

***Genetic Testing in Epilepsy: Understanding Results and Their Impact on Care***  
**2024 CURE Epilepsy Webinar**  
**(Transcript)**

Laura Lubbers: Welcome everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer for CURE Epilepsy and I'm delighted to have you join us today to learn more about epilepsy genetics.

Since our founding in 1998, CURE Epilepsy has raised millions of dollars to fund epilepsy research that supports our mission, which is to find the cure for epilepsy by promoting and funding patient-focused research. Cure Epilepsy provides grants that support novel research projects that advance the search for cures and more effective treatments.

In this second webinar of our 2024 CURE Epilepsy webinar series, we will be talking about epilepsy genetics. The webinar is entitled Genetic Testing and Epilepsy, Understanding Results and Their Impact on Care. This is the first of two webinars this month that address CURE Epilepsy's ongoing focus on epilepsy genetics. Genetic testing actually has increased our understanding of the causes of epilepsy exponentially in the past two decades, specifically helping researchers understand the many genes responsible for rare childhood epilepsies. In addition to ending the often way too long diagnostic odyssey for patients and their loved ones, genetic testing can help enable tailored treatment options and family planning decisions. However, there are still many individuals who lack a genetic diagnosis, including adults who may not even be aware that they could benefit from genetic testing. In this webinar, attendees will learn about who may want to discuss genetic testing with their doctor and prepare them to ask key questions after genetic testing has been completed. Today's webinars, 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 Katie Angione, who is a neurology genetic counselor at Children's Hospital Colorado in Aurora, Colorado. She provides genetic counseling for a diverse population of patients with complex neurological disorders with a focus on developmental and epileptic encephalopathies. Her primary goal as a genetic counselor is to support patients and their families through education, advocacy and research efforts focused on understanding the natural history of these conditions and eventually working towards precision diagnoses and treatments. Before Katie begins, I'd like to encourage everyone to ask questions. We'll address the questions during the Q and A portion of the webinar. Please keep in mind you can submit your questions anytime during the presentation by typing them into the Q and A tab located on your WebEx panel and click send. We'll do our very best to get through as many of the 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 make your questions general and not specific to a loved one's epilepsy. So with that, I'll turn it over to Katie.

Katie Angione:

Thank you so much, Laura. Thanks for the introduction and thank you to CURE Epilepsy for the invitation to do this webinar. And thanks to all of you for joining. So hopefully this is informative and we have plenty of time at the end for questions. So please, like Laura said, put your questions in the chat and we'll have time for discussion at the end. So as Laura said, I am a genetic counselor at Children's Hospital Colorado in Colorado, and I'm going to be talking today about some basics of genetic testing.

So we're going to talk a little bit about just some genetic testing terms and how to read a genetic testing report. I think sometimes genetics can be like another language, so it's helpful to just understand what all of those terms mean, everything that you're looking at when you're trying to decode that very complex report. We'll discuss some different types of genetic changes, the difference between different types of variants, so benign, pathogenic and uncertain variants. And then explore a little bit about what to do once you've received a genetic diagnosis or even an uncertain diagnosis and talk about how those results can potentially impact treatment or management of disease moving forward.

This is an image we share all the time in just explaining the basics of genetics. So we all have our bodies that are made up of cells. Our DNA is stored in chromosomes, so that's the X shaped figure on the picture. So chromosomes are comprised of large continuous DNA molecules all very tightly wound up and packaged. And those chromosomes contain genes. So genes are just a segment of DNA that encodes a protein product. So something that gives our body an instruction for how to build something that it needs to grow, develop, and function properly. Those proteins are complex compounds that are composed of hundreds or thousands of amino acids. So those are the units that make up the proteins.

So this is an analogy I use a lot. So genes and proteins are like recipes and the final product. So the gene is like that recipe. It's the instructions that tell your body how to make a protein that your body needs to function. The protein itself can have a lot of different important roles in the body. So it can provide structure and support, it can transport materials from one place to another or send signals, protect the body from things like viruses and bacteria and carry out all the complex chemical reactions that we need to keep our bodies going. Like I said, those proteins are made up of smaller units called amino acids. There are 20 different types and the sequence of those amino acids is what determines the proteins 3D structure and what their specific function is and how they might interact with other proteins in the body. So the genes are like the recipe, the protein is like the final product, that cake in the picture, and the amino acids are kind of all of those ingredients that go to make up that final product.

A genetic variant is any alteration in that DNA sequence that is different from what's seen in the majority of people. There's no perfect genetic sequence. We all have differences, although everyone here today we share about 99.9% of our

genetic information. So there is very little left that is different from one person to another, but those differences are what make us all look different, make our bodies function differently, and they're also what can lead to genetic diseases. So a variant which we sometimes refer to as mutations when they're pathogenic or disease causing variants. A variant can be benign. So meaning that it doesn't cause any problems, it's just a normal variation within our DNA sequence. It can be pathogenic, meaning that it does cause some sort of disease or problem. Or it might be uncertain, which just means it's different from what we see in the majority of people, but we don't know enough about that specific change to know for sure whether or not it causes any problems.

So I'm going to go really quickly through this, but we can always come back if there is specific questions. So there are a lot of different types of pathogenic variants or mutations that we can see, and this is something that is typically indicated on a genetic testing report. So we can see missense mutations, which is a way to describe kind of a typo. So it's a change in one DNA based pair or one letter in that code for a different letter. And that is what causes the substitution of one amino acid for another within the protein. So it's a change of one little unit of that protein. A silent mutation is something where the DNA code changes, but that final product actually doesn't. So if you think about the recipe analogy, it's like if there's a really minor typo on a recipe, you're still going to understand what it means. It's not going to alter that final product.

A nonsense mutation is a change that signals the cell to stop building the protein too early. So that causes a shortened version of that protein also called an early truncation. So this, in a lot of cases, can be very severe because there is a big portion of that gene that's missing. Depending on where that change happens within the DNA sequence, we can sometimes see differences in how severely impacted somebody is. There's also insertions, deletions or duplications where there might be just a few letters or even much larger pieces of DNA that are added or deleted or duplicated. So there's things that can alter the number of pieces in that DNA sequence. And because the DNA has a very specific way that it is read, that can alter what's called the reading frame of the gene. So that's called a frameshift mutation and that often eventually results in an early truncation. So the DNA can only be read three letters at a time. It's very specific. So you can imagine if you insert two letters or you take away four, it's going to throw off that three at a time reading frame.

But this is an example of what a missense mutation looks when you're talking about that three to time reading frame. So you can see the sentence the cat ate the rat, if you change just one letter in that sentence, you end up with the cat ate the bat. So it changes the meaning, it changes the final outcome of what's going on just with one letter being different. And then you might also have a different type of missense mutation where instead of the cat ate the bat, you're changing it to the car ate the rat, which is a much bigger change. It doesn't make any sense, whereas the last one made a little bit of sense. So depending on where that mutation is located, you can see more or less impact.

So this is an example of a silent mutation. Sometimes if there's a particular letter that is changed, it doesn't impact that final product too much. So I think in this case we have the letter C just becoming lower case and that doesn't change the final outcome of the sentence. A nonsense mutation, so this is we're talking about an early truncation, so where that sentence or that DNA code stop short, and you can see here if that letter A is taken away or changed and the rest of the sentence isn't there, we don't know what happens, we're just left with the cat. And then insertions, so these next few slides we can go through quickly, but insertions, deletions, duplications, all of these are adding or taking away letters that either they might not shift that reading frame.

So here we have the bat cat ate the rat, which definitely changes things but it still makes sense and it doesn't alter that sentence going forward because that's an in-frame insertion. So it's not messing up that three at a time reading frame. Other times we might add, we might see additions or duplications that do alter that reading frame and that create a sentence that doesn't make any sense anymore. So if you can click through a few times. There we go.

All right, so just a quick way to illustrate those different types of mutations. The other thing that you'll always see included on a genetic testing report is the inheritance pattern for that particular disorder, that particular gene. So there are a few of mean inheritance patterns that we tend to see. Autosomal dominant in which a mutation in just one copy of the gene. Each copy of the gene is called an allele. We have two copies or two alleles for each gene. So for autosomal dominant conditions, a mutation in just one allele is sufficient to cause disease. These types of mutations can be inherited from a parent who is also affected by the condition or they might be brand new in the patient. For a lot of rare disease we see that there are autosomal dominant changes, but they are brand new in that child, so they're not something that was necessarily passed down. And that's something that we talk about a lot is the difference between saying that a disorder is genetic and saying that it's inherited.

So genetic does not imply inherited. Not every genetic disorder is passed down from a parent. We can see a few things called reduced penetrance, incomplete expressivity and mosaicism. These are all things that can alter how a genetic change is expressed. So reduced penetrance means that someone might have a mutation that has the potential to cause disease, but it might not cause as severe disease in each person who has it because maybe it's being influenced by other things. We also see incomplete expressivity, which is very similar, but that just means that not every single person who has a disease causing or potentially disease causing change has any symptoms at all. And this is where we can sometimes see a mutation being passed down from a parent who doesn't have any apparent symptoms of that condition so they did not know that they're at risk to have an affected child. We can also see mosaicism, which just means that not all the cells of the body have the exact same genetic makeup.

So there might be a portion of cells that have a damaging mutation and a portion of cells that don't. And depending on what particular tissues or what

parts of the body are important in that condition, we can see someone being affected more severely or less severely. In autosomal recessive conditions, someone must have a mutation on both alleles or both copies of the gene in order to cause disease. So in most cases, when we see a child with an autosomal recessive condition, typically each parent is what's called a carrier for that condition. Carriers don't have any symptoms of recessive diseases because they have a second copy of that gene that's working just fine and that is enough to not have that disease. But if two parents happen to be carriers, and we are all carriers for a few things and we don't usually know what they are unless we specifically get carrier testing or have a child born with a recessive condition, if each parent passes that mutation down to a child, then we would see a child who's affected with a recessive disorder.

We can also see X-linked conditions. So those are disorders that are caused by a mutation on the X chromosome, which is one of the sex chromosomes. So biological females typically have two X chromosomes and biological males typically have an X and a Y. There are some variations that we can certainly see and a handful of different genetic conditions that can be caused by differences in those chromosomes. So for X-linked conditions, we typically see that biological males and females are affected differently. So we might see in some cases that the majority of patients with that condition are female because it is a mutation that if it were present in a male who only has one copy of the X chromosome that would be so severe that that fetus might not actually make it to birth. Or we might see that males who are born with those conditions might be more severely impacted than females.

And then sometimes we see conditions where only males are affected because it only takes one mutation to cause that disorder. And females who have two X chromosomes and have a copy of that gene without a mutation do not actually express that condition. So again, there are some things that can impact expression in X-linked disorders, the biggest one being skewed X inactivation. I know these are a lot of terms I'm throwing out there and not explaining in detail, but for the sake of time, X inactivation is basically just the process where, in females, our cells turn off one copy of the X chromosome in each cell so that we're not over expressing all of those genes compared to males who only have one X chromosome.

And if there is a genetic mutation on the X chromosome, there are sometimes females who their body might just randomly turn off more copies of the cell that have the mutation, which means that they would be left with more normal copies or typical copies active. So they may be more mildly affected, whereas others might have more of the normal or typical copies turned off in their cells and so then they're left with a larger proportion with the mutation, so they may be more severe. Next slide please.

So why is genetic testing important? There are definitely a lot of reasons. I'm going to try to run through them pretty quickly here. But first of all, we are hoping when we do genetic testing for an improved understanding of the

diagnosis, so an understanding of why we're seeing the symptoms we're seeing. When we're able to make a genetic diagnosis, it might give us a better understanding of the natural history of that condition, the disease course over time so we can answer questions about what to expect as somebody gets older. In some cases it can impact medical or surgical decision making. It might help us to select medications that are known to be effective in that particular disorder. It tells us if there's any other things we should be watching out for. So do there tend to be kidney problems in this particular disorder? Should we be doing brain MRIs for any structural changes looking at the heart, things like that. So just knowing if there's anything else we should be paying attention to.

And then it can also help to correct any misunderstandings. So if there's concern that, for example, something was caused by a traumatic childbirth or caused by something like that, a genetic diagnosis can help to clear up some of those misunderstandings. It can help with family planning. So understanding if this is a brand new or if it is a condition that was passed down from parents helps families to understand recurrence risks and if there's a chance of having another affected child in a future pregnancy. The inheritance pattern tells us, like we just talked about, whether this is recessive, dominant or X-linked condition, which again helps us understand recurrence risks for both the parents or if we're doing testing on child, for those parents and then for that child once they get older, if they have children of their own. It helps open the door for prenatal or even preconception testing options.

We typically would refer to a prenatal counselor if this was something that a family was wanting to discuss further and it could lead to earlier diagnosis and potential improved outcomes in an affected child. Prenatal testing doesn't necessarily mean that you don't carry that pregnancy to term, but it does mean that if you know that you are pregnant with a child who is affected with a genetic disease, you can start implementing different management things early on which tends to lead to better outcomes. And it can also help to identify any at risk family members or anyone else in the family who might be a carrier for the same condition. So it can help them to make informed choices about their family planning. Anytime we make genetic diagnoses, we are improving research, improving understanding of those conditions. So identifying more patients helps to have better natural history studies, to have a better understanding of longitudinal data, so how that disease looks over time.

And eventually, and this is the direction we're moving and very excited about, is exploring the efficacy of precision therapeutics. So ultimately getting to drugs that might target specific genes, specific variants and help to improve outcomes in patients with those disorders. Diagnosis can help to identify other families or other similarly affected individuals, which for a lot of people can be really helpful to just have that community and be able to talk to other people who understand what that disorder looks like and everything that's involved with it. And it opens the door for involvement in patient advocacy groups, patient and family meetings. A lot of rare diseases are starting to have conferences for their specific conditions. So that's another way that we can build that community.

And then it helps to access specific resources. So sometimes having a genetic diagnosis can make it easier to get therapies approved, to advocate for coverage of medical supplies or medications that might be helpful for that particular diagnosis. And then it just helps to provide more money for disease specific support and research, drug development, all of those things.

So I want to walk through a couple of different genetic testing panels and the different elements to focus on when you get one of these results back. So this is what things tend to look like. Obviously from one lab to another there'll be some differences, but every report is going to list the name of the gene. So over here you can see this particular report is for STXBP1. It will list the variant, and this first part where it says C.969 del, so C stands for coding. So that's the change in the actual DNA code. 969 is the address. So it's the number, it's the 969th letter in that DNA sequence that makes up that gene. And del means there is a deletion at this location. The P after that stands for protein. So that is the corresponding change in the protein that happens as a result of the change in the DNA code.

So this one it says p.met324cysfs\*8. So that's a lot of mumbo jumbo when you're not familiar with what all these terms mean. So again, P stands for protein, change in the protein. Met and cys are both abbreviations for different amino acids, so different elements that make up those proteins. That 324, again, is the address of this change. So it's telling you that that position 324, there's usually a unit called met or methionine and instead it's been changed to this different unit, abbreviated cys or cysteine. The frame shifts or the fs means frame shift. So there is a resulting shift in that reading frame, that three at a time reading frame that we talked about. And the asterisk eight means that eight units later in that protein there is an early truncation so that gene stops being built and we don't get the rest of that protein product.

Heterozygous just is describing whether a variant is present on one or both alleles. So alleles is just the two different copies of the gene. Heterozygous means that it's present on one allele. Homozygous would mean that it's present on both. Inheritance pattern is something that's typically listed in that main part of the report. And then the variant classification. So you might see most labs are not going to report out benign and likely benign variants because they are thought to be normal, they're not causing any problems. But on a report you might see pathogenic, so this is definitely a disease causing change. You might see likely pathogenic, which means that the lab is pretty confident that it's disease causing, but it's not quite 100%. And then you might see uncertain significance. So a variant that we don't have enough information about to definitively classify, but that potentially fits the symptoms for which that test is being sent.

This is just an example of what that might look like at another lab. So again, you can see a lot of those same components are present. It tells you the name of the gene, the inheritance pattern, the change in the DNA code and in the protein. This one says de novo, you can see under this genotype section. De novo means

new in the patient, which means that this was a test that included some parental samples. So the lab was able to tell that this is a brand new change in that patient and not one that was inherited. It also tells you the type of change. So you can see a missense change and, again, it says that it is classified as pathogenic or definitely disease causing.

This is an example of whole exome sequencing, which again contains all of those same components but also has this part on the top that talks about everything that exome sequencing looks at. So did they find a causative change in a gene that's associated with the symptoms or the phenotype that was reported? Were there any variants and genes possibly associated with that phenotype? So those would be what we might call candidate genes or other findings that might be relevant, but we don't know enough to say for sure. Secondary findings are changes that the labs that do whole exome sequencing can choose to look at, or not, depending on the patient and family's preference. So those are genes that have to do with risk for mostly adult onset predispositions for things like cancer, serious cardiac issues and other disorders that have medical implications if you knew that you were at risk for them.

And then this particular test also included M-T-D-N-A, which is mitochondrial DNA. I'm not going to get too much into that today, but that's just a separate chunk of DNA that we have that is only passed from others and that's not included in standard genetic testing. It's something that needs to be looked at separately. So this report also lists results of that testing. Next slide please.

So this is an example of a report for another type of testing, a microarray. So the first couple that we looked at were panels and then whole exome sequencing and this is a microarray. So whereas panels and whole exome sequencing read through either all of the genetic material or all of the genetic material that's relevant to a specific phenotype or a specific set of symptoms, a microarray is like if you took a textbook and you're just making sure all of the pages are there. So you're not reading every single thing. It doesn't look at tiny, tiny changes within individual genes, but it looks for larger extra missing pieces. So this report is describing a copy number loss and a copy number gain that were found in chromosome eight. So this first copy number change part is telling you the size of those changes, the location within the chromosomes.

Again, in this example they're both on chromosome eight. The P, and the P that's there, sorry, I can't see because it keeps wanting me to gain control of the slides. The P is just describing where on the chromosome this change is located and then all those numbers at the end are, again, an address. So it's showing you exactly where that deletion and duplication are within that chromosome. Regions of homozygosity is describing if there are areas found where genetic content is the same on both copies of the chromosome. So we expect when we have a child, that things get rearranged and combined and so that we are a blend of our parents and sometimes there are regions of the genetic material that just end up not mixing quite as well or there might be shared ancestry that causes just more similarity between the two copies of the genes.



That's not an issue in and of itself, but it can cause a higher risk for recessive conditions because basically if you had one mutation and things are exactly the same, you're definitely going to have another mutation on that same gene. So that's something that is often looked at during microarrays to see if there's any risk for recessive conditions in those particular regions. And then down at the bottom there's going to be a description of the change and what genes are involved that might be clinically relevant. And a lot of labs will include references, so links to publications about that specific gene or that specific disorder and they might include details on how a variant was classified, whether it was found to be disease causing or if it's uncertain, they might include some of that evidence as to how they came to that conclusion.

So not every report is straightforward. When we're doing these larger panels, we often will land on an uncertain result and sometimes that uncertain results might involve a lot of different genes. So you can see here there are variants of uncertain significance that have been identified in 10 different genes, which is not the most common outcome, but it is something that we can see when we're looking at a lot of genes at once. And particularly, and I always point this out to families in pretest counseling before we're sending testing so that they know what to expect. We see this more often in families who have any ethnic background aside from Caucasian. And that's because the databases that labs are using to determine what's just normal variation and what's potentially disease causing, historically have not done a good job at accounting for just normal variability between people with different backgrounds.

That is finally changing. There's been a lot of efforts more recently to diversify those databases more so that we're getting less and less of results like this. Most of the time when we do get a result like this, doing parental testing clears up the majority of that uncertainty, but it is an area of genetics that we're still working on improving our understanding a little bit better. Next slide please.

So I always use this meme when talking about variants because it is one of the most difficult things that we do as providers is when we get a test report back, we have this variant of uncertain significance. What do we do with that information? A lot of families, they'll see a variant and they'll say, oh my gosh, that sounds exactly like me or that sounds exactly like my child. This must be the answer. But it's not always that straightforward. So when we do get these uncertain variants, we might do family testing to get a better understanding of is this change present in other people in the family who maybe don't have the same symptoms or is it tracking in the family with people who all do have the same presentation? We might assess, does it fit really well with what we're seeing in this patient? So if there are other symptoms that are always seen in that particular disorder, is that something we're seeing in our patient?

And sometimes that might mean doing a more targeted exam or doing additional testing, whether it's biochemical testing, imaging, things like that, to look for other components of that condition. And then sometimes we just need to wait and give it time. We're always learning more about our genes and about

specific variants. So oftentimes a variant of uncertain significance ends up being reclassified down the road and then we have a better understanding of whether it's something we can ignore or if it's something that actually is diagnostic for that patient. Next slide.

And then what do you do when a test is just completely negative? It's important to know that a negative genetic test doesn't mean that there's no underlying genetic diagnosis. It just means that maybe there's something there that we're not able to identify at this point in time. So sometimes if a test is negative, there might be a more broad or a more comprehensive test that we can move to as a next step. So moving to something like whole exome or whole genome sequencing. If we've done the biggest and most comprehensive testing and we still don't have an answer, again, we just have to give things time. So typically if we do something like whole exome sequencing and that's negative, we usually recommend waiting about two years and then asking the lab to reanalyze that testing. Your genetic data doesn't change over time. Your genetic information is going to be the same, but our ability to interpret it is always getting better. So that's where reanalysis can come in. And when we don't have a genetic diagnosis, we just continue with symptom-based management and go from there.

So when you do get a genetic diagnosis from testing, what comes next? So all of the things on this list, or at least most of the things on this list are definitely individual and some of them are not the right move for everybody. So I think it's always helpful to discuss when you get that diagnosis back, have a good thorough discussion with your ordering provider about any management or treatment recommendations that might be different because of that disorder. That's not always the case. A genetic diagnosis sometimes just gives us a reason why and does not give us any specific management changes, but sometimes it does and sometimes that changes over time. So definitely a good idea to check in with either the ordering provider or if there's a specialist who they refer you to, to talk more about it just to talk about any changes to your healthcare plan. Inform other members of your care team or your child's care team.

Sometimes it can be really helpful for people in other specialties, not just genetics, but all the specialties that are involved with what that disorder causes. It can be helpful for them to have that context and that background in managing those symptoms. If you are comfortable with it, informing the school, any therapists, other caregivers, so whether it's family members, babysitters, other people that are involved in that person's care, that can be really helpful for them to have a better understanding of what's going on. When it comes to school, it can help to advocate for individual education plans or IEPs. It can help to advocate for one-on-one attention during class. So having a genetic diagnosis can sometimes open a lot of doors to resources that can be really helpful. Sometimes you might be able to identify specialty clinics or family meetings or conferences that are specific to that diagnosis and that can be a really great place to learn more and to help your providers have some backups.

So there's a couple of specialty clinics at Children's Hospital that I'm involved in that we basically see children with very specific rare diseases. We make recommendations that go back to their primary team so the primary team doesn't have to feel like they need to be an expert on this super rare condition. They can get support from people who've seen more children or more patients with that disorder. Again, as I mentioned before, it can help to connect with other families or patient advocacy groups if and when that's something that works for you. It's definitely not for everybody. There's a lot on the internet as we all know. So I think we always recommend that families take the things that they're reading online, on message boards, on online communities, with a grain of salt and we try to just point people in the direction of good resources.

For a lot of disorders, there might be ongoing or upcoming research or clinical trials. So it's always good to ask about those things and to check in about those things regularly to make sure that you know about anything that you or your child might qualify for. There's also [clinicaltrials.gov](http://clinicaltrials.gov), which is somewhere that you can search for those things directly, but working with a provider who's able to be the in-between can be really helpful in making sure you're in the loop about those sorts of things. And I'll say that's another thing that family groups are really good for is informing people who are part of that group about those sorts of opportunities. And then it's also helpful to consider any implications that diagnosis might have for family planning. So again, whether it's you have a child diagnosed with a rare disease and you're wanting to know if there's any chance of that happening again in future pregnancies or if it's someone who might have biological children down the road and wants to know their chance of passing that genetic change down, it can be helpful.

Just some quick online resources. I'm not sure if these slides will go out, but I know this is recorded. So just a few things that I use all the time and pass on to families all the time. GeneReviews is really in depth information about a lot of different genetic disorders and then they include surveillance and management recommendations over time. So that can be a helpful guideline on the type of providers you might need to see and how regularly you might need to have certain testing done. MedlinePlus is a more paired down version of GeneReviews. So it is the basics and this is something I often recommend, if you have family members or people that are involved that want to know what's going on, but they don't need to know every detail, that's a good resource to turn to. Nord Rare Disease Database and Unique are both kind of additional places where there's a lot of information about different genetic disorders.

And also same, MedlinePlus has a lot of great resources for just learning more about genetic concepts. So that's a good place to go if you're looking at any of these reports and you want to know a little bit more about the terms that are used or some of the terms that we briefly talked about today, that's a really great place to turn.

Laura Lubbers:

Thank you so much, Katie, for all of that information. Loved all of the animations. Start with the Q and A portion of this webinar. Just a reminder, if

you want to ask your questions, please submit them via the Q and A tab on your WebEx panel and click send. We're getting some thank yous from the audience and we have some questions. One is, this person was informed that the gene that's been identified for Doose Syndrome has been found but not for JME. Is this the case, do you know?

Katie Angione: So I know that Doose Syndrome or EMAS has a couple of different terms for it. It's something that we've been trying for years to find the gene and there are definitely some genes that have been associated with it. There's still multiple different genes that can cause that presentation. Doose is a clinical presentation and so there's not one gene, one clinical diagnosis, there is a little bit more complicated than that. JME, I know that there are some gene associations. I'm not sure off the top of my head what they are. There's so many genes at this point to keep track of. But again, I think there's a lot of patients who have a JME presentation who we're not able to find a genetic cause for. So that might mean there is a genetic cause, but we don't know the full list of genes that could cause that type of presentation yet.

Laura Lubbers: Another question for you. What about roadblocks to insurance paying for genetic testing? Do you have any recommendations for families who face that issue?

Katie Angione: Yeah, that can be really tricky and my experience has been that insurance providers are always changing their policies. I would say that if you work with a provider who's comfortable with ordering genetic testing, they might be able to go to bat for you a little bit. So we often will write letters of medical necessity. A lot of our physicians will have peer-to-peer discussions with insurance companies to explain the reasoning behind doing testing. But it might be helpful if you're seeing that testing as getting denied, you might be able to request a copy of their policy and some, sorry, I'm losing my voice, some insurance providers actually cover very limited genetic testing, so maybe single gene or a very small panel or microarray. And then very extensive genetic testing, like whole exome sequencing, but they might not cover a lot of the panels that we typically send in between.

So that's something we struggle with a lot is wanting to send something more targeted, but then only having the option to send something really comprehensive like whole exome sequencing. So I would say have that discussion with your provider that you're talking with about genetic testing, about what those options are and if there's something that would make sense to send that would fit within that insurance provider's policy. There's also some genetic testing labs that have pretty good self-pay options and patient assistance programs. So some of the labs that we work with commonly, Gene DX and Invitae, Prevention Genetics, worked with [inaudible 00:42:31] over time depends on the tests we're wanting to send, but a lot of those commercial labs do have really good programs for self-pay options. So that's something else to consider. I know sometimes going through a hospital system can lead to higher

costs, but going directly to the lab might be more feasible. So that's something to look into.

Laura Lubbers: I know that there have been some free testing programs. Is that still the case for our community?

Katie Angione: Yes. So I work in neurology and with epilepsy, so that's my bias here. Those are the things I'm most familiar with. But Invitae does have a program called Behind the Seizure that is sponsored by a bunch of different pharmaceutical companies that are working on or that have treatments for some of the genes on that panel. So that is an option for children who have epilepsy that are under the age of eight would have access to that program. I know Invitae also has a long list of other sponsored programs that is always changing over time, so I'm not sure exactly what's on that list right now. And then Prevention Genetics definitely also has some sponsored testing options as well. I would say that that's another thing that family groups and patient advocacy groups are good at informing their community about. So that might be a place to turn if you're looking for a sponsored test that would work for you or for your child.

Laura Lubbers: Great, thank you. Here's a question. Would you recommend siblings get genetic testing?

Katie Angione: So it depends. So if there is say a diagnosis of a rare disease in a child and their siblings are also children, so they're under the age of 18 and they're not expressing any symptoms of that disease, we don't typically recommend what's called asymptomatic or predictive testing for siblings until they're old enough to participate in that conversation. So that doesn't necessarily mean 18. We definitely have those conversations with teens depending on exactly what the disorder is and what their level of understanding is. But in general, we try to avoid testing minors unless there is a specific treatment or something that could really impact the course of the disease. So if a sibling, for example, is diagnosed with CLN2 disease, which is a genetic disorder that does have a gene specific treatment, we might test a newborn sibling to see if they have that same disorder because we know that it can be helpful to treat very early on and can see potentially better outcomes when treatment is started earlier. So that would be the exception to that, is if there are potential treatment implications.

Laura Lubbers: Thank you. Yeah, there's encouragement for doing that if there's evidence to suggest that it would be helpful. If children develop epilepsies, but there's no known history for at least two generations, is there a benefit for the parents to get tested?

Katie Angione: I do think it is still potentially beneficial for parents to get tested. So if a diagnosis is made in a child and there's no family history. It depends on the specific gene, but there are some disorders where someone might actually carry a mutation but not have any apparent symptoms. So that could be helpful for knowing about potential recurrence risks. I would say tuberous sclerosis is a pretty decent example of that. It has a very wide range of severity. So we

sometimes see patients in clinic who have that diagnosis, they have the genetic diagnosis, there's no apparent family history, but then we test parents and one of the parents has the same change. So for things like that where there is a wide range of presentation, I think it can be helpful if you want to know for sure.

Laura Lubbers: Here's a question relates to somebody's experience. This person had their son tested and turned out negative. It sounds like it was a panel with a handful indicating limitations. Could you define the term limitations?

Katie Angione: So I think every genetic testing lab will include this paragraph, sort of a disclaimer in the reports, about the limitations of current genetic testing. And I think the biggest one at this point is just our understanding as a whole scientific community of our genes. So we know we have about 20, 22,000 different genes within our bodies, but at this point we only have a good understanding of what about 8,000 of them do. So there is a lot left that we still need to learn about. So that's the biggest limitation in genetic testing at this point, is just our understanding. The other limitation, depending on the type of testing, would be the technology. So not every single genetic test can test for every single thing. Every test is looking for something different. So even whole exome sequencing, which is meant to and understood to be very broad and very comprehensive, there are certain types of genetic changes that whole exome sequencing or even next gen sequencing, which is how most panels are done, is not able to detect.

So there are things called trinucleotide repeat disorders, which involve repeating sequences of the DNA code. That is something that requires very specific testing. There are changes called methylation changes that are seen in disorders like Prada Willie Syndrome and Angelman Syndrome, that requires very different specific testing. So I think that's why it's really important to try to work with a provider who has some understanding of genetic testing if you can. I know that access can be an issue when it comes to genetic specialists, but making sure that everything that is within the differential diagnosis has been tested for with the testing that's been sent.

Laura Lubbers: Explain the difference between whole exome sequencing and whole genome sequencing.

Katie Angione: So whole exome sequencing is looking at the exome. So our genes are made up of exons and introns. So I think of this like a train. So the exons are like the cars on the train that have most of the content of those genes and the introns are these linking pieces in between that link that gene together. But when the body reads it and makes it into a protein, those introns get cut out and the exons get put together into that final product. So the exome is looking just at the exons, it's looking just at the train cars and not at the parts in between. Historically, we used to call those parts in between junk DNA, which is a terrible term because we've learned over time that it is still very important. There's a lot of components outside of the exons that help to regulate how genes are expressed, that help to might work with gene and protein interactions.

There's a lot in there, but we don't understand everything that's in there quite as well as we understand what's in the exome. So the exome is only about 2% of our genetic information, but we think it makes up 90, 95% at least of disease causing changes. So we've started doing whole genome sequencing to look at all that other stuff, but we're still working on understanding what all that other stuff means and what it does. So whole genome is more comprehensive. It's looking at more but, at least in my clinical practice, we haven't seen a huge increase in yield between whole exome and whole genome sequencing. So it is a direction we're starting to move. We're starting to send whole genome sequencing more and more often clinically, but we still have a ways to go and understanding of the other stuff that's in that that's not included in exome.

Laura Lubbers: Genetics is so complicated, isn't it? And there's still so much-

Katie Angione: It really is.

Laura Lubbers: Somebody asked a question, in the gene code in the report for some of the transcripts, there was an NM in front of the information. Can you explain what NM means?

Katie Angione: So that's the name. That's just identifying the transcript that the lab is looking at. So for a lot of our genes, there's kind of one DNA code, there's one sequence that the body's reading, but it can take that and cut it up and put it back together in various ways. And there might be multiple different transcripts or versions of that final protein that are important. Sometimes there might be some that are more important in one part of the body and some that are more important in others. That transcript is just the lab listing which version of that gene that they're looking at and how they're mapping that final change. It's based on that transcript and not on a different transcript. I don't know if that answers your question.

Laura Lubbers: So complicated with all of those genes resolving into different kinds of proteins even from similar sequence. That's really cool. I think you've already talked about this, but if you could just answer it again, how often is it recommended to go back for an update or re-analysis as new genes are discovered?

Katie Angione: I would say if you have done a lot of genetic testing and gotten uncertain or negative results, I would recommend trying to touch base with either with the provider who coordinated the original testing or with a genetic specialist, whether it's a geneticist or genetic counselor, every one to two years. That actual reanalysis, once we get to the more complex testing, we recommend waiting two years in most cases, unless there's a major change in symptoms or there's a decline of if things are progressing, if there's a hospitalization, some of those things might trigger us to do things earlier just to be like, we definitely want to make sure if there is any new information to find that we find it, but we don't want to jump the gun on doing reanalysis because if we do testing today and we don't find anything. If we do that same test again a month from now,

the chances that we're going to find anything new in a month's time are not very high.

But the chances that we learn more over two years, it's actually really decent. Our understanding has improved a ton over the past several years, and I think that will continue to kind of grow exponentially. So I think that's a reasonable timeline. If there is a diagnosis, I would also recommend checking in every one to two years for more information. There might be new research that's come out, new publications, more patients that have been identified, and there might be research opportunities that would be relevant. So I think that's a good timeline for checking in, even if a diagnosis has been made, sometimes things change there too.

Laura Lubbers:

Great. So important to think about the research components of this, of course. I know we're coming to the end of our time and I know that there's still some questions, so if anybody wants in, the audience wants to send your questions directly into CURE Epilepsy, feel free to do so at [research@cureepilepsy.org](mailto:research@cureepilepsy.org). I want to thank Katie for a great presentation. Thank you so much for breaking it all down for us and providing answers to the questions. I also want to always thank our amazing audience for all the great questions you offer and get us thinking about what needs to happen next. Again, if you want to learn more about CURE Epilepsy, our research programs or our webinars, please do visit our website. And again, you can email us at [researchatcureepilepsy.org](mailto:researchatcureepilepsy.org). This is actually, again, as I said, the first of two epilepsy genetic webinars this month and the registration has already begun for our second webinar, which is focused on genetic testing for adults and specifically how testing can help adults with epilepsy and their diagnostic odyssey and in some cases identify new treatment plans for their epilepsy.

That webinar is going to be hosted on March 22nd and will feature doctors gemma Carville and Elizabeth Gerard, who lead the Adult Epilepsy Genetics Clinic at Northwestern Medicine in Chicago, Illinois. You can scan the QR code right on your screen and it will take you right to the webinar registration page. I encourage you to do that. And each of you who are on the webinar today will receive a follow-up email with a link to register for the webinar if that's more convenient for you.

So thank you all again for your participation and especially Katie for all your information and we hope you have a great day. Thank you.