Dr. Zack Grinspan: Hello everyone, and welcome to this webinar, this Lunch and Learn session. I have my script. Welcome to the first day of Unite to CURE Epilepsy. My name is Dr. Zack Grinspan, and I'm proud to present our first Unite program. My talk will be entitled: A Learning Healthcare System for Pediatric Epilepsy, Focus on Early Life Epilepsies.

And a note, you can submit your questions anytime during today's presentation by typing them into the chat feature on your WebEx and clicking send. I'm going to make sure to make time at the end of the session to go through as many of the questions as possible. All right.

And thank you also for your patience with Zoom. Even though we've been doing this for years now, it's never quite the same as being in person. So even though we're in a virtual space, I hope that I can communicate some informality. And please feel free to ask any kinds of questions. I am quite an informal person and really enjoy the chance to interact.

So as I said, I'm Zack Grinspan. I'm Interim Chief of Child Neurology, Director of Pediatric Epilepsy here at Weill Cornell Medicine in New York City.

These are my disclosures.

And here's an outline. I probably have too large of an agenda, but when I spoke with the organizers, they suggested that folks that attend these conferences are a knowledgeable group, and so, I'm going to dive into a couple of different areas with the time we have together. I want to focus on early life epilepsy, and so I'll talk about what that is, how common it is, and lay out a research agenda. We've learned a lot about how to take care of children who have epilepsy that begins early in life, and so I'll talk through some of the examples of those discoveries. I want to share with you a pilot study we've been doing for two rare epilepsies, STXBP1 and SLC6A1 using a drug called phenylbutyrate, and then I'll share a little bit about the Pediatric Epilepsy Learning Healthcare System that I lead, talk about some infrastructure and common EHR form. And then my goal is to leave some time for questions. I can be very chatty, but hopefully we'll have enough time for a Q&A and a back and forth.

I wanted to start with thinking about parents and caregivers of children who are newly diagnosed with an early life epilepsy. My colleague and dear friend, Scott Demarest at Colorado, and his colleagues, put out a publication in which they interviewed parents of the disease. He's one of the world's experts in CDKL5. And I wanted to start with this, to acknowledge that at the moment of diagnosis, it's a really deep low for families, and that these diagnoses can be devastating. This is a parent who talked about how they felt such desperation, "We felt so low." And another parent talked about how when they read and learned about what CDKL5 was, all of their hopes and dreams felt like they were thrown away. It's important to ground ourselves in these stories that really drive the urgency for the research and the work that we do in the clinic, both in clinical care, taking care of families and children, as well as driving that urgency for this discovery.

When I think about early life epilepsy, there's four flavors. There are neonatal seizures. These are most typically symptomatic. A child has an infection, a child has hypoxic injury to their brain, and most of these fade away and don't go on to be epilepsy. There are neonates that do develop epilepsy. This is a baby who has an early life neonatal onset epilepsy, and you can see that the baby is having these clusters of tonic seizures. Infantile spasms is something that we think quite a bit about. This is a child with tuberous sclerosis who's having clusters of infantile spasms. There's one right there, and I think he has another one in a few seconds. Here it comes. There is another one. This is an epilepsy we think a lot about, because early treatment is critical, and can dramatically alter the course of these children's lives. Then there are many other epilepsies that begin in early life. This is an example, Dravet Syndrome, that can begin in the first or second year of life. And this child is having the characteristic hemiclonic seizures where half of the body is shaking.

There's this beautiful, beautiful study out of Scotland, where they were able to do a prospective cohort study of the entire population, all five and a half million people. And they looked to find any children who had recurrent seizures before the third birthday, and they gathered data over about three years. What's lovely about this study is that it gives us really strong population-based epidemiology about early life epilepsy. What we find, for example, is in this group, most of the children, or rather, a plurality of the children, are having their first seizure as an epilepsy diagnosis in the first six months of life, and it trails off into the second and third year.

It also gives us an appreciation of how common epilepsy in early life is, it's one in 400 live births. And this compares to things like Down syndrome, which is one in 700, and cerebral palsy, one in 500, that the general public, I think, knows more about.

We've learned through their study a bit about the population characteristics. In this early life epilepsy, about a third have a known genetic cause. One in five have some other known cause. But almost half the etiology of the epilepsy is still unknown. It's a charge to us, as the physician scientist community, to figure out what's going on with these kids.

The presenting seizure type is typically focal, although maybe one in eight has epileptic spasms, and then there are other seizure types for another third. The epilepsy type, about a third, have DEE, Developmental and Epileptic Encephalopathy. This is a somewhat new term from the past five to 10 years that describes children where two things are true. They have developmental delays, and they have seizures and epilepsy. And the thought is, for that population, that the seizures and often very abnormal EEG is contributing to the developmental delay. The implications are, if we can fix the epilepsy, we can improve the development, and we certainly see that with infantile spasms. Again, the epilepsy type for about half is sort of unclassified. Then about half of these children that have early onset epilepsy also have global developmental delay, and about a third of them, medications are insufficient to control the seizures.

In thinking about the early life epilepsies, and in conversation with my colleagues over the past several years, I've put together a research agenda for clinician scientists, to outline what are the major questions that we should be thinking about over the next decade. We can imagine the timeline, where a child is born, they're a neonate for 28 days, then they become an infant. Neonatal seizures in epilepsy are in that neonatal period. Then in infancy, you've got spasms, which behaves differently than other epilepsies and the other early life epilepsies. Then two things happen. You try to take care of them and maybe the seizures continue, or maybe they stop, based on the treatments they get. If the seizures stops, sometimes they come back and sometimes not.

So we can frame a bunch of questions on this timeline. For everybody we wonder, what is the value of genetic testing? What are the best medicines to use? When do you know that the child has epilepsy? Are there early biomarkers that can warn you about that? And then, once you start treatment, how long should you treat them?

There's also a set of investigations called clinical trial readiness, where we're asking questions, not necessarily for discovery and for understanding more about the diseases, but rather to set the foundation for clinical trials. There's all these genetic therapies and repurpose therapies just on the horizon, and if we're going to prove that they work, you need to have enough data about how things look in the absence of treatment, so that you can make a study. We want to then do those trials.

And then, many of these diseases are genetic, and so I think the community is increasingly starting to think about newborn screening. That should we have a panel of epilepsies included in the newborn screening so that we know what's coming, we can be prepared and give the earliest possible treatment?

There's also questions about refractoriness. How do you know whether someone's going to respond or not? And then, questions about whether we can prevent relapse. Underlying all of these questions are all of the disparities that we know are there. We know that the care you receive, and the outcomes that you get from that care, depends on your race, your ethnicity, what insurance status you have, and where you live. And then, doing this work requires teamwork across multiple centers, state to state, and sometimes internationally, and there are a variety of infrastructures that have been built over the past decade to help do that work.

I'm going to focus on three areas. I'll bullet through some of these questions. I'll talk about a repurposed drug trial that I'm leading, and then I'll talk a bit about my piece, contribution rather, to the infrastructure via the Pediatric Epilepsy Learning Healthcare System.

Okay. So let's go through these questions. I want to bullet through them just because there's a lot, and I just want to give you guys a heads-up on what some of the latest and greatest is from the consortium work that we've done.

So for what is the value of genetic testing? It is highly valuable. This is a review from 2019, that shows that as your test gets more sophisticated, this is microarray epilepsy panel, whole exome sequencing. The yield increases whole exome in this macro, in this analysis of multiple studies, shows that it gets an answer about 45% of the time, and some of the studies are showing even higher hit rate, 70%, 72, 78.

In neonate, the yield of genetic testing is particularly high. This is from the Neonatal Seizure Registry. They found that among babies that were tested, 83% had a hit. Meaning, 83% had a value, had an answer for the neonatal epilepsy. This was back in 2017 published, and so these rates are undoubtedly even higher today.

What's the best first-line medicine? So for neonatal seizures, we have an answer. They tested in a randomized control trial, levetiracetam versus phenobarbital. Phenobarbital won. We've had it for 100 years or more, but it still works. And the effect size was enormous, 80% versus 28% efficacy. For second-line, we don't know. Some people use phenytoin, some people use levetiracetam. I'm hoping to be able to tell you the answer in four or five years. We just got a grant to answer this question.

What about for infantile spasms? Well, the first-line therapy, there is no question, it's one of these three. ACTH, prednisolone, vigabatrin. This has been proved again and again, to the point where it's no longer in question, and it's now a quality measure, i. E., if you're not giving one of these three medications for infantile spasms, it means that you haven't delivered recommended care.

Second-line, we're less certain. There was a nice study by the neonatal, sorry, by the National Infantile Spasms Consortium, that suggested that if you started with a steroid or ACTH, you should switch to vigabatrin. And if you started the vigabatrin, you should switch to ACTH or a steroid. But this is not randomized controlled trial data. We've recently reconfirmed this, and we've got a manuscript written. We need to set it out for review.

What about other early life epilepsies, seizures that start after a month? We published an observational study that compared levetiracetam and phenobarbital. And then interestingly, whereas phenobarbital won for the neonates, levetiracetam won in the infants. With a pretty decent effect size, levetiracetam was 40% effective versus phenobarbital 16%. And when we did all of the statistical work, given that it was observational in study design, we found that it held up, and that the odds ratio was four.

What about that second-line therapy? We do not know. We've done some observational work to show that what you choose for your second-line therapy depends on how old is the child? And also depends on what center you're getting care at. What's nice about these variations is that, they mean that observational studies, like we did with phenobarbital and levetiracetam, may work well to uncover what's the most efficacious. So this is still sort of a thought balloon for future work.

Early biomarkers. This is an incredibly exciting study, and we're waiting to hear the replication from an American group, but this is the European EPISTOP trial. They enrolled children with tuberous sclerosis, which we know puts you at risk for seizures and epilepsy and infantile spasms. They did serial EEGs. And if your EEG showed spikes, they treated you with vigabatrin. And what they found was that this presymptomatic treatment, i. e., treating a child, without epilepsy but an abnormal EEG, with vigabatrin decreased the risk of subsequent future development of epilepsy, and this also held up for infantile spasms. It was a multi-centered multi-country study, and so there were some quirks in their study design. They had a randomized group, an observational group, but the findings held up regardless of how they analyzed it.

We're interested also in neonatal seizures, and which of those very young ones will develop epilepsy. We have a clinical risk score based on the EEG, MRI, and examination of tone, that we think can predict epilepsy reasonably well. If we have all three abnormalities, then your risk of developing infantile spasms in this case was more than half. The grant, that I mentioned before, will also fund us to reconfirm whether this prediction rule holds.

Another question, how long to treat? Again, the Neonatal Seizure Registry looked at infants with acute symptomatic seizures, who had been treated with either phenobarbital or levetiracetam, and then compared what happened if the physicians decided to continue the medicines for the first few months of life, or stop the medicines entirely before discharge, and they found that it didn't matter. The developmental outcomes were the same at 12, 18, and 24 months, and the likelihood of developing seizures and epilepsy also was not different. Interestingly, in this graph, higher is better, and the discontinued group actually did a little bit better, further supporting the idea that, once you're done treating the acute symptomatic seizures, that you can stop the medicine safely, and send those vulnerable newborns out without these medicines.

This is another really exciting result. One question has been, when do you know that a child is refractory? And one of the most important reasons is, that if the child is a surgical candidate, i. e, if they've got a focal cortical dysplasia, that maybe you could send to the neurosurgeons to take out, and thus potentially cure the epilepsy. We've always wondered, how long do you have to wait? Many seasoned physicians have this kind of sense, after you've used two or three drugs, you're sort of done and you have to move them to surgery. Nate Cohen at Children's National did this brilliant study, where he tried to understand, after how many drugs do you know that the child is refractory? Our current thinking is two, but he found that it's really after one. If you have a focal cortical dysplasia and you've already failed one drug, the likelihood that you'll attain seizure freedom without surgery is 7%. That is a really strong argument to start thinking about surgery earlier for children with focal cortical dysplasia.

And then, we've also been thinking about preventing relapse. This is particularly relevant for infantile spasms, whereas many as 40% may relapse before they're two years old. And honestly, we haven't figured this out. There's some work where they looked at zonisimide and topiramate, it did not help, neither. This is observational data. And then the same group, this is Shaun Hussain's group at UCLA, they looked at tuberous sclerosis, and they did find that if you used a higher vigabatrin dose that the likelihood of relapse was a little bit less. So there's some signal there, but we're still really working this out.

Okay. So that's my kind of rapid bullet through recent findings. Let me now change direction and talk about repurposed drugs.

And I want to, in particular, talk about a study of phenylbutyrate, that we've led here out of Cornell, in collaboration with Children's Hospital Colorado, for STXBP1 and SLC6A1.

I should expand a bit on disclosures. So for the study, I think it's my next slide. Yeah. For the study and the data I'm about to show you, Pharma, Horizon Therapeutics, provided the medication, but it was parent led advocacy groups that funded the study itself. And I don't have any IP in this game.

So this was Cornell and Children's Hospital Colorado. We worked together. We were funded by a variety of parent-led advocacy groups. Lulu's Crew, SLC6A1 Connect, the Orphan Disease Center, helped STXBP1 raise money, which they gave to us in the mini grant at another organization, Clara Inspired, and then Horizon provided the medication.

Briefly, STXBP1 is a rare disease, a rare cause of developmental epileptic encephalopathy. It's about one in 30,000. Most have epilepsy, most have intellectual disability, one in five have autism. Low tone and movement disorders are common. The gene itself, STXBP1, is this little blue peanut here, that is involved in the synaptic vesicle tracking and docking mechanism. So here's your vesicle, it's loaded with neurotransmitter, and STXBP1 helps get this situated. People also call it Munc18-1.

The other disorder that we looked at is SLC6A1. This is roughly as common, one in 35,000. They also have developmental delay, low tone, intellectual disability, seizures, movement disorder, and autism, as well as attention deficit. This gene is associated with a protein called GAT-1. GAT-1 is this little coffee bean in this diagram. It's a GABA re-uptake transporter, that helps bring sort of expended GABA back into the cell so they can use it again.

My colleague, Jackie Burre, and her graduate student, Noah Guiberson, and their team here at Cornell, published a report, suggesting that they could rescue these mutations in vivo and in vitro models, using something called chemical chaperones. And then Munc18-1, as you'll remember, is STXBP1. Katty Kang and her group at Vanderbilt in Nashville had a similar idea for SLC6A1.

The molecule that both groups found worked was phenylbutyrate. Phenylbutyrate is a drug that's FDA approved for urea cycle disorders. What happens, for those of you interested in biochemistry, is that phenylbutyrate gets turned to phenyl acetate, and that provides you an alternate pathway to clear ammonia. The ammonia is getting mixed up. It sort of gets attached to glutamate glutamine and then it goes out in the urine. People have tried this with other disorders. They tried it in cystic fibrosis, with a little bit of benefit. They tried it in spinal muscular atrophy, without benefit. And then recently, they tried it in ALS, Lou Gehrig's disease, and found that in combination with taurursodiol, which is a bile acid, that it slowed progression of that disease.

I'm going to show you that it worked, and I'm also going to revealed that I have no idea why. There were a bunch of ideas that led to us trying it, but every time I talk to a basic scientist, they give me a somewhat different answer about why it might work. These are a list of the reasons that they have given me, and I don't know which one is right.

It might improve protein trafficking, i. e., getting the well folded proteins to where they're supposed to go. Some models in STXBP1 misfolded proteins aggregate, and this phenylbutyrate seems to help clear those aggregates. It may directly improve the function or stability of the protein, either the mutant proteins, that's the chaperone idea, or the wild types. There's this idea of endoplasmic reticulum stress, that when you have a lot of unfolded or misfolded proteins around, that this leads to this stressed response, which can be toxic, and that phenylbutyrate may ameliorate those effects.

And finally, there's this HDAC inhibitor idea, i. e., that phenylbutyrate somehow helps the large mass of chromatin fold or unfold in a way that's favorable for expression of the necessary proteins, genes and proteins for cellular function.

Phenylbutyrate, as we said, is FDA approved. It crossed the blood-brain barrier. It comes in two flavors. There's sodium phenylbutyrate. That was the initial approved version, and it is super gross. It's salty, it's bitter. Neurotypical children will take it. They put it in water, they mix it up, they hold their nose. But children with developmental delays, I've gotten this into zero children. It's gross. They spit it out, and you just can't get it in. The major exception is if a child has a G-tube. I have had some patients where I've been able to get sodium phenylbutyrate into the G-tube.

The drug we use is glycerol phenylbutyrate. These look different, but they're not. Glycerol phenylbutyrate is a glycerol backbone, and they took sodium phenylbutyrate molecules, three of them, and they kind of just shove them on there. And so what you're seeing is, there's this glycerol backbone with three phenylbutyrates stuck to it. These really are the same thing. It's just, the glycerol is a different delivery mechanism for the same drug. Oh, and it doesn't taste bad. It's a liquid. The kids don't mind taking it. It's just expensive. The challenge with glycerol phenylbutyrate is that it's still on patent, and it costs on the order of sort of high hundreds of thousands to a million dollars a year, is what they charge the insurance company. So with off-label stuff, sometimes you can just write for it and see how it goes, but this drug is too expensive for that kind of approach.

We ran a trial. I'll spare you the details of our inclusion and exclusion criteria. But I will show you that what's nice about the glycerol phenylbutyrate is that it's safe and well tolerated. This is a list of the side effects. We have seen decreased appetite, a sweet body odor, a metabolic acidosis, and one child requiring that child to withdraw and some sleepiness, but not worse than that. The child that withdrew actually re-enrolled, because the seizures came back, and we've been managing the acidosis with Bicitra or baking soda.

Let me share with you some early results from our study. What we did is we enrolled kids. We did a baseline for four weeks. We brought them in for EEG. We gave them the drug for six weeks at home. We admitted them again for a second overnight EEG. We had planned to taper them off, and we did that for one child, but most children have actually stayed on for an extended use period.

Here are two examples of what we found. This is an 11-year old with STXBP1. He was having seizures in clusters. He'd have a couple nights where he'd have one, sometimes two, he'd be seizure free a bit, and then they'd come back. He came up to New York for the study, and it kind of put him into a tailspin. He had a bunch of seizures, I think because of losing sleep in the new environment. But then on the drug, he essentially went weeks with only a single breakthrough.

The effects in SLC6A1 were even more dramatic. This is a child who had, mom was saying about a dozen seizures per day, brief absence seizures. His eyes rolled back. He'd lose attention, last two or three seconds. Once we started him on the drug, he had a big reduction, and then eventually became seizure free. And that seizure freedom has continued, I think for like a year and a half.

These are our 10-week outcomes, which I've displayed in abstract form. We're still trying to get this published. And you can see that, there were 11 of the 20 that we treated that had a good story for 50% or more seizure reduction. There were three, where maybe they responded, we're not really sure, or we couldn't totally attribute it to the drug. And so, that's three. There were two who clearly did not respond. They were both children with STXBP1 and epileptic spasms. And then in the SLC6A1 group, there were four children enrolled who ended up not having seizures at all.

We are very encouraged by these results, but I should be cautious in how I communicate these to all of you. This is open label, a single pilot study. It's me at Cornell and Scott Demarest and his team at Colorado. We don't know if this is replicable. We don't know if we did something special. We don't know if we're biased in some way. And so, we are keen to replicate this, to see if this promising but preliminary and early result holds out. So I want to be cautious in expressing both enthusiasm, and a great deal of caution in interpreting what this means.

One of the things that did come out of this trial was the power of biomarkers. And I just wanted to share this with you. This five-year-old, the one that I showed you before, who's now seizure free, this is a snapshot of the EEG that we saw when he first came in. For any of you who are EEGers, you will see that there's this high amplitude delta that lasts for a few seconds. There's some embedded spikes. It sometimes has more of a spike wave morphology, and it lasts two or three seconds. These were symptomatic. He would pause, he would stare off. His eyes would flutter a little bit. So we called these seizures.

This is a compressed spectral array. Each one of these vertical lines, these little spikes, represents one of these brief seizures, these brief sort of three second seizures. You can see he has quite a lot of them, and this is one hour of data. And so, this mother had been telling us that he was having maybe a dozen a day. He was, in fact, having dozens every hour. Six weeks later when he came back, his EEG had essentially normalized. This is a snapshot of normal EEG. And here's an example of his compressed spectral array, and you will see none of those spikes.

What's particularly nice about this biomarker is that it gives us something to measure. And so, if we can quantify this, it'll be much easier to design a trial with fewer participants, because we can show the effects with this kind of quantitative rigor.

Limitations. Just reemphasizing what I said. Open label. In SLC6A1, they're absence seizures. They're very hard to count. And in the STXBP1 population, most of the seizures in that group are tonic seizures, they happen at night. And I am consistently worried that we haven't counted them all, even though we're finding good effects. Are people not seeing them at night?

Okay. We've got 23 minutes. And so, let me segue to the third topic, which is the Pediatric Epilepsy Learning Healthcare System. Again, we talked about a bunch of recent questions. I told you about a repurposed drug trial we're doing, and this last piece is really about infrastructure innovation. How can we work together nationally and internationally to collect data through routine care, so that we can learn together about how to best take care of these children?

I'm the PI for the Pediatric Epilepsy Learning Healthcare System. There are two of these efforts that are parallel and aligned and working together. PELHS, Pediatric Epilepsy Learning Healthcare System is the one that I lead. And then the other organization is the Epilepsy Learning Healthcare System, led from the Epilepsy Foundation.

PELHS, the Learning Healthcare System, is born from PERC, the Pediatric Epilepsy Research Consortium. This is a group of more than 50 sites now, that have been working together for more than a decade, to do largely observational work to understand how best to take care of children with epilepsy. And we've had some nice big wins. Papers in JAMA Pediatrics, papers in the Annals of Neurology, for example.

The idea of a learning healthcare system is relatively straightforward. The idea is, you take care of patients, you collect data to see how you're doing, you learn something about what works and what doesn't work, and then you do it again, and again, and again. And the concept is to have these virtuous cycles of continuous improvement, so that every cycle that you do of this practice data knowledge leads to more and better outcomes.

The group that has inspired us is called ImproveCareNow. These are pediatric gastroenterologists focused on diseases like Crohn's disease and ulcerative colitis in children. They improved outcomes for their disease from about 50% of their population in remission in 2007, to nearly 80% just five years later in 2012. So we saw their data like this, and we thought, man, we need to do this for epilepsy also.

So we built PELHS. We have a mission and a vision. The mission is to reduce seizures and their consequences for children with epilepsy, through cycles of health data collection analysis, and dissemination of new evidence and practice change. And our vision is, that all children with epilepsy receive timely and optimal care, according to standards that are continuously improved.

This is our group. I lead the group. And honestly, it has been such a privilege and honor to work with some of these amazing and brilliant physicians and scientists, Anup Patel, Anne Berg, Renee Shellhaas, and Jeff Buchalter.

The concept at a high level is that we gather data, we centralize it, and then we use it to conduct a variety of investigations. What makes this a learning healthcare system is that the data is fed back to the investigators as fast as we can do it. And we can put up these big numbers for the amount of data that we've collected. Our database now has data from 20 centers.

Let me skip this, because I want to make sure we have time to talk.

I wanted to highlight one of our early wins. One of the major things that makes a learning healthcare system work is that, you have to collect data through routine care. I. e., if a kid comes to see you with their parents or their caregivers for epilepsy, and you just do your routine stuff, you'd get some labs, you get some imaging and EEG, that we capture that data in some kind of formal structured way, so that we can learn from every single encounter. The major challenge with that is that, we all write our notes in different ways. And so, one of our early initiatives was to figure out a way to collect data through routine care, all of us in the same way.

We thought we could do it in a year, 18 months, it took us four years. And we looked at notes, existing databases, research databases. We had discussion groups, we looked at papers. We then piloted a set of questions, and iterated them for months and months, and then sent it to the EHR vendors to build.

These are our questions. It's too small to read, but what I wanted to show was two things. One is that, we recognized that although epilepsy purists and the International League Against Epilepsy, those groups think about epilepsy as having 20 or more different seizure types. We didn't think we were going to be able to capture that with good fidelity. And so what we did is, we grouped seizures at a higher level and said, we're interested in generalized tonic-clonic seizures, particularly because they put you at risk for sudden death for SUDEP. Motor seizures, because you can see them. Non-motor, because you can't. And then epileptic spasms. As pediatric epileptologists, we were very interested in tracking those separately. And then what we did is, we took all of the ILAE seizure terms and mapped them to four.

This is a video of us using the form that we created. This is in my electronic health record system here at Cornell, but this is replicated, I think there's 10 centers using this now. The main idea is that the physician can click through important aspects of the history. All of these questions are based on hours and hours of discussion. They can jot some notes down, and then they can pull all that information into their note. And so, the win is that the researchers get high quality structured data for their analysis, which we can also use for quality improvement, and for clinical operations. And the bedside clinician, at the point of care, gets sentences to pull into their note, to help with their billing, and to reduce the time that they need to document.

So the Learning Healthcare System, we've got a ton of work that we're hoping to roll out over the next five to eight years. We have studies in comparative effectiveness, quality improvement, surveillance and epidemiology. And then, we have some future work that we're excited about. And our goal is to change practice and to change outcomes.

I'll leave this slide up. This is sort of the overview. And then let me stop there and take some questions with the 15 minutes we have. And I think my instructions are now to stop sharing, and then go to the Q&A. And I see all these questions in the chat. All right.

Thank you all for listening. One of the challenges of virtual is that I don't know if anybody actually is listening, or was interested in what I had to say. But I'm glad to see some questions. So I'm going to take that as a good sign. So I'm going to go through these questions and I'll answer them.

All right. So the first question, are medications that have been developed more recently better in regards to the side effects they caused? My son had many mood and cognitive side effects for some of the older medicines he would prescribe. I think so. I think that the group of medicines we have to prescribe today are far superior to what we had when I started in practice.

This is not GME, or CME rather, so I'm allowed to say things by name. There was an article in Epilepsia by several prominent epileptologists, and it was a little bit of a tirade, where they basically said, "Hey, listen, the new drugs...", and they were pointing to Fintepla and cenobamate, Xcopri, Fintepla is fenfluramine, as examples of these drugs with substantially better efficacy than our old drugs, and lamenting the fact that the physicians weren't really using them as much. So I'm finding, for example, I typically start with Keppra, because it's so easy. But my second and third-line have really evolved over the past few years. Even for Dravet, we're trying to move to Fintepla quickly, if we can get it. I've got a couple of kids on cenobamate, this new one, and have been really happy with the results. I don't take any money from them. So that's an unbiased experience. And in general, certainly the tremor and the needing for routine blood draws feels like a generation ago.

The next question, is there a timeline around LHS? Yes. We are working very hard to accomplish our goals. One of the downsides of academic medicine is that there's always this balance between administration, clinical care, and then actually getting research done. So things never move as fast as I would like, but we got our first R01 grant that was funded this past Spring, so we're very excited about that. And that's going to help us keep the ship afloat, and allow us to answer some questions with the data that we have.

Next question. Any kind of research on people using the amino acid leucine to reduce seizures? I'm not familiar with that particular approach to reducing seizures, so I don't have a good answer to that one. But what is interesting is that, I field questions like this all the time. What about this? What about this? And there's often literature, sometimes dozens of years old, using a variety of things for epilepsy. And I think there's an appetite for revisiting some of those studies, to see if some of these older concepts work.

Has there been improvement in cognitive aspects or side effects of, it says AI-based post epileptic surgery? I think the question is about sort of advances in epilepsy surgery, and whether that's improved cognitive and other kinds of side effects. I think the jury is still a little bit out. And I'll be honest, I don't know the surgical literature as well as I might. The kinds of innovations in epilepsy surgery that are relatively recent, at least in this country, is there's really been widespread adoption of stereo-EEG. Stereo-EEG is the use of implanted electrodes to locate the seizure focus. And that's made the surgeries less morbid. Less side effects, because it's an easier surgery, you're under anesthesia for less time. And it's allowed us to find seizure foci that we might not have been able to find using some of the older methods.

There's also new techniques like laser ablation. LITT, I think, is the tool. And then the devices, the VNS has gone through multiple iterations. We published a paper showing, not funded by industry, we did it ourselves. We published a paper showing that some of their new models seem to be a little bit better than the older models. And then, RNS is super exciting, particularly for difficult to resect seizure foci or multiple seizure foci. And then finally, DBS, I think we really... The anecdotal and case series work around DBS has all been really, really encouraging, particularly for Lennox-Gastaut syndrome. So we have a lot more surgical options.

One of the major challenges with epilepsy surgery is access, and some of the racial ethnic disparities around access, particularly black populations in this country, repeatedly through study, after study, after study, have lower rates of epilepsy surgery. But we don't think their epilepsy is any different. So that is something that is another area of innovation. We've measured it enough, and now we actually have to do something. And I think that's still an open question, really for implementation work. Let's see.

Why do many anti-epileptic medications have a honeymoon period following initial administration? Why do some medications become less effective over time? And are there certain medications that are more or less prone to a honeymoon period? That's a great question, and my answer will be a bit off the cuff. I'm not an expert in the mechanisms of anti-seizure drugs. We sure do see that effect. And I honestly don't know exactly why. You get this sense that there's this relentless underlying process, and you sort of tame it briefly with the medications you choose, but that they don't always work.

One of the strategies that some people use, is that you have a medical therapy regimen that includes both traditional anti-seizure drugs, as well as anti-inflammatory drugs, particularly steroids. And so, for some refractory epilepsy, where there's not a good surgical candidacy, my colleague, Srishti Nangia, I have to give her a shout-out, because she's really brought this to our center with great success. She'll often give IV steroids for a few days. Sometimes she'll give a dose of, a course of home steroids for a few days. We don't have great literature to guide us. It's all kind of case series single center stuff. But I've used this idea in my own practice with good success. And whether we're calming things down with an anti-inflammatory thing, or kind of resetting the responsiveness to the anti-seizure drugs, I don't really know.

And then, are there certain medications that are more or less prone to a honeymoon period? The one medicine that I would highlight is clobazam. Most benzodiazepines seem to lose their efficacy with time, and you're kind of chasing your tail with them, always increasing, increasing, increasing the dose. Whereas with clobazam, you seem to get to a dose that you like and it kind of stays. That's no data. That's just me in my own experience as a clinician saying that.

Here's a question. Can you help me understand what types of epilepsy respond better to VNS, versus RNS, versus DBS? Great question. I'm going to speak based on experience. I know there's literature on this, and I have a slide deck that I go through it, but those details are escaping me at this moment. I will offer devices to any child who is not a surgical candidate, i. e., for resection, and who is continuing to have seizures. I have a sense that VNS tends to work better in the kids that have a generalized quality to their EEG and their epilepsy.

Sometimes focal epilepsies are more resistant to the VNS, that's sort of my gestalt. RNS and DBS. So what's interesting is that, the RNS device actually does both sort of responsive neurostimulation as well as deep brain stimulation. So if we sort of separate those two concepts, RNS as we sort of think about it, like you've got some electrodes that are sitting on the seizure focus kind of listening, waiting for it to fire, and then it zaps. That is really a focal epilepsy thing. And it's useful in cases where someone has a lesion, where you can't take it out because it's too close to what we call eloquent cortex. It's sitting on the motor strip, or it's by language. And the surgeons are like, "Listen, if we take that out, they're going to have a hemiparesis. They're going to have a language problem." So in those cases, you can put the RNS on, and it provides often, has a good efficacy of reducing seizure frequency, which improves over time, without risking the loss of that function.

The deep brain stuff I think about for the generalized epilepsies. And there may be case reports or examples that contradict that, but at least in my conception, that what you're kind of doing, is you're disrupting these reverberations, these electrical epileptic reverberations, between the deeper structures, the thalamus and the cortex. And so, you get those electrodes into those deep brain structures, and that stimulation helps modulate that.

So those are the high level principles that I've kind of thought about. Oh. And that was the last question. And so, I'll speak out this last comment.

Thank you all for joining us today. This presentation was recorded, and will be available shortly on the CURE Epilepsy website. Thank you all for joining me today. And be sure to check out the other presentations that are part of the Unite to CURE Epilepsy. These presentations are coming up over the next few days. Thank you again, and I hope you all enjoy the rest of your day. Be well.