FDA CBER OTP Warrior Families Webinar

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Welcome Remarks

ANNE ROWZEE, PHD: Hello, everyone. Thank you for joining us for our RegenMedEd webinar, Warrior Families: Advancing Regenerative Medicine Through Science. Today's webinar is hosted by the Office of Therapeutic Products (OTP) within the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration. My name is Anne Rowzee, and I am a senior policy advisor in OTP. I will also be your host for today's event.

Some of you may have joined us for previous RegenMedEd events, including our April workshop, Clinical Trials: The Patient Experience, which focused on gene therapy clinical trials. If that's you, welcome back; thanks for being here. If today is your first time attending one of our events, welcome and thank you for joining us today.

The theme of today's webinar is warrior families. Through our patient-centered work, such as workshops and webinars today, patient listening sessions, and patient-focused drug development meetings, through those events where we hear directly from patients and caregivers, we see that sometimes the most effective driving forces in the rare disease space are the passionate families that rally around their loved ones. We at OTP hope to provide patient and parent communities with resources, which help empower them to connect with researchers, industries, and other partners to help advance the state of the science for their rare disease communities and to help advance regenerative medicine as a whole.

Today, we are fortunate to be hearing from three caregivers, specifically three mothers of children with rare diseases. Our panelists will speak about their experiences with advocacy, especially as it relates to research activities that support therapeutic product development.

Before we get started, I'd like to offer a sincere thank-you to everyone who helped make today's event possible. To our panelists, thank you so much for spending time preparing for today's webinar and for being here to share your stories. Next slide, please. Thank you.

We have an exciting agenda planned today. We'll kick off our webinar with a brief welcome from Dr. Nicole Verdun, director of OTP. Then we'll hear from Allyson Berent, who, in addition to her work as a veterinarian, is also chief science officer at the Foundation for Angelman Syndrome Therapeutics, or FAST. Dr. Berent will talk about her experience in advocating for research and drug development as it relates to Angelman's.

We'll then invite two more parents to join our panel discussion and answer questions on their experience in advocating for rare disease drug research and development. This Q&A session will feature some questions that were submitted during registration, and we'll also have some time for live audience

questions. So I'm now going to turn it over to Dr. Verdun for some welcoming remarks. Thanks.

NICOLE VERDUN, MD: Thank you, Anne. Hello, everyone. It's great to be here at today's RegenMedEd webinar. As Dr. Rowzee mentioned, my name is Dr. Nicole Verdun, and I'm very pleased to be leading the Office of Therapeutic Products and all the exciting work happening within OTP. I've had the pleasure of working at FDA for more than a decade, starting my FDA career in the Center for Drug Evaluation and Research and making the switch to CBER in 2016. I most recently served as the director of the Office of Blood Research and Review within CBER before moving into my current role as OTP director.

Just to share a little more information about myself, I am a board-certified pediatric hematologist/oncologist. After graduating from medical school, I did complete a residency in pediatrics and fellowship in pediatric hematology/oncology and moved to work on adeno-associated viral gene therapies at the Children's Hospital of Philadelphia. Since then, I've had the pleasure of practicing medicine at several different places, including most recently Children's National Health System right here in D.C.

In leading OTP, I will be able to apply the experience I've gained throughout my career to support and continue the important cutting-edge work of the office. Given the fast-paced and evolving landscape for gene and cell therapy development, it is vital that OTP keep an open line of communication with its many important stakeholders, especially parents, caregivers, patients, and advocates, to inform the regulation of these biological products and do what we can to advance these products and get them to communities and patients that need them.

I'd also like to note that today's webinar is part of a series of virtual events we call "RegenMedEd." The RegenMedEd event series includes educational webinars and workshops where we invite parents, caregivers, patients, and advocates to learn about topics related to regenerative medicine therapies. Our previous RegenMedEd events can be found on FDA's website, and I also invite you to use the hashtag #RegenMedEd on your social media channels if you'd like to share your thoughts on today's webinar or share an idea for a RegenMedEd topic that you'd like to learn more about in the future.

And now, I'm excited to hear inspiring stories from our panelists today, who will share their experiences as caregivers of individuals with rare diseases. With that, I will pass the mic back to Anne. Thank you again.

DR. ROWZEE: Great. Thank you so much for joining us today, Dr. Verdun. Now, I just want to take a couple minutes to share a few notes about today's event. The webinar is being recorded. The recording and slides will be posted on FDA's website in the next few weeks. Closed captioning for the event is available directly in Zoom. As I mentioned earlier, we're going to have some

time at the end of the webinar for questions, so if you have a question for our panelists, please type it directly in the Q&A box in Zoom, and that can be found at the bottom of your Zoom screen.

Regarding your questions, please note that we are unable to answer questions about specific medical conditions or diagnoses. We encourage you to discuss those questions directly with your health care team. We also understand that folks may have questions about the status of specific investigational products or drug applications. However, there are laws that FDA must follow that limit the information we can provide about investigational products. We very much appreciate questions and comments and will do our best to address as many as we can.

Finally, please use the chat box if you want to share a general comment with our panelists or if you are experiencing technical difficulties. We will monitor that box for any of those difficulties, and someone will assist you.

Now I'm very excited to introduce our first warrior, Dr. Allyson Berent, who will be giving today's presentation. Allyson is a doctor of veterinary medicine and the director of interventional endoscopy at one of the largest specialty animal hospitals in the world. Allyson has spent the last 10 years performing clinical research and designing various clinical trials to develop and evaluate novel therapeutics and medical devices in animals. But today, Allyson will be presenting on her experience and challenges advocating for drug development as both a parent of a child with Angelman syndrome and then also as the chief science officer for FAST. Allyson, please take it away.

Presentation — Advancing Regenerative Medicine for Angelman Syndrome Through Science

ALLYSON BERENT, DVM, DACVIM: Okay. Thank you. Well, thank you, Anne, so much and Dr. Verdun for giving me the opportunity and to the OTP and CBER for really inviting me to talk to you today about my personal journey. It's really an honor and such a pleasure to be able to share that. But it's not a personal journey. It's a journey of an entire community, and I hope that I can really inspire and share some of our experiences to help others that are really leading the same charge. The title of this talk is "Advancing Regenerative Medicine for Angelman Syndrome Through Science" and how parents and patients have to and are taking the lead in doing so.

As Anne said, I'm Allyson Berent. I am the chief science officer for the Foundation for Angelman Syndrome Therapeutics. I also serve as the co-director for the precompetitive consortium, the Angelman Syndrome Biomarker and Outcome Measure Consortium. I'm the co-director of INSYNC, the International Angelman Syndrome Research Council, a group of experts around the world that are working to do a gap analysis on the drug

development landscape of Angelman syndrome to ensure that no stone is ever left unturned for this condition. I'm also the chief development officer for a company called Mahzi Therapeutics, who is developing novel therapies for other rare neurodevelopmental disorders.

I am a veterinarian. I'm an internal medicine specialist, as well as — I lead the interventional endoscopy services at the Animal Medical Center in New York City.

My most important job is, I'm the mother to three beautiful little girls. This is my middle daughter, Quincy. She is 9, and she lives with Angelman syndrome.

In disclosure, I'm the co-founder and former chief operating officer and an equity shareholder of GeneTx Biotherapeutics; that was acquired in 2022 by Ultragenyx Pharmaceuticals, and I still serve as a consultant for Ultragenyx. I consult and advise numerous drug development initiatives specifically for Angelman syndrome, as well as other rare neurodevelopmental disorders and their organizations, and I am a member of the N=1 Collaborative.

I was asked to take you through a journey. I'm going to take you through a patient journey, a clinician journey, the community journey, and then the industry journey. Ultimately, what I hope you'll be able to see is that all of us as parents wind up traveling many roads as a holistic journey. I'm going to start with a movie that just really encapsulates our life. This is just a day in the life of one single child, but I'm here representing 500,000 children and adults around the world living with Angelman syndrome. This is just one single day of one single girl, and her name is Quincy.

[Video start]

FEMALE VOICE: When you meet her, the first thing you will notice is her smile and her laugh. You'll also notice that she can't talk with her mouth. She talks with an iPad. Quincy has so many strengths and so many challenges. If I ask her to say hi, she opens her mouth and says, "Ha." She has Angelman syndrome. It is a deletion of one of her genes and it's totally random.

I had a normal pregnancy with Quincy, but we started noticing things about her that were a little bit different. It was weird how unfussy she was. She never cried, and she was incredibly smiley. But she wasn't happy when she was looking at people. She was just happy looking at the fan. We were worried something was seriously wrong with her, so we asked if we could see a neurologist.

The first words out of his mouth were, "Ms. Berent, I have catastrophic news for you. What she has been diagnosed with is Angelman syndrome." I looked it up. What stuck with me the most was not walking, not talking, and having severe seizures. Under treatments, it said, "No treatments available." My

head just started spinning. She'll never go to college. She'll never go to school. She will never get married. She will never have kids — all of the things you dream about for your beautiful newborn little girl, just taken away in a minute. It was at that moment that I knew I needed to educate myself and I needed to learn how to fix this, because mommy and daddy fix everything.

Bad news either paralyzes you or it motivates you. For me, it completely motivated me to figure out a way to ensure that a treatment for Angelman syndrome gets outside of the mouse and into humans. The gene that Quincy is missing is actually present in all of us, including her, but it's silent. All we would need to do is unsilence that copy of that gene, and that would be a mechanism in which we can actually cure this disorder.

Two weeks after she was diagnosed, a paper came out, and it was in adult mice with Angelman syndrome. They gave these mice a drug called an antisense oligonucleotide in their brain, and it reversed many of the symptoms that the mice had. I realized at that moment that, if they could do it in mice, why can't they do it in humans? How can we get this to my daughter?

So in order to get this from mice to humans — is incredibly expensive. It requires a tremendous amount of work, and it requires a tremendous amount of expertise. Most of the time, the steps between mouse and human are done through a pharmaceutical company. We didn't have that luxury. We had a concept, and we had a proof of concept and a mission with timelines that were not negotiable. We had a passion, and we were able to bring on the best people in the world virtually to help our company of five drive a drug to a human clinical trial that could impact children living with Angelman syndrome.

Now, after all of this, the trial is open for enrollment, and I may be able to enroll my daughter in the study. This drug that we have worked so hard for could be in the brain of little kids. This is a miracle that I can't believe I'm a part of.

My hope is that this is transformative. I want to see her life improve. I want her to tell me the things that she can't communicate in any other way. But I'm mostly thinking about who she is and who she might be. I just want her to say hi. That's what I want.

[Video end]

DR. BERENT: When someone says to you, "I have catastrophic news for you: Your daughter has Angelman syndrome," the first thing I said was, "How do you spell that?" This was over the phone. I was told there was nothing wrong with her, and I demanded genetic testing at 5 months of age. This is the phone call that I received. I did what every parent should never, ever do: I Googled it. I opened the first thing that popped up, which was Wikipedia — everything I tell my clients to never do. I read all of the "nots," all of the things that this little girl will never do in her life. She will never walk. She will never talk. She

might not sleep. She will have seizures. She won't go to college, and she will certainly never live an independent life.

Then I went to, "Well, what will she be able to do? What is the prognosis for survival? Is this degenerative? Is it nondegenerative?" I learned it is nondegenerative, and she should live a normal length of life. But how do I give her that best life and advocate for everything that she's capable of? How do I ensure she's accepted and as independent as possible and lives the fullest life? I realized super quickly that I had to advocate for Quincy, just like I had to advocate for that genetic test. I had to learn and execute if I can change the trajectory of this child's life.

Then about 10 minutes later, I went through this period of remorse: "I can't do this, and I don't want to." What kind of mother doesn't want to manage the challenges that they're faced with for their daughter? I've worked my entire life since I was 8 years old to be a veterinarian. I was finally in a position as a veterinarian exactly where I wanted to be. I wrote my first textbook. I was finally promoted. I was in a position running the trials I wanted to run, patenting devices, advancing them for pediatric use. I was exactly where I wanted to be in my career. This was not part of my plan.

"How am I going to handle this as a mother? How am I going to handle this as a family? How do I handle this with my husband and her older sister?" I was soon to be pregnant with her younger sister. "How do I navigate a world of disability that I never signed up for? How do I manage a life of therapy and a full-time job?" There has to be a solution to this problem.

As I say at work, knowledge is power. Things are either possible or impossible. There's absolutely no in-between. So far, no one has told me that it is impossible to cure a neurodevelopmental disorder. Until that is a fact, I committed to her that I would work night and day to do so. I had to be brave, and I had to be smart.

So I called every senior author I could on every publication I could read. I attended every scientific conference that I could. What was incredibly clear to me was that amazing work had been done for Angelman syndrome well before her diagnosis, thank goodness. Thank goodness for so many brilliant minds that were already working on Angelman syndrome. Why? Because it's a very unique genetic condition, which I'll talk about in a moment, but they were actually delivering gene therapies and antisense oligonucleotides into the mouse model of Angelman syndrome and rescuing so much of the phenotype and giving us so much hope and promise that this could change the lives of our kids.

But what was also very clear was that it was the perfect decade to be a mouse with Angelman syndrome. But unfortunately, as I talked to everybody that has published anything on Angelman syndrome therapeutics, it was not the right decade to be a human with Angelman syndrome. Really developing

drugs is outside of the wheelhouse of a lot of the most brilliant minds that were working on this condition. The clinicians who were doing such an amazing job caring for our kids and wanting to see these therapeutics come to fruition for their patients, trying to see how we can get it to them, really didn't understand that valley of death of drug development, because they were clinicians handling patients. This gap, this valley of death, was so super clear to me that we needed to do something to fill that and build that bridge. Translational science is generally outside of the wheelhouse of most neuroscientists. That is changing, thank goodness, over the last decade.

Really, what I realized is that we couldn't wait for someone to decide it was time to develop a treatment for Angelman syndrome from the mouse to the human, but we could help shepherd one, because that's what I did for a living. I took proof of concept, and I brought it to patients. If I could do anything with my skill set to help her, maybe that was it. I had to behave like a clinician and a translational researcher.

So I learned everything I could about Angelman. It's a monogenetic, nondegenerative, random neurodevelopmental disorder affecting chromosome 15, but it's incredibly unique and has elegant genetics, in that the maternal and the paternal copies of the gene generally are both being read in all cells of the body, except for neurons. It's imprinted in neurons only in the brain in me and in you and in Quincy. This imprinting is caused by a long noncoding RNA called the UBE3A antisense transcript. Ultimately, it silences the paternal copy of the gene in all of us. And individuals living with Angelman syndrome are also either missing or have a mutated copy of the gene on the maternal allele, resulting in no *UBE3A* expression in neurons but haploinsufficiency everywhere else. Ultimately, it is only a neurologic disorder, and if we can turn on the paternal copy of that gene by unsilencing that long non-coding RNA or replace the missing gene, maybe we can get somewhere.

But the impact of that single gene on neurons is tremendous. It causes severe impact both on caregivers and the patients. The symptoms of Angelman — as I already said, the most profound being the universal and total lack of speech. Most kids never speak a single word, and if they do, it's less than five words. Some kids have life-threatening and debilitating seizures, some only sleep 2 or 3 hours a night, and they are definitely unable, with any genotype, to live an independent life.

The impact that that can have on a family cannot be understated: the inability to maintain employment, significant anxiety and depression, loss of sleep and stress with social isolation, the impact on family relationships, and then difficulty caring for themselves or their other children or their spouses at home. It is tremendous, the impact disorders like this can have on our families.

One of the first papers I came across after discovering the paper on the antisense oligonucleotides was one on somatic mosaicism in Angelman syndrome. This paper saved my life, and I can't wait to thank the author. What this paper showed was that with 1% to 5% of *UBE3A* expression, individuals with Angelman syndrome that have mosaicism, which is less than 1% of our population, have few to no seizures, are ambulatory, and have some speech. Those that have 20% of *UBE3A* expression have no seizures, have minimal to no ataxia, and can speak in some sentences. Those with over 40% of *UBE3A* expression, as you can see in this chart here, basically are considered nondiagnostic for Angelman syndrome, because they are probably not clinical and considered neurotypical. So the clinical signs only appear at 40% expression and below.

If you can only imagine what 1% to 5% of *UBE3A* expression would look like in my daughter, that would be a different child, and 99% of kids living with Angelman syndrome have less than 1% to 5% *UBE3A* expression. What does that mean? A little bit can go a long way. The enemy of good might be better, and we don't have to necessarily get it perfect the first time. But giving them something is better than giving them nothing.

I went on a community journey at this point. This is all within the first 3 days of her diagnosis. In October of 2015, I was lucky enough to be asked to join the board of directors for FAST, the Foundation for Angelman Syndrome Therapeutics. I soon became their chief science officer about 6 months later. FAST was already doing such incredible work, and I am here just riding on the coattails of the amazing work that the team had done prior to my daughter's diagnosis.

They had brought together a consortium of scientists to work outside of their own silos and to work as a consortium in order to really consider all therapeutic strategies, scientifically de-risk those strategies, and consider different approaches that may benefit different populations with Angelman syndrome. They were doing such an incredible job really proving what can work in cell lines and in animal models.

I was tasked with creating a road map to a cure: "How do we get from mouse to human? What is it going to cost, and how are we going to get here?" What we didn't have was an ask. We didn't have a number. We didn't have a plan. We didn't have an exact path to get there, because we were just discovering all of the ways we can do that. It was a really serendipitous and a perfect time for me to join the organization, because this is the space that I live in.

We created an ask, and that ask was $5.8 million. Up until this point, we had really never raised more than about $700,000 a year for the organization and before that, $400,000 or $500,000. This is an incredible, amazing grassroots effort that was on the backs of parents and caregivers. How the heck are we going to raise $5.8 million for this single gene disorder? We needed to

commit to six different therapeutic platforms to get from bench-side to human candidate with go and no-go decisions. To do that was a huge price tag. So we went out, and we asked.

We were so blessed to raise that money in about 6 weeks from a family that was so touched by Angelman syndrome and so impressed with our plan that they were actually willing to front this money to accelerate and make a difference for this disorder. For that, I will always — and our whole world, our whole global community — will always be grateful.

We committed to this family that we would do this in 24 months, and we had to get it done. So we created a plan, and that plan was, we can replace the missing gene or protein. We can activate the silent copy of that gene. We can look at downstream targets and understand the synaptopathy of the disorder and try to repair the dysfunction downstream, and we needed to be prepared for clinical trials. We needed the right models. We needed the right cell lines. We needed the right endpoints and biomarkers. We needed to understand how to design these trials and how to attract pharmaceutical companies into this space. This was incredibly important for us to be successful as an organization and as a community.

Pillar number 1 was replacing the gene or the protein, and that could be done through AAV gene therapy, hematopoietic stem cell gene therapy, or enzyme replacement therapy. We robustly funded programs in all three of these areas, and there are four additional programs that are being pursued by others in this space, as well as other pharmaceutical companies in this space, to do exactly this.

The second pillar is, we can activate the silent copy of that gene. With all of the technology, we can do that with antisense oligonucleotides, with zinc fingers, with miRNA, with CRISPR, with gene editing. These are all the people working in that space, and much of this work was funded by our foundation or our sister foundation, the Angelman Syndrome Foundation, working as a global community to ensure that we can get this across the line to patients.

This is just an example of CRISPR, in an adult mouse model treated with CRISPR paternal activation. The wild-type mouse is on the left. The Angelman syndrome untreated mouse is in the middle or was in the middle. The Angelman syndrome mouse after gene therapy treatment is on the right. This is an adult mouse who got CRISPR gene therapy intrathecally and ultimately was behaving just as well as, if not better than, the wild type on the left. This gave us a lot of promise not only about age but about platform — that we had a lot of shots on goal here that we had to really commit to, to see what works best in the human patient, not in the mouse patient.

Then, certainly, downstream targeting. There are many downstream targets that have been investigated and some that are actually in clinical trial

currently.

Then the fourth pillar, which really is an important pillar that's always underestimated, is that of preparing for clinical trials and ensuring that we have global patient access and accessibility over the course of the drug development life cycle. That is incredibly important to our organization and to our global community.

This is a busy slide. I'm not meant to have you go through all of this but just to show you the unbelievable amount of work that goes into how we support clinical trial readiness for innovative therapies. Developing models, we have a rat, a pig, multiple mouse models, organoids, iPSC cell lines, landing pads to test all of the different genes and the combination of genes, the INSYNC council that I already talked to you about to help us do a gap analysis on everything we need for clinical trials and for approvals, an unbelievable natural history study that I'm going to talk about momentarily that started in 2006 and still goes on today that has over 17 years of data and is global, the Global Angelman Syndrome Registry that has over 2,300 patients enrolled, and a search and rescue initiative that has actually been able to try to engage people around the world living with Angelman so that when there are therapeutics and when there are clinical trials in their region, we can ensure that it is very easy for them to have access to that information. The Angelman Syndrome Foundation, our sister organization, is working on something called the LADDER Network, which is really allowing the electronic medical record of holistic care clinics working on Angelman syndrome to put all that data together and incorporate that with the natural history data so that that data is de-identified and available for all individuals, industry partners, or academic partners that really want to utilize that data for research in order to help advance clinical trials.

We have multiple newborn screening efforts in multiple states around the country. We have developed clinical trial training centers in order to ensure that we have the right clinicians able to execute on clinical trials and, of course, our Angelman Syndrome Biomarker and Outcome Measure Consortium, which is really geared toward understanding the meaningfulness and the impact that different symptoms of the disease have on families and patients living with Angelman syndrome.

The Angelman Syndrome Natural History Study started in 2006, thanks to a generous grant from the NIH. Then that was eventually subsidized after the NIH grant went away, by the FDA. Then in 2022, that money went away, so the ABOM, the biomarker consortium, continued to fund that, and that's a precompetitive funding between pharmaceutical companies as well as FAST and the Angelman Syndrome Foundation.

Then we also have global natural history studies in the U.K., Belgium, Spain, and Latin America. We are really working hard to ensure we understand this

disease in all entities around the world and that we understand the longitudinal progression and the trajectory of change over time in this disorder.

This is just an example of the schedule of assessments. It's a very, very robust assessment that is being done in person and remote at different time points being assessed longitudinally. This is just some of the data that have come out of that study showing that the Bayley scale of development can show that really, the individuals with Angelman syndrome have a totally different trajectory than neurotypical age-matched peers. Ultimately, they're very, very flat. They don't really change much over time, particularly in areas of communication, fine motor skills, and gross motor skills.

So ultimately, that natural history data is incredibly robust with over 30 publications and five additional manuscripts that are either submitted currently or in preparation, thanks to the support by our incredible team, Drs. Wen-Hann Tan, Lynne Bird, Anjali, Anne Wheeler, Laurent Servais, and so many others that have made this a life dream to really get the natural history of this disease explained and published. We are so grateful for the work that they have done.

In 2016, we really were left with having to establish an ABOM, the Angelman Syndrome Biomarker and Outcome Measure Consortium. It's a precompetitive consortium that was really meant to be established with a collaborative spirit. It was the two leading patient advocacy groups, the Angelman Syndrome Foundation and FAST, as well as five academic partners and three pharmaceutical companies, focusing on priorities and industry gaps on what the endpoints and the biomarkers are that are appropriate for Angelman syndrome. We understand that the industry really chooses the diseases and the disorders they work on based on biology and developability. Part of the developability is understanding if we have a clear path with endpoints and biomarkers. We didn't have that yet, so we really had to dive into understanding parent and caregiver surveys. What is meaningful? What are the priorities? A disease concept model. We were able to engage with the FDA with a listening session, and we were able to bring all of these people to the table precompetitively and do a gap analysis on the natural history data we had to understand if we needed to develop new endpoints for this disorder.

This is just an example of how we collected patient experience data in really trying to understand what is important to caregivers. What are their perspectives, and what are their priorities? We understand that we have to be data-driven in how we figure this out, so we did a robust disease concept model that was published in 2020. We did just a simple parent survey in which we gathered the feedback from 332 caregivers just over social media, which totally mapped with the disease concept model showing that communication and speech, seizures, motor function, and cognition are the

most important symptoms to be impacted with a transformative treatment for Angelman syndrome, and the meaningfulness of that is so important to understand. So we have to collect patient preference information and think about how parents and patients think and feel when we talk about emerging therapies for Angelman syndrome.

In 2018, we were lucky enough to meet with the team at the FDA. So FAST met with CBER, CDER, Orphan Products, Rare Disease staff, and many others. This was really a patient-led initiative that the FDA had put out a request for, and we were able to share the perspectives of these families. It was five families that brought their children, and we were able to really have them talk to the agency about what's important and meaningful.

There were some really clear messages there. That was in 2018, and those messages certainly were made very, very clear, but feedback needs to continue, and engagement needs to continue over time. It's been a long time since we've had that engagement. They really encouraged us to develop a novel communication endpoint for Angelman syndrome, and it was out of that meeting that the ORCA, or the Observer-Reported Communication Ability Measure, was born from the FDA's guidance and from their recommendation. Ultimately, the FDA has now supported that measure for 15 other neurodevelopmental disorders, giving a $2.5 million grant to the Duke University School of Medicine to develop that not only for Angelman syndrome, which we funded as a foundation, but also for many other neurodevelopmental disorders, which is really excellent news.

The ABOM went from three pharmaceutical companies sitting at the table to a steering committee of 42 members, four patient advocacy groups, 15 pharmaceutical companies, and FAST committed a million dollars a year to accelerate priority endpoints for all stakeholders that will remain in the precompetitive space so that clinical trials are run in a similar way using similar endpoints, and we all can really learn from each other and really grow the clinical trial example so that other companies can really follow suit and people are getting similar feedback and similar information.

This precompetitive group really engages in pilot studies, publishing abstracts, progressing on the priorities of parents and caregivers, and then engaging with the FDA. It's really important that we are able to engage with regulators as a community of industry, foundation, and academics so that information is not siloed in the industry and not siloed in their IND but actually made fully transparent and available to the foundations who are funding the endpoints. Engagement in that is incredibly important to understanding the feedback that the agency has on these endpoints, because it does take a very long time to really understand the true acceptability of some of these endpoints for clinical trials and for potential approvals.

We really had to be methodical on how we thought about these endpoints in

all of these domains, and we had to really ensure that we were developing them appropriately and got the feedback that we needed in order for them to be incorporated into clinical trials, which all of our industry partners are now utilizing. That has been incredibly important as we've really tried to learn and are trying to gain some of the feedback from the FDA on the context of use for these measures.

So then in 2017, everything really changed. What changed was, the foundation in one of our funding mechanisms discovered a human antisense oligonucleotide, and we got to human candidate as we said we needed to. We had data in the rodent to support that there was prospect for benefit, and we had a pharmacodynamic effect to show that we could activate the silent gene in the rodent model of Angelman syndrome.

This was the time that, unfortunately or fortunately, the foundation decided that we need to start our own company. We started a company called GeneTx Biotherapeutics to advance an antisense oligonucleotide therapy for the treatment of Angelman syndrome. We had to do that ourselves, and ultimately, we did that, because we knew that if we didn't, it was going to take a very, very long time to get the engagement we needed as a priority program from pharmaceutical companies — that we were sitting at the bottom of their pipeline, and we needed to be at the top of the pipeline. The only way that we knew that could happen is if we did it ourselves.

Now I go on an industry journey. GeneTx Biotherapeutics was born in 2017 through the investment of angel investors, and our nonprofit started a for-profit company. We advanced this with the support of many experts in the field with a very small team and a large virtual team through IND-enabling studies, including pharmacodynamic/pharmacokinetic and toxicology studies. We obtained orphan drug designation, rare pediatric designation, and fast-track designation. We filed our own IND. Then we were lucky enough to partner this program with Ultragenyx pharmaceuticals to help us get through the phase 1/2 clinical trial, and they've acquired the company as of last summer in 2022.

Eight years ago, when Quincy was diagnosed, this is what the road map looked like. We had five therapeutic programs, three of which were funded by FAST in early discovery and basic research, with a few pharmaceutical companies at the table, but we were not priority programs. Then 1 year later it was 10 programs, 6 of which were funded by FAST, and that was because of the impetus of that $5.8 million grant. We had more people interested in Angelman syndrome, and we had an IND that was submitted. Six years ago, it was 15 programs, with 10 FAST-funded programs. Two years ago, it was 34 programs, with 12 FAST-funded programs.

Then this happened. One and a half years ago, in 2022 in May, there was a biotech crash. Ultimately, priorities shifted. This pipeline went to this. We lost

10 programs in a matter of weeks, because the priorities of different drug companies where Angelman was not the priority program fell off of their pipeline. The programs were either paused, canceled, or shelved. That was devastating to our community, and that was only a year ago.

Then 6 months ago, we had advanced another program, but we lost, 3 months ago, three more. Unfortunately, what that shows us is that, if we don't advance these programs ourselves or have some type of control over how these programs move, we can't let programs fall because of good science but changing priorities. We have to let them fall because they proved that they have no-go decisions based on science. Science is what really matters.

The chutes and ladders of drug development are real. Today, we have 14 FAST-funded programs, 23 in the pipeline, many in IND-enabling studies, many in clinical trials, and we are hoping to see that change over the next 3 to 4 years as well.

We have to think about Pillar 4 — all of the other things we needed to get there: animal models, patient registries, diagnostic efforts. This is where we were 8 years ago, and this is where we are today. We're moving mountains for these kids in order to advance all of these different programs, but I want to acknowledge this is on the backs of parents. This is on the backs of caregivers. This is on the backs of cupcake sales, bake sales, and lemonade stands. This is incredibly hard to do as patient advocacy groups, because it's crazy expensive.

We made an investment in order to train clinical trialists to run the clinical trials, because we understand, as more and more therapies are coming online, the innovation and the way that they're delivered is novel and unique, and we want to ensure that we have the best clinicians out there that are able to do it and that are able to do it quickly and are able to treat a lot of patients, because we're hoping that as these trials open, more and more patients can be enrolled. So we invested $5 million in this training program, and the goal is to train people around the globe in order to ensure we have these centers of excellence for gene therapy and innovative regenerative medicine therapies.

Really, our urgent mission to bring transformative treatments to our global community starts with discovery; moves to preclinical; really supports endpoints and biomarker development; engages the community to know where people are, know what they want, know what their preferences are, and know how they feel; and then, of course, ensures that we can execute on the clinical trials to ensure that we get to approval, which is the ultimate goal for everyone.

Then 2 days ago, there was an announcement. For the first time, the largest NIH grant ever given to Angelman syndrome was to advance a CRISPR program. This is a collaboration of Yale University, our foundation, and Rush

University. This is the perfect example of how this trajectory of discovery bench-side to clinical trial bedside can happen with the foundation in the middle shepherding that through. This grant is the perfect example of how all of our hard work is coming to fruition, because we are able to help our basic scientists meet the clinicians and advance through IND-enabling studies.

When we look at all of our disease modification strategies, we can see that we have a lot, but all of that is on the backs of our amazing scientists, our amazing clinicians, and our incredible community. We can't take that for granted, because developing a single drug can cost more than $100 million and our foundation is committed to this space, the valley of death, where priorities change and programs drop. As a foundation, we are not willing to let that happen.

I assure you, drug development is hard, but living with rare disease is so much harder. I can tell you that from firsthand experience, and so can all of my other warrior parents on this call, as well as all of them in the world that are fighting every day for their kids to even eat or to sleep.

FAST works to accelerate and de-risk for all living with Angelman syndrome. It's hard to rely on other parties to make your disease a priority. We understand that, because their priorities can change overnight. But FAST will continue to accelerate excellent science for all shots on goal, because the only experiment that will tell us what works, fortunately or unfortunately, is the human experiment. That is the truth, and that is where risk tolerance has to be really considered. The preferences of parents and the understanding of those risks are real. We have to talk about that, but that can really only be decided by the parents who are living every day, taking the risk of doing nothing. The priorities for FAST in the Angelman syndrome community will only change when every individual around the world has access to the therapies that they want.

Understanding patient preferences and experience data does provide insight to consider what is meaningful change, what is important to these families, and these conversations need to be ongoing with the agencies, because this is really the ultimate answer to how drugs are going to get approved. We cannot do this alone, and we beg everyone to join in on this mission to help us do this, because this is way too much to put on the backs of rare disease organizations.

I thank you for listening to our story. Quincy is only my reason, but she's only 1 of 500,000 other reasons that I fight every day. Her fight is certainly my fight, and my fight has become their fight. So thank you so much for listening. We are working really hard to make the impossible possible.

DR. ROWZEE: Allyson, thank you so much for such an amazing, informative, and inspiring presentation. It's amazing to see the impact that you and your colleagues and all the advocacy organizations and the researchers in

collaborating with companies — the impact that you've had on drug research and development for Angelman syndrome.

Panel Discussion

DR. ROWZEE: I'm going to now welcome two more warriors to our panel, Erin Ward and Suzette James, whom you may recognize from some of our previous RegenMedEd events. Welcome back. Erin is the president and co-founder of MTM-CNM Family Connection, which is an organization that helps bring families of individuals with myotubular myopathy and centronuclear myopathy together and connects these families with top researchers in the field. Erin, I know you're at a conference this week, so thanks so much for carving out some time from your busy schedule to join us today. I should also mention that Erin's Twitter handle was part of the inspiration for our warrior families theme today, as she is @mtmwarriormom on that platform.

Our warrior panel is complete today with the addition of Suzette James. Suzette is on the Board of Directors for the Batten Disease Support and Research Association and is a strong advocate for the CLN2 Batten disease community. Thanks for your time today, Suzette.

Allyson, we're going to give you a break for a couple of minutes, but we're going to bring her back for the panel discussion in a little bit. But I'm going to get started by asking Suzette and Erin to just take a few minutes to introduce yourselves and talk about your families and take us through your path to advocacy from your child's diagnosis to now. How did you find your way to the organizations that you're currently a part of? Maybe I'll call on Suzette first, if that's okay. Please go ahead and introduce yourselves. Thanks.

MS. SUZETTE JAMES: Thank you, and thank you, FDA, for having us on here. We really appreciate it. Again, my name is Suzette James. I have four children, two of whom are living with CLN2 Batten disease. My children's phenotype is considered atypical or late-onset Batten disease. Maya is age 20, diagnosed at 10, and Xavier is 15, soon to be 16 this Saturday. He was diagnosed at 9. They both receive infusions — enzyme replacement therapy that they've been receiving for 7 years now.

Most people may be aware or may not, but Batten disease is a neurodegenerative condition. It affects children, and most children develop normally and then start to have delays, which begin with seizures, loss of motor skills, ataxia, speech delays, and cognitive decline. It usually ends in death between 6 and 12, with the exception of the later-onset version.

I think advocacy, for me, has changed quite a bit from the beginning. I am much more vocal and public with how I talk about our disease and how it impacts our children, as well as our entire family and anyone who comes into

contact with them. I'm much more proactive, within reason of having four children, with networking. I'm unapologetic in my approach, and I know I belong in the room. I think that's important for new individuals, for new folks being diagnosed. It's extremely critical that you are comfortable taking up space. I think each person is going to have their own way to advocate.

In the beginning, for me, advocacy was doing what I could do and affecting what I could affect. That included doing a ton of research on nutrition, exercise, physical therapy, occupational therapy, and other topics. I was really focused on creating the best possible health that I could, and my husband was focused on more creating white papers that didn't exist, because our disease really wasn't at the forefront yet, and connecting with those researchers and creating a campaign to fund those researchers individually.

MS. ERIN WARD: Thanks so much, Suzette. As Anne shared, my name is Erin Ward. What brought me to the world of rare disease is, my son, Will, lived 20 years with X-linked myotubular myopathy. Unfortunately, he passed away 2 years ago now from complications from X-linked MTM.

Will lived during the time where, as a community, we were continuing to understand the disease and maximizing life and support through medical technology, so Will lived with a tracheostomy, a ventilator — wheelchair user, assistive technology — all of that. But even despite all of those incredible challenges he had physically, he actually lived a very full, rich life and contributed to his family, his community.

He attended school completely included with his peers and graduated from high school and was on his journey of being his own FDA advocate, participating in listening sessions and also within his own community, in terms of making presentations at the local high school with the biotechnology team, educating individuals about rare diseases and the opportunities that exist within the space to even pursue careers in that way.

I think many of you may be starting out on rare disease journeys. My husband and I learned very early on that, having a rare disease individual in your family, you almost are born into advocacy. I never want you to underestimate the advocacy that you do just even on a daily basis to achieve the basic needs of your loved ones, as well as every encounter you have — the way that you're able to educate and bring awareness in all the things you do, just even out in society, but also in the partnerships you build with researchers, as well as medical providers that are caring for your child.

I was really fortunate: Even though we were a very small rare disease — ultra-rare, in fact — we were able to connect with other families and have grassroots efforts to have annual conferences in 2009. A few years later, my husband and I and our partner, Maureen Wood, as well as other family members, formally came together and decided to form a nonprofit, MTM-CNM

Family Connection.

But we also work really collaboratively. That's a space that we continue to pursue right now, is looking at, "How can we continue to bring the entire community together?" Current efforts are underway in terms of — we just recently co-created with the Myotubular Trust from the U.K. and the existing patient registry out of Newcastle University a liver consortium to look at issues that are emerging for us in that space.

Q&A

MS. ROWZEE: Thank you both so much for that introduction and how you started your work in these communities. Suzette, I'm going to come back to you, if you don't mind. I was wondering, what advice would you give to parents or caregivers of children where gene therapies may not be in development? Where can parents start, and how can they create momentum in this space, maybe not just for gene therapy but therapies just generally?

MS. JAMES: Right, exactly. Thanks. Well, I think I'd go back to what Mr. Rogers used to say. He would say to people to find the helpers. To me, that's really part of what you do when you get in this space, when you're catapulted into this space. I think you really have to reach out to those. You have to look at best practices, going back to my management consulting background. You have to go and look at those individuals, those folks who have been able to make it happen, and look at their playbooks and see how you can actually move forward with some of the work that they've done. You reach out to industry partners.

Again, first of all, though, you need to be comfortable taking up space in the room and know that you belong there. You absolutely 100%. If you don't believe it, then fake it until you make it — kind of thing.

You need to reach out to the family advocacy groups — create relationships, connections — networking with other rare disease organizations, because we do need to band together. I mean, rare disease, collectively, is a very large number. We need to work together to elevate our cause. That just doesn't happen enough. We don't cross-pollinate, so to speak, enough. I just can't say it clearly enough. I mean, really, at this time, as I've been probably clear before, it's a frustrating time in our Batten world. We have been waiting on treatments and gene therapy for a very long time, and they are within reach. This is really a clarion call right now for, I think, rare disease, and we need to band together, and we need to say enough is enough when it is enough. We need to be bold now. We really do. We have to work together.

MS. ROWZEE: Erin, I'm going to turn back to you. Tagging onto what Suzette was saying about banding together and bringing folks together, you and your

family have participated in several observational and natural history studies, and you've helped also facilitate and support some of those studies through your organization's work. Can you tell us more about what those experiences were like and what it's like to bring folks together and if there's any advice that you'd like to offer parents or caregivers in rare disease communities that are trying to get this type of work underway?

MS. WARD: Yeah, especially for communities that are early in the process of really defining the disease and needing to do basic natural history studies and observational studies that will hopefully help with IND applications for future trials, a big part of what our organization was able to help and support that way is at our biannual conferences. We would be partnering with researchers that were working on efforts, either in natural history or observational studies that needed participants. We partnered with them to allow them to collect data on site.

Over the course of a weekend, we had a team working on respiratory management, trying to define physical movement that would then be used in these applications for future trials. In a very short order, over the course of a weekend, they were coming out with data on over 25 participants without having to use the resources to go out to multiple sites throughout the country and use all of those resources in that way.

It really did add to accelerating the collection of that important data. It also was such a meaningful experience for many of the families that participated, because although, at that time, there were no active clinical trials, it was a way for them to actively participate in that process and that run-in to the trials. They were making very meaningful contributions.

Thinking about natural history studies in general and also observational studies, I think a real focus right now for the rare disease space is to be thinking about and making sure you're putting it to your planning how that data from those studies is going to be curated, how it's going to be stored, how it's going to be shared, and how accessible it is going to be. We absolutely, in this space, need to be prioritizing transparency and data sharing. We are too small of communities to not have that in place and to really be insistent on it.

I think that individuals that are participating in studies need to take some accountability in that process, have conversations with those that are conducting the studies, and really better understand how the data is going to be used and how it's going to be accessible to them and to others in the future. I think that's a real key takeaway right now that I see in our community, as well as other rare disease communities. How can we make sure that every piece of data collected for these rare diseases is being held in a way that's sustainable and will go into longevity?

MS. JAMES: Right, a central repository, if you will, because especially when you

have a protracted disease and when the symptoms transpire over 8 to 10 years, you don't have the luxury of a natural history study. Your child will be dead by the time you even get to it. Then to have to start it over again, because it belonged to someone else — it's super critical.

We all need an Allyson in our respective diseases, because you see from her presentation — Allyson, I would love your take on this. You see it from the presentation — everything that it took. It's almost a case manager perspective when you think of health care. You need a case manager to run this. What we have now are silos. You've got industry. You've got academia, etc., and beyond that. But it's really difficult, because then what happens is, you have all of our patient advocacy groups and organizations that really are working very individually on certain tasks. You see all of the tasks that Allyson put out there that need to be managed. It gets really, really difficult very quickly to keep all those intact.

DR. BERENT: I totally agree. I think it even gets worse as you get into clinical trials, because then the silos become proprietary information by companies, but it's actually patient information that the community should have. If people aren't willing to share baseline data or placebo data in order to ensure that other families and individuals living with these very rare diseases are not having to reinvent the wheel every study, that's a travesty, frankly. I think that if we can't share information — no one's saying, "Share your post-treatment data," but if you can't share your pre-treatment or placebo data so that other people can have fewer placebo groups, it actually is a disservice to the rare disease communities. All of this needs to be in one repository so it gets de-identified properly and people can feed into it. The natural history data as well — all of the *n* of 1's that need to be in this place where people can understand safety risk; people can understand what other people have seen that companies oftentimes are siloing a little bit. I think it's a disservice to the community, and most of the reason the companies are in this space is because the community got them there, and they're not giving back to the community who gave so much to potentially get them there. I find that to be really troubling. I find it to be very troubling.

MS. WARD: Yeah, we have a good example of our efforts to try to bring some collaborative efforts around this. It kind of actually ties into the natural history study, something that hasn't been well documented in our disease, even though it is pretty well characterized through prior natural history studies: As a muscle disease, it affects all muscles. Priority has always been on pulmonary issues, because of course you need to breathe to survive, so that's where a lot of the focus is. Our individuals can do quite well over time when respiratory management is under control, but in the background, there had been liver issues that had emerged here or there over the course of the disease. As there is more longevity and people are surviving longer, we are seeing some other issues cropping up around liver issues. In my son in

particular, his last 2 years of life had two liver issues that had never occurred in his prior years. At the same time, as regenerative medicines are happening and trials are underway, the two first trials in our community had serious adverse events surrounding liver. It became this, really, stop point. One trial ended, and one has been put on hold.

We knew that in order to overcome these barriers, we had to start talking about the liver and getting as much information as we possibly could. I will say it was challenging, waiting for the industry partners to take a lead in that, and there were many things happening that they were doing, but it wasn't always open to our participation. Instead of looking for an invitation to join the table or the meeting, we decided together with our sister organization in the U.K. that we would start inviting people to the table. We would create the table.

We developed an MTM-CNM liver collaborative that pulled together medical experts, our allies in the community, our researchers, and our industry partners. We started meeting on a monthly basis to try to uncover what's happening here and, in a very short period of time, developed a liver survey that can now start to gather the natural history data that hadn't specifically been gathered in the past. Within 3 short months in our small community, we had 110 participants. We were able to do a data cut, and that's why I'm here at a conference today at the World Muscle Society to help share that information and try to get others interested in looking at this to hopefully de-risk and mitigate not only participation in trials but also what Allyson and Suzette, I think, are saying: This doesn't just affect even people that are on trials. This is helping to advance and better understand the disease for people living with it today. That natural history data has to be transparent. It has to be open and available to all.

We understand that post-dosing or a product — data is one thing, which — I also feel strongly that should also be shareable at some level, but when we're talking about natural history development and data, that has to be done in a way that's more transparent across the community.

MS. ROWZEE: Thank you so much for this just interesting and rich discussion. I'm noticing time, so I'm going to span between our pre-submitted questions and some of the questions that we're receiving live. I'm going to kick this next one to Allyson. These two different parts, I think, tie together and bring in what Erin was saying as well: What advice would you offer parents or caregivers who are trying to help move the needle on research and development for rare diseases? How can you effectively work with the different players to bring them together to help move these products into development? What's coming from our live questions is, specifically, folks were asking about building the precompetitive group and how you were able to get these folks all together and get them on board to participate.

DR. BERENT: Yeah, so these are all really great questions. I'll start with the last one, because I think it will lead into the first one. Staying precompetitive, for us, has been incredibly important. We don't even have CDEs or NDAs. The reason is, when we tried to have contracting and we tried to have a charter, every company has to review the charter with their legal people. It takes four and a half years to get anybody to agree to a charter. So what we said was, "You know what? Don't give us any confidential information that you don't want to tell us, and we're not going to give you any confidential information that we don't want to tell you. The good news is that we'll tell you everything. You'll tell us very little, but you will learn what we know, and therefore, your drug program will be better for it, which means our kids will be better for it. Our main return on investment is our children's success. Your return on investment might be a little bit different than that. But for me, they're one in the same. You win. We win. All I want is for our kids to win."

We found that people came to the table when there were no contracts. People came to the table even more so when we said we're going to give a million dollars a year to develop endpoints and share them freely. Now, some of those pharmaceutical companies develop their own endpoints and are not sharing them freely back. That's devastating. We gave and gave and gave, and people are tweaking a little bit, and they're taking everything, but they're not giving back. But we had to be okay with that. We had to understand business is business, but us giving has created a spirit of people coming around the table and sharing where they can.

I think the biggest issue is that the FDA gives feedback to some companies and they don't share the feedback. Now, that is really problematic to our consortium, because people are spending more and more money validating endpoints that the FDA already told somebody is not going to be ever used as a primary endpoint, but they haven't told anybody that. That's their advantage, and that is really hurting our kids, because these trials may fail not because a drug doesn't work but because we have bad endpoints, because we got bad advice. We need engagement with the agency on the precompetitive level so that all of this information is shared back.

So from the consortium perspective, pay for it; don't have any contracts. You get much farther that way, at least in our experience, and we have amazing people around the table because of it. So we're very lucky we have really good players.

Where do you start? For me, I think the best place to start is, "What models do you have, and what is the biology of the disease to treat it best?" and understanding that and then having a champion in an academic setting or in a CRO setting that can understand the biology and try to come up with a way to treat it. If you can leverage a treatment, whether that's a gene replacement therapy, a CRISPR gene editor, or some type of lentivirus hematopoietic stem cell therapy, you get some ground.

Then around that, while things are cooking, because it takes a while for results, you start building out the infrastructure, which is more models. You might need a mouse and a cell line. You might need to start looking at your natural history studies. You want to look at how you're going to gather more patients and improve your diagnostic abilities and improve your visibility. But that can happen kind of on the outskirts.

I am a strong believer in developing the drug early on. Fund the people to do it right that are your champions, and then you'll have a lot of time on the outside to develop everything else that is needed in this infrastructure, which we're trying to create a playbook for everyone to do so it's easy. There are checkboxes of what you need, but it's going to be different based on the biology of your disease.

MS. JAMES: Allison, how do you think it could have been? I look at 8 years. We don't have another 8 years. I'm not sure how gene therapy is going to go, whether it's going to get approved through the FDA. It's been difficult. How can you even pare that down? What do you think when you look at the process? How can we reduce that even further?

DR. BERENT: I think we can in every spot preclinical and discovery in the IND-enabling studies and in the clinical trials. All of that together would pare down a lot of time. I personally feel, now that I know much more than I knew when I started, all of this proof of concept that we're trying to get before we declare human candidates is ridiculous. It's ridiculous. You need some proof of concept in some type of model. Then you need to make a decision if the biology makes sense, because the human is going to tell a different story, but the expectations of "Do you have the young animal model and the older animal model and the cell line and the organoid?" — you're wasting 5 years right there.

I think if you have data in an adult model that you're rescuing — phenotype — move on. In my opinion, if we're in a rush — we have children dying; we have adults dying — we need to move this faster. We need proof of concept, and then we need an IND-enabling package that the FDA can actually look at and say, "This is giving me the information that I need." We're being flexible in the time it's going to take to get there and the cost it's going to take to get there. Sometimes we have to do two species. Then we have to wonder, "Why are we doing two species? Is it necessary in this disease to do two species? If we have a PK/PD model, do we need to do another species that's not a PD model just because the guidance says we need to do two species?" That adds another year and another $3 million.

So these are things that we need to have an open conversation as advocacy — with the why and the how. I think there's common ground, but it's just that we're held to the same standard in rare as common. That's hard, because we don't have the resources or the time. Then what happens is, drug developers

drop the program, because they can't afford it. They can't afford the chronic tox and the acute tox and the two species and the time and then the endpoint conversations that take 10 years. So the drug development piece takes a long time and costs a lot of money, and I think we can work there as advocacy to streamline that with the agency. I think [crosstalk] a lot of spots.

MS. JAMES: Yeah, especially with the accelerated path to gene therapy that we keep hearing about. I know Peter Marks is a supporter of it. I just wish other people would get the memo.

DR. BERENT: Yeah, we need to act on it and show them —

MS. WARD: I'll just add that I think a big priority, too, is something that Allyson had mentioned prior: really putting a lot of attention and effort into risk–benefit conversations and how to be supportive of potential participants and shared decision making, because having lived through that experience in our community, unfortunately, we did have four deaths in the gene therapy trial. I think that's something — there's always going to be risk, so how do we better support families in that process of risk–benefit analysis for their particular case with as much information as possible going into it? There will always be risk, so I think that patient preferences and those important conversations also need to be prioritized.

DR. BERENT: We need to understand: What are the risks you guys are willing to take that have kids that are going to die from your disease? What risk am I willing to take when my daughter may not die from this disease but is never going to live an independent life? It's hard to listen to someone say it's all about safety and not worth the risk when you're not living in my shoes for a single day to understand the risk I'm living by doing nothing and the risk of my child's lack of growth or contribution to society by doing nothing. So these are conversations that are raw and real and hard that we need to have, and we need to have them openly, because I think people will have a different perspective if they can understand what we live through. It's very different than what paper looks like.

MS. JAMES: True, yes. I think, Anne, I can say that I've given that raw viewpoint, I think, in our last presentation. It is. I mean, informed consent is a big deal. We make those decisions every day. I'll say it again: It's okay for us to make the decision on how to help our child die a dignified death, but it's not okay to make those decisions about how to have a treatment or a therapy that can help them live. I mean, we're making those decisions every day already.

DR. BERENT: I agree. I agree. It's a conversation that needs to be had.

MS. JAMES: Huge, huge.

Closing Remarks

MS. ROWZEE: Sorry to have to wrap up this really engaging conversation. I see that we're at time. I just wanted to thank you all again for joining and for sharing your perspectives and for sharing your family stories, your stories from your organizations, all of the work that you've been doing to bring people together to move the state of the science forward in your field.

We're looking forward to these continued conversations and hearing these again from our panelists today, other families, folks that are supporting the rare disease space. I'm sorry that we have to wrap this up. I think we could probably continue this conversation for a long time. To let folks know, I know that we're going to get this question, but our presentation is being recorded today, and it's going to be available on our website. I think a lot of folks could see Allyson's presentation on a primer of how to do this, and we'll probably refer back to it. It will be available on our website.

Just to underscore my thanks again for your time and for taking our audience questions. I would say, to those of you who haven't visited our website, you can find our recordings there. You can sign up for the "What's New at CBER" email listserv, and you'll get a digest every day of what's new on our website. You can follow us on social media on the platform formerly known as Twitter at @FDACBER and on Facebook. We encourage you to use the hashtag #RegenEdMed on social media to share your thoughts about today's event and find some resources about what you've heard today.

Once again, thank you all so much for your time, for joining us from a conference, for joining us from the West Coast, and for joining us from a little north of here on the East Coast. We hope to see you all at our next event. Have a great day, everyone. Take care. Bye-bye now.