CURE Webinar
Genetic Testing to Develop Personalized Medicine in Epilepsy
(Transcript)

Kate Carr:	00:06	Welcome everyone to today's webinar. And thank you for joining us. I'm Kate Carr, the CEO of Citizens United for Research in Epilepsy or as we're more commonly known CURE. Today, we are live from Columbia University's Institute of Genomic Medicine in New York city. This is our partner in CURE's Signature program, the Epilepsy Genetics Initiative, or EGI. Thank you so much for joining us.
Kate Carr:	00:37	Today is the first webinar in CURE's 2018 Leaders in Epilepsy Research Webinars Series. This series will consist of multiple webinars throughout the year that highlights some of the key research that is being done today in epilepsy. We want to thank our sponsors SUNOVION for providing resources to bring you today's webinar. And I'll let you know that this webinar will focus on genetic testing and the corresponding precision medicine movement within epilepsy. And our presenter is Dr. David Goldstein.
Kate Carr:	01:15	CURE's mission is to identify and fund cutting-edge research so that we advance towards a cure. We are currently celebrating 20 years of impact in the field of epilepsy research. CURE has been instrumental in advancing the science in many areas including post-traumatic epilepsy, infantile spasms, SUDEP, devices and technology, and of course our topic today. Epilepsy Genetics just to name a few.
Kate Carr:	01:47	Today's webinar will outline the importance of genetic testing in epilepsy, discuss available options once a person receives their testing results, and highlight some of the successes resulting from our work. Just to provide you with a little background information, EGI was launched nearly three years ago with the aim of collecting the genetic data of epilepsy patients, and their family members, analyzing and reanalyzing this data every six months. And reporting back any new findings to the patient's treating physician.
Kate Carr:	02:24	This data is also made publicly available to researchers to help advance the science of epilepsy genetics. To date, EGI has over 800 enrollments with nearly 20 medical institutions from around the world contributing data. We want to thank the National Institute of Health and the National Institute of Neurological Disorders and Stroke, along with the John and Barbara Vogelstein Foundation for their generous support of EGI.

Kate Carr:	02:57	Our featured expert today is Dr. David Goldstein, the Director of the Institute of Genomic Medicine here at Columbia, and he's the professor of medical and surgical research. Dr. Goldstein's research focuses on many aspects of human genetic variation including human genetic diversity, the genetics of disease and pharma genetics. I've said that correctly. First at Duke University and now at Columbia university, his group along with large networks of collaborators has been responsible for a number of well-known discoveries including the gene responsible for alternating-
Dr. David Goldstein:	03:43	Hemiplegia.
Kate Carr:	03:46	... hemiplegia [crosstalk 00:03:47]. I've got a little bit of help there. Hemiplegia of childhood and the role of IL28B gene in treatment response to Hepatitis C infection. As Director of the sequencing biostatistics and bioinformatics core of the Epi4K Consortium, he has led the collaboration that discovered three novel epilepsy genes to date. His group has also been involved in some of the early applications of next generation sequencing and the study of undiagnosed diseases.
Kate Carr:	04:22	Before Dr. Goldstein begins, I would like to encourage you to prepare to ask questions. You can submit your questions anytime during the presentation by typing them into the questions tab of the go to webinar control panel and click send. My colleague from CURE, Brandon Loughlin will read them aloud during the Q&A portion of the webinar. We want this webinar to be as interactive and informative as possible.
Kate Carr:	04:53	However, to respect everyone's privacy, we ask that you make your questions general and refrain from being specific about a loved one's epilepsy. We are unfortunately not able to provide diagnosis during this webinar so we ask you please keep your questions general. I also want to mention that today's webinar as well as all previous and future webinars will be recorded and available on the CURE website, which is cureepilepsy.org. If you like this webinar or others, please pass them along to your friends. Now let me turn it over to our expert, David, take it away.
Dr. David Goldstein:	05:37	Thanks so much Kate. And it's really terrific to be here and to have an opportunity to talk about some of the work that's going on here in epilepsy genetics where we're really trying to improve the way genetics is used to diagnose and hopefully ultimately treat epilepsy. First, just a few words about epilepsy. Epilepsy unfortunately, is a very common serious neurological disease affecting around 65 million people worldwide which is

approximately the population size of France as indicated on this map.

Dr. David Goldstein: 06:28 So, a fundamental starting point is the question of what causes epilepsy. In a proportion of cases of epilepsy, there's a relatively clear cause or at least very strong contributor to the epilepsy that is recognizable clinically before any kind of genetics is done. And examples of those kinds of recognizable causes are indicated, including things like tumors and trauma and stroke and others representing about a third of presentations. And the remainder starts out clinically as of unknown cause.

Dr. David Goldstein: 07:14 And there's a presumption of a genetic contribution to many of those. Now let me just emphasize that even in the so-called known causes, we're not saying that genetics doesn't contribute at all, it's just that there's a presumed primary cause. Now following genetic testing, a proportion of the epilepsies that were previously of unknown cause become identified as genetic epilepsies. And that proportion that becomes identifiable as a genetic epilepsy of course varies depending upon the type of epilepsy presentation.

Dr. David Goldstein: 08:15 So far, there are more than a 100 genes that have been identified as clear epilepsy genes with a larger number that cause epilepsy and a number of other conditions where the epilepsy may not be a primary. And given that there are so many different genes that can cause epilepsy and indeed that there continue to be new genes associated with epilepsy regularly, the primary way now that people think about genetic testing for epilepsy is in fact not to just focus on a set of known genes because there are so many, and because the set of known genes continues to evolve.

Dr. David Goldstein: 08:57 Instead, what is increasingly done and what we do here at Columbia is focus on nearly all the genes in the human genome, when we look in a patient's genome to try to find the cause of disease. And this is done using an approach that now is called whole exome sequencing. And this is just a genetic test that's increasingly in fact applied clinically as we'll hear more about it a little bit. But it's just a test that looks at what genetic changes an individual has in any of the approximately 20,000 genes that are in the human genome.

Dr. David Goldstein: 09:39 The best way to perform this test for presentations that start relatively early in life is to sequence not only the individual with epilepsy, or if let's say another presentation that's being looked at, but also to sequence that individual's parents. And the reason this is done is that a proportion and in fact an important

proportion of patients that have a genetically caused epilepsy have mutations that are brand new in the individual with epilepsy.

Dr. David Goldstein: 10:15 That is to say it's a mutation that we can see in the patient's genome with epilepsy, but that is not present in either his or her father or mother. And we refer to those mutations as de novo mutations because they have arisen brand new in the individual. And a lot of the early onset genetic epilepsies are due to exactly these kinds of mutations including for example, and well known cases such as SCN1A, the cause of Dravet syndrome.

Dr. David Goldstein: 10:54 So what are some of the benefits of performing this kind of a test in individuals that have epilepsy? One thing that needs to be emphasized and that is sometimes I think less appreciated than it should be is that even if there isn't a change in the management of the patient pharmacologically, for example, due to the genetics, there often is what we refer to as a utility or personal utility and knowing the cause. That for example, can sometimes just simply provide information that is reassuring to families that they finally know what the cause of sclerosis condition is.

Dr. David Goldstein: 11:42 It can provide information about risk for other family members. And of course puts an end to what can be an emotionally difficult but also costly and time consuming diagnostic Odyssey. But beyond those kinds of benefits, which as I said can be very real for families, performing this kind of test and providing an answer for why the individual has epilepsy can sometimes also have real clinical implications.

Dr. David Goldstein: 12:17 The ideal of course, which I'll say more about, would be that the genetic diagnosis would tell the physician how best to treat the epilepsy and that does sometimes happen. But there are other benefits clinically too, for example, having a genetic cause identified may give you a clearer indication of the prognosis of the patient.

Dr. David Goldstein: 12:45 Here are some illustrations of genetic epilepsies that do routinely emerge in genetic testing, and some management implications that would result from having a diagnosis in one of these genes. I won't walk through all of them, but these are well known examples, where if you see that the patient has epilepsy because of mutations in one of these genes, you might change the order in which you've tried a potential known epilepsy treatments, for example, if you have one deficiency, it would indicate trying to ketogenic diet.

Dr. David Goldstein: 13:28 If for example, a patient was identified as having a disease causing mutation in SCN1A that would suggest avoiding sodium channel blockers, which of course is a common mechanism of action of antiepileptic drugs. I would like to emphasize that while there are such examples of ways in which the genetic diagnosis can influence management, I think it is fair to say at this point, the impact on management of genetic diagnosis is usually modest, not negligible, but modest.

Dr. David Goldstein: 14:10 And the reason that I say it's usually modest is that the management changes that are indicated by the genetics are often, or probably even usually really just changing the order of treatments that would have been tried anyway. A very good example of that is if a genetic diagnosis indicates that you might want to try instead of avoid sodium channel blocker, that might result in trying them sooner than would otherwise have happened, but it would have been done any way with seizures that are difficult to control.

Dr. David Goldstein: 14:47 So I think that we need to really not overstate the clinical impact at this stage and emphasize that there are management implications, but they are often modest but still often important. So other benefits of performing the exome sequencing in a research environment really relates to improving the way that genetics is done. And this includes allowing us to discover new genes for epilepsy, but also allowing us to really improve how the diagnostic work is done.

Dr. David Goldstein: 15:36 And it's important to emphasize that the human genome is a very big, very complex place, and methods for determining whether variants do or do not cause disease are constantly evolving. And so it's really important to work with these patient genomes in a research environment that can really optimize the way that genomic interpretation is done. And of course, ultimately what we want to do is use these genetic diagnoses as the starting points for the development of new therapies.

Dr. David Goldstein: 16:16 So what I'd now like to do, having set the stage with what's happening in genetics in general is try to move into what we are doing specifically in EGI to try to improve the way the genomes of patients with epilepsy are analyzed. So what happens in the EGI workflow is that we start with the data that are generated when patients have been sequenced clinically.

Dr. David Goldstein: 16:50 What happens when a patient is sequenced clinically is that they either get a diagnosis, meaning that the clinical laboratory reports that there is a genotype identified in the patient that is thought to cause the patient's disease, or they do not. And of

course there's some grey area in between, but for simplicity, we'll just think about that dichotomy.

Dr. David Goldstein: 17:18 And unfortunately, the majority of patients even with the most comprehensive genetic tests currently available sequencing the entire genome, most patients do remain unresolved. And it is those patients that we seek to enroll in EGI and to move into a research database that we commit to reanalyzing on a regular basis in order to see if we can find any genetic diagnosis in patient genomes that just happens to be missed for whatever reason when the clinical lab did their first interpretation of the patient's genome.

Dr. David Goldstein: 18:05 And I do want to say that some clinical labs do reanalyze up over time, but usually there isn't a guarantee about how those re-analysis will be performed. And just one very simple illustration and I'll give further examples soon. But one simple illustration of why it's so important to do these re-analyses is that genes are constantly being discovered that weren't known about in the past. And if a patient genome is analyzed before a relevant gene has been identified and they have epilepsy because of a mutation in that gene, it's going to be missed and it wouldn't be identified until you reanalyze the patient's genome after that gene had been connected to epilepsy.

Dr. David Goldstein: 18:58 So, where are we so far in EGI enrollments? We have enrolled 332 families or a bit more at this point representing a total of 839 individuals. And for about 167 of the families we've actually been able to go over the genetic data within EGI, and 139 of those were individuals that had genetically unresolved epilepsy the time of the re-analysis, which is to say that when the clinical lab give the interpretation, no genetic diagnosis have been identified for those individuals, and an overall summaries for those 139 previously unresolved cases, EGI has actually been able to identify a genetic diagnosis in nine of them representing just under 6% of that total.

Dr. David Goldstein: 20:09 Now, if you're thinking about moving a patient from having an epilepsy of unknown cause to having a clearly identified genetic cause, 6% I think is an important deal. I think that, that is a very important deliverable for EGI. But I'd like to emphasize that the rate of diagnosis is actually in some ways more important than it sounds from the 6% figure.

Dr. David Goldstein: 20:35 And the reason for that is that of course, from the first analysis, the majority of patients go unresolved as I indicated before. And so this 6% figure out actually represents an approximately 25% increase in the overall diagnostic yield of performing the

genetics in the first place. Excuse me. And so this really strongly emphasizes the importance of this kind of dynamic re-analysis that we are undertaking within the context of EGI.

Dr. David Goldstein: 21:06 So what I now like to do to try to give you a little bit of a feeling for exactly how this works is provide some examples of diagnoses that were identified by the team of people that are working within EGI. And here I'd really like to highlight that the EGI team at work at both Columbia and CURE has really been very, very dedicated in performing these analyses in a really the most timely fashion possible.

Dr. David Goldstein: 21:40 So for this example, a four year old female with epilepsy, seizure started early in life, accompanied with a number of other symptoms and whole exome sequencing, clinically interpreted in 2014, did not yield that genetic cause. She had a reanalysis by EGI performs just last year a clear cause was found in the FGF12 gene and that had been reported in other individuals in the scientific literature only in 2016. And this very, it was reported back by EGI to the referring provider and then returned to the family thus ending a three year diagnostic Odyssey for that family.

Dr. David Goldstein: 22:31 So here's just an illustration of this timeline for FGF12 showing the onset of seizures for the patient and the time at which the diagnostic whole exome sequencing was performed, the time in which that the community identified FGF12 as being an epilepsy gene. And then when we reanalyzed here at EGI, able to make note of this discovery in 2016, thereby allowing us to identify the disease causing mutation in that patient's individuals genomes.

Dr. David Goldstein: 23:10 Here's a second example of an EGI diagnosis, seven year old male with epilepsy, early onset seizures, again and again, a whole exome sequencing in 2014, with a so-called variant of unknown significance indicated in the PP3CA gene. And at the time that gene was not recognized as a disease causing gene which was the reason for inconclusive findings.

Dr. David Goldstein: 23:43 The individuals exome data was reanalyzed by CURE in 2016, we identified a strong indication in the type of variant that we saw that variant in that gene may actually be responsible for disease. And we discussed this with other researchers in work that was led here by Aaron Heinsohn, a part of the EGI Initiative.

Dr. David Goldstein: 24:15 And in discussing with other researchers identified quickly a number of other patients with the variance in the same genes. And this led to a rapidly put together research paper

introducing de novo mutations in this gene as a clear cause of a severe neurodevelopmental disease. And then once the paper has been published, we and others can refer to that paper to make clear that the relevant type of de novo mutations in this gene, it's the right presentation are likely pathogenic or pathogenic mutations for the patient's epilepsy.

Dr. David Goldstein: 25:00 And the third example actually is a different type of example. The other two examples were examples in which the diagnosis was missed because the gene was not yet known at the time. This third example is an example of a known gene, but with a variant that was missed. And without going into the details here, what happened is that there are alternative forms of this gene.

Dr. David Goldstein: 25:40 And when the genomes were first analyzed, the clinical labs ignored variants in one of the forms of the gene, but on close evaluation, it's clear that that form of the gene is also important and that mutations in that form of the gene can also be disease causing. And that allowed us to not only reinterpret the genomes of patients with mutations in this form of the SCN8A gene but also to write a paper coming out of EGI indicating that this form of the gene has to be considered too when you're looking at genetic data for patients.

Dr. David Goldstein: 26:24 So here are just highlights overall summarizing what we've done. There are nine diagnoses so far in the first three years of the efforts in EGI, which I would emphasize again, are diagnoses that had been missed for whatever reason when the first clinical interpretation of the exome was provided. And there have also been candidate variants identified. And so far, we've published on a new gene and on how to interpret more effectively an already known gene, SCN8A.

Dr. David Goldstein: 27:04 Finally, we have a paper summarizing all of the experiences to date in EGI that's in progress, and have put together a variant database showing the variants we've seen in all the exomes that have been analyzed that can be found at the website that's indicated. So that's where we are so far. What I'd like to now turn to in the remaining just two minutes before we move on to Q&A really is where we're headed next.

Dr. David Goldstein: 27:37 And there really are two distinct directions that we think are important to pursue at this point. One is trying to identify the causes of epilepsy in patients that still are unresolved even after having been reanalyzed. And I would say that it's increasingly important that we explore new ways of looking at those patient's genomes because the rate of new gene discovery in

epilepsy is actually beginning to taper off. And so I don't really anticipate that the majority of the currently unexplained cases will be resolved in the near future simply due to new gene discovery.

Dr. David Goldstein: 28:27 I think a lot of these currently unexplained cases genetically are due to genetic causes that we can't see in the current genetic data for one reason or another. And in EGI, this represents the majority of what we're looking at where we've only been able to resolve a relatively small proportion of the cases that we are looking at. Now, of course we're looking at the hard cases because they're already negative at a clinical lab, but this represents really a lot of patients with epilepsy where we can't get the answer out of their genomes.

Dr. David Goldstein: 29:01 And what we would like to do is explore their genomes much more thoroughly, not only moving from whole exome sequencing to so-called whole genome sequencing to be able to look through the entire genome, but also doing things like using new and better sequencing approaches that can allow us to get at tough parts of the genome. That current whole genome sequencing approaches don't do a good job of for example, regions of the genome with a lot of repetitive DNA or other challenging features like that.

Dr. David Goldstein: 29:34 But also other approaches such as sequencing the messages that are used to translate genes into protein so-called messenger RNAs, sometimes if we sequence those, we can actually see signatures of mutations that we can't see by looking at the patient genome. So we're interested in pursuing a variety of approaches in the community to try to figure out how to find the mutations in these unexplained cases. And this is going to be a really important focus for us and many others in the field in the years ahead.

Dr. David Goldstein: 30:15 The next thing I want to emphasize in terms of where to go next really addresses this fundamental question of what happens after you do get a genetic diagnosis. I already indicated that there are some modest impacts on management for a variety of the diagnosis, but I think without overhyping things, I think that it's fair to say that for a number of genetic epilepsies targeted treatments will become increasingly effective.

Dr. David Goldstein: 30:48 And what I mean by targeted treatments is a treatment that really is designed to address the mechanism of disease that is caused by the particular mutation that causes that patient's disease. And so for example, if we think about an SCN8A epilepsy, what's happening mechanistically is that there's a

mutation in this particular ion channel that means that, that ion channel works too hard and that's actually how you get the epilepsy.

Dr. David Goldstein: 31:20 And a targeted treatment for that kind of epilepsy would go after that channel and try to make it work less hard. That would be a targeted treatments. For a variety of genetic epilepsy, I really do personally believe that these targeted treatments are on the way for a number of them, I do not mean to say it's going to be easy to find them.

Dr. David Goldstein: 31:40 I do not mean to say that there aren't going to be some false leads or have been, and there will be, I do not even mean to say it's going to be very quick, but I do believe it's coming. And if it's coming, I think that what we can think about in EGI is to really create the environment that will allow these kinds of targeted treatments to be most efficiently evaluated.

Dr. David Goldstein: 32:04 If you think about it, when targeted treatments become available, it's a challenging problem to test them in the appropriate patients because you don't just go to a medical center and enroll epilepsy patients. You have to go to medical centers and enroll epilepsy patients that have epilepsy because of specific mutations in specific genes that have been carefully vetted and really are responsible for the patient's epilepsy.

Dr. David Goldstein: 32:27 In EGI, we could really, I think, create an infrastructure that would facilitate this by having a set of genetic diagnoses that are carefully vetted, and where we have relationships with care providers and families where we know whether individuals are interested or not in being contacted by any entities that wish to trial targeted treatments for their kind of genetic epilepsy. This is, I think going to be a central challenge for the field. How do we address running these kinds of trials effectively?

Dr. David Goldstein: 33:01 And I think we might have an opportunity within EGI to really make a useful contribution to really this critically important aspects of the development of precision therapeutics in epilepsy. That is where I will stop. And thank you on behalf of the whole EGI team and CURE for the opportunity to talk about this work, which we really are very excited to be a part of here at Columbia.

Kate Carr: 33:31 Yeah, that was a wonderful presentation, Dr. Goldstein, we thank you for your time and thoughtfulness in preparing that and for showing us a path forward as well as an explanation of what we have happening now.

Kate Carr:	33:46	So now we'll begin the Q&A session. Again, if you have any questions, please submit them in the questions tab of the go to webinar control panel and click send. We've already seen a number of you, providing some questions and Brandon, I'll turn it over to you to begin this part of our discussion.
Brandon Laughlin:	34:10	Okay. The first question actually corresponds to the last slide that you presented, Dr. Goldstein. And that is where can patients get information on clinical trials?
Dr. David Goldstein:	34:25	You can go to a government website which lists the clinical trials that are ongoing clinicaltrial.gov or something like that.
Kate Carr:	34:34	Clinicaltrials.gov.
Dr. David Goldstein:	34:34	Yes. And that is a comprehensive listing of ongoing clinical trials, meaning that when the compounds get in demand, they'll be there. Trials that are being planned, but aren't at the stage of being tested in people. It's much harder to get a sense of what's coming. And that's actually one of the things that I think would be good to try to organize information around too to really try to figure out what's coming down the pipe. But for things that are being tested one you go to that government website.
Brandon Laughlin:	35:12	Great. Thank you. The next question, actually it's a good question. It's talking about we talked a lot about the benefits of whole exome sequencing, but are there any consequences of whole exome sequencing or any adverse situations that one would be aware of?
Dr. David Goldstein:	35:28	I think it is fair to say that, that there can be concerns in performing whole exome sequencing. One example is that it is possible that you would find out something depending on what's done with the whole exome sequence data that would cause anxiety without providing a compensatory benefit.
Dr. David Goldstein:	35:53	In most cases where this kind of sequencing is performed to explain an indication, for example, to explain a patient's seizures. In most such cases the patient and care provider in fact will only find out about genetic variants in the individual's genome that either are responsible for the indication or that are on a particular list of genes that have been highlighted by the American College of Medical Genetics as being important to communicate results back for.
Dr. David Goldstein:	36:34	And these so-called incidental findings are communicated back because they represent genes that cause presentations that are

not only serious but whether it's something that the individual can do about it. So, for example, on that list are genes that cause cancers where there are certain screening regimes that are recommended.

Dr. David Goldstein: 36:59 Genes on that list include genes that cause heart arrhythmias where there are certain interventions that are possible, and where certain kinds of evaluations, lifestyle changes are important. So usually those are the only things that individuals will hear about.

Dr. David Goldstein: 37:17 But in some settings they might hear about other things for whatever reason once the data have been generated. And there are examples of things that one might find in one's genome that could cause anxiety without clearly providing benefit. A very famous example of that is whether individuals carry a relatively common and very strongly acting risk factor for Alzheimer's disease where there really isn't anything that you can do about it.

Dr. David Goldstein: 37:46 But in most settings it's possible to choose what you would hear about and not hear about. And so there you can make a personal choice about whether you want to know about these other things that are not related, for example, to the reason for the sequencing.

Brandon Laughlin: 38:03 Great. Thank you. A lot of questions came in about the benefits of testing the entire family. Can you explain why you'd want to have a patient and possibly their parents sequenced?

Dr. David Goldstein: 38:16 There are really two ways in which we use family members. One is really just to better diagnose the affected individual. And there it really does boil down to finding out what's in the child, for example, that's not in the parents. And that could be, as I already highlighted a so-called de nova mutation.

Dr. David Goldstein: 38:44 So a variant that's not in the parents at all, or it could be a genotype where the child has two mutation, one from mom and one from dad and mom and mom and dad have only one. And so this is so-called recessive gene. And we can actually then use the fact that it's not present in two copies in either of the parents to help reassure us that it's actually responsible for disease.

Dr. David Goldstein: 39:17 In other cases, we might test other family members to help us, for example rule out a possible cause in an affected individual. If for example, there was an affected person with an unaffected

siblings, we might test a candidate variant in the unaffected siblings. And if it's present too, we might say that we're disinclined to believe that that variant is causing disease.

Dr. David Goldstein: 39:47 And of course, when there are multiple affected members of a family, then we're looking for genotypes that are in common across the multiple members. The only final thing I'll say about this is that there are in genetics always wrinkles in stories and often you need to do careful testing to see whether there are any wrinkles. I'll just highlight one that's important.

Dr. David Goldstein: 40:10 The so-called de novo mutations. Those actually often start in the gene cells of the parents. So in either cells leading to eggs or sperm, and sometimes the mutations that are in those cells of the parents are in other cells too, but just not all cells of the parents.

Dr. David Goldstein: 40:36 And in those situations, we actually can sometimes in fact look for maybe even modest effects in the parents or the possibility, even though it's say an apparently brand new mutation of transmission to other children. And so there's a whole bunch of different contexts in which we would look more broadly through families.

Brandon Laughlin: 41:00 Great. Thank you. The next question, actually there's two questions that have come in that are somewhat related. If a family has had a single gene testing done or even a panel of genes for epilepsy, when should they or should they go on and have whole exome sequencing? And then also in that same vein with new genes being discovered, how often should a patient actually undergo testing?

Dr. David Goldstein: 41:31 So, in terms of the first part, if the test was either a gene or indeed even a large epilepsy panel and was negative, it really is clear that, that individual should have whole exome testing because none of the panels are absolutely complete for genes that cause epilepsy.

Dr. David Goldstein: 41:56 If however, a single gene test or a panel test identified a clear cut cause that when vetted by people that know their way around the genome well, and the identification of pathogenic variants really does look like the cause, then in fact it's not really necessary to perform whole exome sequencing.

Dr. David Goldstein: 42:20 If you for example, had a suspicion of Dravet and you had the SCN1A gene sequence, then there was a protein truncating

variant found there really wouldn't be any reason to sequence the rest of the genome in that context.

Dr. David Goldstein: 42:34 As far as how often you want to reanalyze, given new genes are being discovered all the time. Even though it is tapering off as I said, in comparison to where we're at a couple of years ago, it still is the case that new genes are being discovered all the time.

Dr. David Goldstein: 42:49 And in fact we're learning more about how to recognize mutations in the already known genes. So therefore, it really is better to reanalyze as often as you can. There's of course, of course a cost associated with the analysis and interpretation, and so, it's a question of how often is manageable.

Dr. David Goldstein: 43:12 We came to the view that every six months was a reasonable compromise and trying to make sure that we didn't wait too long. If there was a new gene discovered that would make a difference in an individual patient's genome. But having the re-analysis be generally manageable. And I think that, that's probably reasonable overall something like every six months or a year for re-analysis.

Brandon Laughlin: 43:37 In that same light, maybe talk a little bit about the cost of whole exome sequencing, where can people get information on the cost? How do patients generally pay for their whole exome sequencing?

Dr. David Goldstein: 43:56 Yeah. So let me just clarify to a distinction between the actual generation of the data and the re-analysis. So in general, you actually don't need to redo the generation of the data or get a new test unless you've only had a panel, or a single gene tested.

Dr. David Goldstein: 44:21 With the exception that if the sequence data regenerated a long time ago, there'll be lower quality. And in this context, a long time ago probably means around three plus years ago, maybe a little bit more than that. All the exome data generate after that is pretty high quality. So, it'd be a matter of re-analysis as opposed to retesting or regenerating the data.

Dr. David Goldstein: 44:44 As far as the costs go, it's really difficult to say much about what the costs really are because it's impossible to get one's head around how costing actually works in the clinical space because the advertised costs have nothing to do with the real costs or even what providers are actually paid. And I really don't understand the reimbursement landscape well at all.

Dr. David Goldstein: 45:10 But what I can say is that the cost to actually generate the sequence data in the first place forgetting clinical economy environment this testing happens in, the cost to generate the data in the first place is actually pretty modest now. So, here at Columbia, the costs for us to generate a whole exome sequence data is 300 and something dollars per individual, and so the actual cost of the data generation.

Dr. David Goldstein: 45:36 And then once you have a reasonable scale of ration, the marginal costs of the analysis per individual are not that high either, but of course in the clinical environments, a whole bunch of other costs that get included including the final interpretation by a board certified individual and whether a mutation actually causes a disease or not.

Brandon Laughlin: 46:01 Great. And dealing in that same vein a few questions that have come in. With the re-analysis being obviously taking care of a group through the EGI initiative, how do patients enroll in EGI?

Dr. David Goldstein: 46:17 So patients can enroll in EGI with the support of their care providers and the genetic counselors here at Columbia. And as far as the starting point for those that are at academic medical centers that are already partners in EGI, it's a straightforward process to be enrolled. And there's a listing at CURE's website of those partners for those that are not already at an academic medical centers starting point to approach CURE.

Dr. David Goldstein: 46:56 So, for those that are not at one of the already participating academic medical centers the starting point would be to reach out to CURE for a discussion about how best to enroll, and Brandon I think will indicate how that can happen.

Brandon Laughlin: 47:14 Yeah, absolutely. If you contact CURE, you'll be in touch with me. It's 1-844-EGI-CURE or you can just email directly at egicureepilepsy.org. So that it does get you in touch with the Columbia team and we can get you enrolled remotely, and actually from any part of the world.

Brandon Laughlin: 47:39 A couple more detailed questions involving whole exome sequencing in general. Are there specific types of seizures identified with the information gained by genetic testing to date? And if so, is that an indication of who should be sequenced and who shouldn't be?

Dr. David Goldstein: 48:00 Yeah, that's a great question. And in general, the answer is that it is the more severe and earlier onset epilepsies not specific seizure types, but really severity and age of onset where the

genetic diagnostic yield is the highest. It's not a zero in any of the so-called non acquired epilepsy.

Dr. David Goldstein: 48:26 So when we sequence patients with more common forms of epilepsy such as genetic, generalized epilepsy, non-acquired focal epilepsy, we actually do still see apparently a contributing variants in a number of known epilepsy genes. And this is very strong statistical evidence that they do in fact contribute and if they're not a sole causes.

Dr. David Goldstein: 48:50 But if you consider those diagnoses, the diagnostic yield for those epilepsies is a much smaller proportion than the earlier onset, more severe epilepsy. So that's where genetic testing is most strongly indicated.

Brandon Laughlin: 49:05 Great. Next question. Dealing there are a lot of genetic testing labs and diagnostic testing that are out there, are the known epilepsy genes, is that list, are they made available to those labs and are they aware of those new and current epilepsy genes?

Dr. David Goldstein: 49:24 I think that the labs actually do now a fairly good job of keeping up with the literature, a fairly good job when they interpret a patient's exome. So I think in general, if there's a mutation in a gene that is known in the scientific literature, most labs are going to catch that mutation and report on it.

Dr. David Goldstein: 49:49 And as far as the lists go, the labs really do go to the scientific literature themselves and identify all of the genes that have been associated with epilepsy from the scientific literature. And now the scientific literature is relatively easy to interpret. There are some genes where when you actually look closely, you see that the strike revenues for them isn't so strong in the literature but in most cases it's relatively easy to interpret the literature.

Brandon Laughlin: 50:16 Great. Thank you. We'll pick a couple more questions here. And this is a good one based off of your last couple of slides. Will there be a future in gene therapy with the database that you've collected?

Dr. David Goldstein: 50:32 Well we were just discussing that exact question before the webinar started. In fact, and here at Columbia and I imagine other places, there are a wide range of views on that. My own personal view is that gene therapy in all of its various forms is something that we absolutely need to explore for serious neurological conditions including epilepsy.

Dr. David Goldstein:	51:01	But I personally feel that in general, that's going to be a pretty difficult path and that there's not going to be a lot of effective gene therapies for epilepsies in the relatively near future. And I'm more optimistic of traditional pharmacological approaches that are targeted to the genetic cause.
Dr. David Goldstein:	51:24	In the near term, and then gene therapy, just because it's really hard. Whatever kind of gene therapy you're talking about, to get the therapeutic agents to the right cells in the brain, it's just a challenging thing to do.
Brandon Laughlin:	51:40	Right. And along those same lines, one of the questions was asked about pharmaceutical companies and does EGI currently work with any pharmaceutical companies?
Dr. David Goldstein:	51:51	EGI currently doesn't work directly with any of the pharmaceutical companies and above my pay grade to indicate whether or not we will. That sounds like Kate may want to say something about that, but what I can say is that there have been a number of conversations that a number of people have had with companies and I do think that there are a number of companies that are increasingly interested in seeing the development of an environment that will facilitate the kind of genetically targeted trials that I was describing earlier.
Brandon Laughlin:	52:24	I think this is a good last question is ended on. As far as future research with EGI and the data, is the database and how is it made available to the public?
Dr. David Goldstein:	52:36	The sequence data is available currently through (inaudible) I believe already. And so what that means is that you can apply to access the sequence data through (inaudible). And in addition the actual variants that we identified through our analyses are available on the webpage that I showed earlier.
Dr. David Goldstein:	53:05	And the final thing I'd say is that EGI really is established on behalf of the broader community. And therefore, anyone who actually has suggestions of ideas of ways that the data in EGI should be analyzed, we are very receptive to discuss it.
Brandon Laughlin:	53:22	Okay. Great. Thank you. I will go ahead and turn it back over to Kate.
Kate Carr:	53:27	Thank you. Thank you, Dr. Goldstein. And Brandon, thank you for moderating our questions. What a wonderful webinar. I hope that our attendees found it as informative as what they were looking for. We have more questions than we could

		possibly answer, and so I'll remind you that you can contact Brandon at EGI at cureepilepsy.org, if you want to follow up on any aspect of this regarding enrollment or your questions.
Kate Carr:	54:02	This has been a wonderful presentation. And again, our thanks to SUNOVION for sponsoring our webinar. I'd like to thank our audience for their very robust engagement. And if you have questions, as I said, you can find more information on our website cureepilepsy.org.
Kate Carr:	54:23	Thanks again for joining us. We actually have another webinar that will take place this Thursday, March 8th at 2:00 PM Eastern. Webinar will feature Dr. Madison Berle from Children's National Hospital in Washington, D.C., and we'll discuss epilepsy's impact on learning and school performance. Thanks everyone. Hope you have a great day.