we'll talk about that, but it's not uncommon to get a negative result, which means that the test that you ordered at this point in time has no significant variance, but a negative result does not mean that your epilepsy is not genetic. And finally, you might get a variant of unknown significance, which you'll hear some more about today. A variant of unknown significance is a genetic change that it's not known to be pathogenic or benign yet. Next slide.

So what happens if you have a VUS? Often, a VUS, or a variant of unknown significance, is coded like that because we don't know enough about the gene yet most variants of unknown significance end up being benign. So it's important not to make clinical changes or plans based on a variant of unknown significance. However, there are a lot of things we can do clinically that can help us resolve the variant of unknown significance. One, is sometimes we can test other family members, and I think you'll hear more about that. You can also request updates on the classification of your variant of unknown significance periodically.

So if you've had an exome or genome analysis, this can be reanalyzed, and genetic testing companies when asked will also review research and reports of other individuals the variant. Finally, these variants of unknown significance, in some cases, can inform further research, which can take many different forms that you'll hear about. And this can include databases that we have available to us to connect with other physicians who found individuals with the same variant and seeing what their experience is and start seeing if we have patterns. Next slide.

So what we do at Northwestern, is we put this through a program. We have a monthly conference where we present the clinical data that we have from the epilepsy evaluation and genetic counseling at a genetics conference, which is attended by all of our interdisciplinary team, including translational researchers. And this helps us with our variant resolution and our vetting of our variants so that we can have better patient feedback and better genetic research. Next slide.

And with this process, you can see that in our first 158 patients, we initially got back about 16% of pathogenic or likely pathogenic results, and about 32% of

variants of unknown significance. And by putting it through this process, including testing family members, going back to the company and doing some testing in Dr. Carvill's lab, we have expanded our solved cases to 20% and identified some of the variants of unknown significance as candidate variants that we want to continue to pay attention to and continue to study. Next slide.

So finally, why might my testing be negative? Well, some might just be because your genetic change is in a gene that we don't yet know about or understand to look for. Another thing might be that the test that was ordered may not cover your specific genetic change. So just one example of this, is that if you've done an exome, which is one of the bigger tests that we sent currently, you're looking at 2% of your DNA. That's the 2% of your DNA that encodes proteins. But we're starting to learn, including Dr. Carvill's lab is starting to study, DNA changes that are between the genes that make proteins, these are known as non-coding DNA. And we are starting to clinically be able to order genomes that cover those areas. But that's just one of the examples why a genetic test right now might not pick up your genetic epilepsy.

Another reason might be that your epilepsy may not be due to one genetic change, but several genetic changes. This is known as polygenic disorders, and this is a common mechanism evoked in explaining genetic generalized epilepsy. So one of the biggest ironies we deal with is the epilepsy that we call now genetic generalized epilepsy or idiopathic generalized epilepsy, is actually one of the hardest epilepsies to identify a single gene for. And that's why because we think that a combination of different genes may be contributing in that case. And finally, genetic testing might be negative because genetic changes that occur in only some cells of the body, which is known as somatic mosaicism, and Dr. Carvill will talk more about this, are harder to detect on tests on saliva or blood. Next slide.

So to end my part, what can I do if my testing is negative? Well, again, if you've had an exome or genome, it can be reanalyzed by the company. And you can also discuss with your genetic counselor or your clinician whether there are other tests that should be considered. Because even though an exome and genome sounds super comprehensive, there are some other tests that we shouldn't forget about that can sometimes pick up other types of genetic changes. You can also consider enrolling in research. And with that, I'll pass it to my partner, Dr. Carvill.

Dr. Carvill: Great. Thanks, Dr. Gerard. Yeah, so if your genetic testing turns out it's been negative, as Dr. Gerard mentioned, at least at Northwestern and some other additional academic medical centers, there's always the opportunity to enroll in research genetic testing. And before I dive into some of the more research type things that we do at Northwestern, I wanted to quickly distinguish between the differences between clinical genetic testing and research genetic testing.

And the way I like to think of this is in terms of people and numbers. And so I like to think about clinical genetic testing as being about the individual. If you

order a clinical genetic test together with your epileptologist and your genetic counselor, so with Dr. Gerard for instance, then that clinical test is all about you and your immediate family. It's about finding a genetic diagnosis for you.

Whereas how I like to think about research genetic testing, is that we are of course interested in each individual living with epilepsy, but the way that we think about research is studying many patients with similar types of epilepsy to understand how their epilepsy occurs. And it's actually pretty rare, though, it does certainly happen sometimes that during research genetic testing, we will find a genetic cause for a specific individual's epilepsy. And at least in our research protocol, we then have the ability to go back to the patient and validate that in a clinical lab.

But this is an important distinction that research genetic testing is more about the collective, a large group of individuals with epilepsy that we study, to then kind of feed back to clinical genetic testing. 'Cause as we learn more about the genetic factors that underpin these conditions, we can improve clinical genetic testing. So I like to think of this as going back and forth between the two.

So, just to take you through some of the research that we do in my lab together with Dr. Gerard and several others now at Northwestern, the group is growing, which is very exciting. But the way I think about this, is a large group of individuals with rare genetic epilepsies. And one of the major goals, as you've heard about today, is really to identify new genetic etiologies in these individuals.

We then, once we've identified either candidate variants, which is what Dr. Gerard spoke about earlier, as well as known disease causing or pathogenic variants, we're very interested in studying these in cellular models. So understanding how, when you have a pathogenic variant in these genes or a candidate variant, how does that variant impact protein function, as well as cellular and neurological function? And I'm not going to talk too much about cellular modeling that we've been doing in the lab, but wanted to point it out.

And then the main goal of this is really to develop these cellular models so that we can start testing novel therapeutics in these cellular models. So again, we can feed back to the patients with potential new therapies, which I'll touch on at the end as well. But really, what I want to focus the next couple of slides on is the work that we do in identifying new genetic etiologies on a research basis in the epilepsies. And I'm going to talk about two themes. So first, somatic mosaicism as well as resolution of variants of uncertain significance.

And so to introduce the topic of somatic mosaicism, I need to just do a little bit of semantics here and introduce you to two topics. And so the first is a germline variant. A germline variant is just basically a fancy way of saying a genetic variance that is present in every single cell in your body. So all of the genetic variants that Dr. Gerard has spoken about so far, we can think of those as

germline. They're present in every single cell and hence why we call them germline.

However, there is another class of genetic variants that we call a somatic variant. And somatic variants can be present in only a subset of cells in our body. And the way in which these occur is essentially the mutation or variance is introduced during development of the embryo. So what I'm showing you here is a slide, so you can picture at zero weeks here, here's an embryo with a couple of cells, all the way through embryogenesis.

And so if that new genetic variant is introduced into the embryo very early on, what can happen is that a large number of organ systems carry that genetic variant. And so this is highlighted here in pink. However, if that genetic variant occurs much, much later, so it arises later, and say for instance only in the cells that give rise to the brain, what you might expect to see is that only half of the brain carries that particular genetic variant. And again, if it arises much later, what can occur is that only a subset of the cells in the brain carry that particular somatic variant.

And so somatic mosaicism is a fascinating topic. There are very few places around the country that will do clinical genetic testing for somatic mosaicism, but it is a very interesting topic in terms of research studies. And so just to give you an idea of where one might suspect that a particular individual's condition may be due to a somatic mutation is very relatively commonly in the focal cortical dysplasias.

And so what I'm showing you here is an MRI of a particular individual. And you'll notice that there are two circles here highlighting specific regions of the brain. And really, I'm not an epileptologist or a neurologist either, so I'm not really qualified to talk about these. But really, in those circles, what I'm pointing out is that there's this region here that's whiter in color and a slightly different shape if you compare it to the other side of the brain.

And so that's because this particular region of the brain has what we call a focal cortical dysplasia, and it's a region of the brain that has a very different morphology or structure as compared to the rest of the brain. And so work over the last five years or so has been performed where individuals who are undergoing surgery as a treatment for their epilepsy have a particular region of the brain resected. So this tissue is taken out as a treatment for an individual's epilepsy.

And in some cases, that individual then goes on to not have seizures anymore, or not be no longer have refractory epilepsy. And so this is a unique opportunity on the research side to then take that tissue and ask, are there any somatic mutations or new variants that are present in that tissue that aren't present elsewhere in the body?

And over about five years of study now, we know that there are about 20 or so genes where you can have a somatic mutation, just in this particular region of the brain, that likely leads to that focal cortical dysplasia or dysplastic neurons and likely is the cause of seizures in that individual. And so this has really progressed the field a lot in terms of the focal epilepsies, but as you can appreciate, it's also tricky to find these variants, in that not all individuals are candidates for surgery, and we can't look at that specific brain tissue.

And so what we and others are doing is thinking of other ways to find these genetic variants. And so one of the ways that we are doing this is with SEEG electrodes. So when individuals are worked up for surgery as potential candidates, small electrodes are placed into the brain and then we monitor the electrical activity to figure out where are the seizures coming from in the brain.

Those electrodes are then pulled out, and in general, discarded. But a very clever colleague of ours, Alica Goldman, thought, "What happens if I try and take the cells off of those electrodes? Could I then capture some of the cells and could I tell what DNA changes were there?" And indeed, it worked. There are now one or two reports of this in the literature.

And so this is actually a study that Dr. Gerard and Dr. Goldman and Dr Ernst and I have sponsored by CURE Epilepsy to try and refine this technique and make it more translatable in terms of using the DNA that sticks to these electrodes in terms of diagnostics as well, and how deeply can we probe the DNA that's present on those electrodes to further diagnoses?

And then the last concept I wanted to talk about was moving away from somatic mosaicism to those pesky variants of uncertain significance. It's every geneticist, and I think now epileptologist, nightmare, in that I would say the vast majority of variants that we get back are these VUSs. And as Dr. Gerard very nicely illustrated, in most cases, it's really just because we don't have enough information to be able to make a call one way or another as to whether these variants are pathogenic.

And so we are very interested in resolving these VUSs. One of the ways in which we do this is a case review, so the case conference that Dr. Gerard spoke about, where we use things like computational predictions and clinical correlations and looking in large databases to make a prediction about whether variants is likely to be associated with disease or not. And so that's kind of the first step what we have right now, but we are also using research tools to be able to tackle these at a much greater scale.

And so one of the things that we're interested in doing is testing these variants of uncertain significance in a cellular system. And so what I mean by that, is that we can introduce tens to thousands of these variants of uncertain significance into a particular cell line and then develop what we call a functional assay. So you can think of it as a readout, where if a particular protein is perturbed, it has

a particular property. So just for now, imagine that it would turn purple, and if that particular variant was benign, it would turn yellow.

And this seems very simplistic, but honestly, it's pretty close to some of the tools that we use, where actually we turn the cells green or not green as a readout for whether a genetic variant impacts protein function or not. And so we are trying to build these massive cellular systems to try and resolve these variants at scale. And so you can imagine, with using a lot of data, we're also interested in using this type of data, but also genetic data to build machine learning tools that then allow us to differentiate between pathogenic and benign variants as well.

And so to end that part, really what I wanted to end on was why get involved in genetic research and what are the benefits as me as an adult being involved in genetic research? And I think one of the exciting things now that is really coming out of the rare genetic epilepsies are future precision therapies and gene targeting therapies, and I'll talk about what exactly those are in a moment. But I really think in the next five to 10 years for some of these rare genetic epilepsies, that there are going to be clinical trial options.

And so along with that means that one missing piece of information that we have, that we don't have rather, is how clinical features for a particular rare epilepsy change over time. And so in general, because there has been a bias towards testing pediatric patients, we have a relatively good idea for a particular rare genetic epilepsy, what those clinical conditions, or clinical features rather, and symptoms, look like in children, but we don't have a good idea of what these clinical features and symptoms look like in adults. And so this is a huge advantage of doing genetic testing in adults, is to kind of get a more complete picture. And this helps us in terms of thinking about prognosis, current treatments, but also as I mentioned, future gene targeting therapies.

So, I just want to end on what our gene targeting therapies. This honestly could be a webinar of its own, but I kind of simplified it just to give you an idea of where we're going in the future. And so before I do that, I'll kind of take you back to biology 101. And so what we have here is a gene, and we can imagine that in this particular case, it's a gene that causes epilepsy, and upstream of it is what we call a promoter. And a promoter you can think of as a piece of DNA that switches on a gene which causes it to make RNA, which then makes protein.

And so right now, the way in which we treat epilepsy is really that we treat the symptoms of epilepsy, we treat seizures, we treat some of the additional neurological features that go along with it, but the goal of gene targeting therapies is to go straight to the source and really just correct that genetic variance that causes the epilepsy. And so in this particular case, I'm showing you that there is normally an A here, a DNA base A and it's changed to a G, and it's represented here by the star, and this is the mutation that causes epilepsy.

And so the goal of gene targeting therapies are either to edit that variant and turn this G back to an A. And this is very much in its infancy in terms of development in epilepsy. We can also replace the gene, so we can just add another copy for instance, so that there's another copy that's making RNA. This also is very much in its infancy in epilepsy research, but an area that is undergoing really rapid preclinical trials at least, are this concept of antisense oligonucleotides.

And these are short fragments of RNA that can recognize the RNA made by this gene, and it can change it in a way that we want. So either increasing the amount of protein or decreasing on it, depending on what we understand about how that particular protein causes disease. We can also use something called CRISPR-guided activation or inactivation. And again, in this case, what we're doing is targeting the promoter and fine-tuning the amount of RNA and protein that is made from this particular gene.

And so just to give you really quickly one specific example of how this can occur. So the gene Scn2a causes a rare genetic epilepsy. And in this case, the Scn2a protein in individuals with epilepsy is overactive. So essentially, what we want to do is we want to knock it down and we want to suppress its activity. And so we do this with a molecule called RNase H and an antisense oligonucleotide. So this oligonucleotide recognizes the RNA from that gene, it binds to it, and then it essentially degrades the protein.

And so folks have tried this in mice, and what they can show is that these are control or wild type mice, and you can see that in the presence of that antisense oligonucleotide, or ASO, you get a reduction in the amount of Scn2a. They also showed in these mice, which have seizures, much like the patients do, that there's also a reduction in the seizures around day 40 to 45 in the mice.

Unfortunately, the seizures do come back, which suggests that these antisense oligonucleotides will need to be given probably in six month to 12 month periods. But again, I think the exciting thing that I want to point out here is I think in the next five to 10 years, we're going to be talking about targeting the cause of epilepsy, as opposed to the symptoms. And again, this is certainly existing right now in the pediatric space and for very rare, very, very rare monogenic causes of epilepsy. But I also think in the future, it's possible that these types of technologies could be broadly applicable to many individuals with epilepsy.

And so with that, I will end, I'd love to acknowledge our fabulous teams, both on the clinical and research side. As Dr. Gerard mentioned, we work very closely together. It's a super fun environment, and it's been awesome being at Northwestern and get to do all the school research. And I think we are both happy to take questions.

Dr. Laura Lubbers: Thank you so much, Drs. Carvill and Gerard. That was a terrific presentation. But as I mentioned earlier, I'd like to introduce Maggie Loesch, a patient for Dr.

Gerard's, who will share her experience with genetic testing from the perspective of an adult living with epilepsy. So Maggie, tell us your story.

Maggie Loesch: Hi, Laura. Thank you. So I did my genetic testing through Dr. Gerard's clinic. It was a long but simple process on the patient end. Basically, Dr. Gerard and I discussed why I should or may want to do genetic testing. And on one side of my family, there is a history of seizures, but not a history of epilepsy. I'm the only one that has the diagnosis of epilepsy.

So I decided, "Let's try it. Let's do it." So we started with a smaller exome panel and no results, so we got bigger. And we went to a larger exome panel. And doing the panel in itself for me was easy. It's a quick swab of the cheek. You can do it at home. It was very simple.

Now, we found that I have a duplication of the HCN2 gene. This gene, for those who don't know, has been associated with febrile seizures and generalized epilepsy. These are two things that I experience and have, but here comes the interesting part. There have not been any reported patients with a duplication of the HCN2 gene. So as of now, the results were varying of unknown significance, and I'm just waiting for science to catch up with my results. I am pleased with my results in a sense. I know that there's no treatment plan to change right now, but maybe science will catch up and we can learn more from that.

Dr. Laura Lubbers: That's fascinating. It's the value of research and driving knowledge forward, and maybe someday we'll have a way to address that genetic change in you that causes the epilepsy. So thank you so much for sharing that, and I'm sure that there may be questions from the audience. If you do have questions, please do put them into the chat. I see lots of questions already, which is exciting, so we can go ahead and move forward with addressing some of those. We've also gotten some kudos for doing this webinar. So again, I want to thank you for coming together as a panel to share your experience. So first question. Will genetic testing tell you if your type of epilepsy could be passed down if you have children or if it won't be? And everybody is on mute right now, so unmute yourself.

Dr. Gerard: Oh, thank you. That's a great question. And I want to say that the way I got into this space in the first place was that I was counseling patients about pregnancy, which is how I started my career. And I felt like I knew everything that they wanted to know about the seizure medications and about epilepsy, and that in most cases, pregnancies are very successful. And I realized pretty early on that I wasn't answering all of my patients' questions because so many patients have the questions about heritability. And that's actually how I started working with Lisa Kinsley, our genetic counselor, and this clinic grew out of that. I will say, and this is something that we want to study, we've been learning that answering that question for individuals is not as clear cut as it might seem, and I'll kind of go through some of the reasons why the short.

So the first thing to know, is that if you don't have genetic testing, depending on your epilepsy type, the chances of passing on epilepsy is not terribly high. We know that for studies of big populations of patients. That of course changes if you have many individuals in your family with epilepsy or you have specific types of epilepsy that are more likely to be genetic. So in those situations, we do recommend genetic testing to help you better understand what the cause of your epilepsy is and what the heritability of it is.

One of the reasons it's tricky, and I want to compare and contrast this with, say for example, prenatal genetic testing you might do with an OB, is that our understanding of what's called the penetrance of these disorders is slightly different. So we may have, in some cases we diagnose a genetic epilepsy that's associated with a single gene and you have to have only one copy of that genetic change to be at risk for epilepsy. And those are the type of genetic changes that we often diagnose if we are diagnosing a genetic condition, and those pass to each individual 50% of the time.

However, just inheriting the variant or the genetic change doesn't necessarily mean the individual will develop epilepsy. So we get into this probability model where it's like, "Yes, we made the genetic diagnosis, yes, you have a 50% chance of passing this on." And again, this is rare, it doesn't happen often, but the likelihood that your child who inherits it will develop epilepsy can be variable, can be 60% in some of the situations that we deal with.

And so yes, it helps. It helps to understand the inheritance pattern. It helps to understand your genetic diagnosis if you have one. Another example is you may find out that your epilepsy is due to a recessive condition, and if it's due to a recessive condition where you inherited a genetic change from mom and dad, the chances of your passing it on are very low.

But we are learning that because there's so much uncertainty in our results, including the variance of unknown significance, including the likelihood of genetic change causes a condition, that a lot of times it's not black and white as it is in some other forms of sort of prenatal genetic testing. So that's why that if you're doing genetic testing with the thought process of, "What's the risk to my child going to be?", that you do this very carefully with a genetic counselor and someone who understands how to explain this. And this is where I think it's really important that your perspective partner also come to the visit as well.

Dr. Laura Lubbers: [inaudible 00:45:32]. So here's a question that I think probably a lot of people are wondering, and even if they haven't said it, but this is a phenomenal capability at Northwestern. Is there a way to use the Northwestern team for genetic testing if we are in another state?

Dr. Gerard: Take that one, too. So, we're very excited and we're hoping to expand this. We do a lot of our consultations virtually now. We also do some in person. And it's not just me, I'm really happy to say that Dr. Scott Adney has joined me and we have other people who are hopefully going to join our team as well. I'm licensed

in a few states, but not all. And if you're not in a state where I'm licensed, then you can travel to Chicago if you're willing to come and see us.

I will also say that interest in this type of specialized clinic is growing and there are several others throughout the country. I just want to highlight some of my colleagues at University of Pennsylvania, University of Alabama and Stanford are some of the people I work with. So if you're in one of those regions, I'm sure there are more developing, but these are people I know and work with who are doing something very similar to us.

Dr. Laura Lubbers: Aren't there resources if it's not through an institution such as yours? Are there genetic testing companies that have focuses on an adult population?

Dr. Gerard: We work with third party companies to order the testing, but I don't believe, and I probably wouldn't recommend doing testing directly with a company. I don't believe it's a possibility, but I think because of the importance of understanding the implications for your epilepsy and understanding the counseling, it's important to do it through your institution and your neurologist. Different programs have different ways of achieving what we are doing. Some have geneticists they consult or genetic counselors, but I would certainly ask, and I think that these programs are building more and more.

Dr. Laura Lubbers: Would genetic testing help determine which medications will help?

Dr. Gerard: Do you want me to take that, too? Yeah, I will. And Gemma, feel free to add onto this, I do want to contrast what we are doing with pharmacogenomic testing. So in the psychiatry space and sometimes in the neurology space, there are testing which tell people how you're going to metabolize drugs. I think it's important to understand that that's different than what we're talking about here today.

Yes, sometimes if we make a specific diagnosis of a genetic condition, there already are specific treatments, including the ketogenic diet or specific medications that you should try or not try based on your genetic diagnosis. Dr. Carvill also talked about that we're more and more gene therapies that are developing, but in many cases, making a diagnosis does not yet lead to an immediate treatment, just like Maggie spoke about. It's more the hope for the future.

Dr. Laura Lubbers: That's how we drive towards that. Right? So would genetic testing help with diagnosis with somebody with generalized seizures? And what type of genetic testing should they start with?

Dr. Gerard: Do you want to try that? Still me? Okay. Actually, I don't know if we can share or if you want, but I had in the extra slides, the sort of algorithm that's recommended by the Genetic Counseling Society to go through testing in general. As I said, that the genetic generalized epilepsy, so I want to first make a

distinction. Many patients have generalized seizures, so generalized seizures can occur in a bunch of different disorders. Sometimes we refer to the term generalized seizures just because you have a convulsion. So I don't want to presume that having generalized seizures means generalized epilepsy. Generalized seizures occur in all genetic conditions as well. So, generalized seizures certainly don't preclude testing.

Having what we often call a genetic generalized epilepsy or idiopathic generalized epilepsy, some of the examples of that might be, for example, juvenile myoclonic epilepsy. It's a combination of having epilepsy usually with convulsions and certain features on your EEG, usually without developmental delays. That particular group of patients has a lower chance of having a positive result on genetic testing right now with what we have available. Doesn't mean you shouldn't do it, I think that's a nuanced discussion we have with our patients, but I would put that way under 5% of getting a positive result.

Which test to do first, I think depends. So the Society of Genetic Counselors recommend for all epilepsy genetic testing now, to ideally start with either an epilepsy gene panel or an exome or genome test. That may be hard cell for the idiopathic or genetic generalized epilepsies. I also would mention that a microarray, which looks for deletions and duplications, like Maggie was describing, if you're really questing for an answer, I've actually found that test to be useful in the generalized epilepsies. Again, with the implications of the results being somewhat variable.

Dr. Laura Lubbers: We've got a couple of questions, or more than that probably, for rare disorders, rare epilepsies. This one is related to Ring 20, and it's recognized that it's very rare, and in this case it's a somatic mosaicism. Is anybody researching this specific type of epilepsy?

Dr. Gerard: So, I'll make one point while Gemma thinks about that, but I'm ultimately going to toss it to her. One point about the ring chromosomes, as I mentioned that if your testing is negative, make sure that every stone has been unturned. Ring chromosomes are extremely rare disorders, can happen in multiple different chromosomes. And there are societies for several of the ring chromosomes disorders, but that is one of the diagnoses that would not be picked up with our big test, with our exome or genome. You actually have to do a very old test called a karyotype to diagnose ring chromosome.

And Lisa and I are unfortunately finding that less and less companies are offering that because it's not been offered as much. So we're actually trying to make that diagnosis on a patient right now. So it's just an interesting point, that a karyotype is the only way to diagnose ring chromosome. As to specific, we are not doing work that I know of at Northwestern on ring chromosome disorders, but there is definitely research and groups working on it. And I was now waiting for Gemma to come up with who they are.

Dr. Carvill: Yeah. No, you're 100% correct. I think the rings are rare, but probably underdiagnosed, because as Dr. Gerard said, right now, at least clinically, karyotype is the only way to detect them. That is changing. There are some newer methods that right now mostly live in the research space. So things like long-read sequencing, optical mapping, these technologies are thought of as probably going to replace karyotyping. And so I think more and more patients will be identified as we shift to those technologies.

But Dr. Gerard's right. Right now, the best place for resources is really the family foundations. So Ring 14 comes to mind. I know there's a pretty strong family foundation for Ring 14, and I think that they are thinking about different ways for targeting therapies. I think it's also, from a research perspective, a very difficult thing to study. Because remember how I spoke about those cellular models and how we use those cellular models to figure out how a particular genetic variant, in this case, a ring chromosome causes cellular dysfunction and then epilepsy? But the problem with ring chromosomes, is that they tend to be lost. So we can't even study them in cells because the cells tend to kick them out and we lose them. And so it makes it really very challenging to study. But yeah, I would encourage to reach out to Ring 14, is I think a good place to start, and they're a fantastic group.

Dr. Gerard: Just Googling, and I'm imagining you've done this, there does seem to be a research and support group in the UK doing work on this.

Dr. Laura Lubbers: Just one more question, and again, a rare diagnosis. This relates to CHD2 and recognizing that it can lead to potentially decline for individuals. And a question is, having a DNA methylation test, would you recommend with a diagnosis of CHD2 that a DNA methylation test to be done?

Dr. Carvill: So I'm happy to take this one. I know a little bit about CHD2. So, CHD2 is rare genetic epilepsy. So just for everybody, so CHD2 is what we call a chromatin remodeler. And when you have a pathogenic variant in the CHD2 gene, what it means is that it changes the DNA methylation pattern in blood cells, and probably other cells in the body, in such a way that we can use a DNA methylation test as another way of diagnosing CHD2.

So importantly, clinically, still the best and first test that should be done is either a panel or an XO. And then in general, if an individual has a VUS, for instance, in CHD2, we can use that DNA methylation test to determine whether that variant of uncertain significance is likely to be pathogenic or benign.

In general, the DNA methylation test is not being used to do prognosis or think about what kind of drugs people should be on. It's more, right now, used as a tool for VUS resolution. That said, I will punt a study that we're doing on the research basis for DNA methylation. And that's a collaboration between myself and Heather Mefford, it's in Jude, where we're interested in probing this DNA methylation signature a little deeper, and trying to figure out how it relates to disease and whether we can use it in prognosis in the future.

And then the last part of that question that I just want to address, is in terms of the potential decline in individuals with CHD2. I think one of the challenges is, we don't really know, as I mentioned earlier, how most of these classically pediatric disorders, how they evolve and how clinical symptoms change over time. And so there are a couple of rare reports in the literature about how adults with CHD2 can have regression and decline, but what I will say is that there is an over enrichment. Because an individual who declines is far more likely to be reported in the literature as compared to those individuals who are adults and don't have testing, and plateau will stay the same. And so there's what we call an ascertainment bias there. And so that's why it's really important for us to identify adults who have a CHD2 variance as well, so that we can get a much more complete clinical picture of how these rare epilepsy, CHD2 and all the others, evolve over time.

Dr. Laura Lubbers: There's still questions, but we have run up against our time. I do want to mention that, Maggie, there were many shout-outs to you for your courage, you're sharing your story, so thank you so much for joining us today. And yes, thank you to Drs. Carvill and Gerard for providing such great information for our audience. And I also always want to thank our amazing audience. Don't they ask great questions? Always great questions. So I want to thank you all.

If you have any other questions, we will try to get the unresolved questions addressed and put those on our website. If you do have other questions, please do feel free to email us at research@CUREepilepsy.org. You can learn more about our research programs also on our website.

As I mentioned at the start of today's webinar, this is the second of a two-part series this month that focuses on epilepsy genetics and research on rare epilepsies. So attendees of today's webinar, you're going to get a link to that previous recording in case you want to view that. And also, please be sure to keep an eye out for the announcement for our April and May webinars, which will be coming out shortly. So thank you all and have a wonderful rest of your day and weekend. Happy spring.