Qualifying Biomarkers to Support Rare Disease Regulatory Pathways
Case example: Heparan sulfate in neuronopathic lysosomal storage diseases
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Afternoon Transcript

Case Study: Animal Model Translation to Human Application

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Susan Winckler: So we're going to continue, we're going to jump right into content. And this actually addresses some of the questions we've been seeing in the Zoom, so I'm glad that it is our next session.

We are going to turn from measurement to exploring the animal model application to human application. And our first speaker for this afternoon is joining us virtually. So I will turn to Dr. Patricia Dickson, who is Professor of Pediatrics and Chief of Genetics and Genomic Medicine at Washington University School of Medicine in St. Louis. She also was just elected to the Association of American Physicians, so we send our congratulations for that.

And Dr. Dickson, that's your introduction. If we could have you come up on screen, we will turn to you for your slides. And I'm pausing just another 30 seconds to make sure that she's there.

Dr. Patricia Dickson: I am here.

Susan Winckler: Perfect. We can hear you, Dr. Dickson.

Dr. Patricia Dickson: Okay, perfect. And okay, can you see my slides now?

Susan Winckler: We can.

Dr. Patricia Dickson: Okay, great. So I apologize in advance that this talk is extremely wonky, so I'm just going to dive right into the science here. Okay. So we're looking at membrane-tethered NAGLU to explore origins of CSF heparan sulfate.

So we had been doing a lot of preclinical research in evaluating intrathecal enzyme replacement therapy. As part of that research, which was being performed in the MPS I, or hurler, dogs, we evaluated heparan sulfate glycosaminoglycans in cerebrospinal fluid.

So shown on this graph are pre-treatment heparan sulfate glycosaminoglycans performed by a non-reducing end method, so the methods are here on the right for those who want to get into the methodology. So pre-treatment and then post each monthly intrathecal dose of enzyme replacement therapy, so this is right before the second dose, right before the third dose of monthly enzyme replacement therapy administered into the cisterna magna of the dogs. And we showed reduction in the cerebrospinal fluid heparan sulfate.

We had also evaluated brain heparan sulfate by this method. And this is just a graph showing a correlation by linear regression of the glycosaminoglycans in the cerebrospinal fluid to the glycosaminoglycans, and again, this is heparan sulfate non-reducing end method glycosaminoglycans, in the cerebral cortex showing that there seemed to be a relationship.

We also, however, noted that intravenously delivered enzyme replacement therapy appeared to have a therapeutic effect when administered very early in animals. And this is in MPS I dogs, that was work done by Matthew Ellinwood and his group. Where dogs that were dosed from birth with intravenous enzyme replacement therapy showed a reduction in brain glycosaminoglycans. And this is an older paper where we looked at the... we used the dye binding method.

So you can see here the normal animals, the untreated MPS I dogs, dogs that received intrathecal intravenous, and then two dose groups of intravenous enzyme replacement therapy, showing that their brain glycosaminoglycans were lower than in the untreated dogs despite having very little levels of iduronidase. But there was some iduronidase activities, enzyme activity, in the brain, so about 2% to 4% of normal. And we also by toluidine blue showed that there was less storage in the treated dogs in the brain.

We also observed that in MPS I patients who had received intravenous enzyme replacement therapy that we saw a reduction in CSF heparan sulfate. And these were the MPS I patients who had been participants in the initial Aldurazyme study that had been published in the New England Journal.

Some of them had cerebrospinal fluid assayed during the study. And we found that all of them show lower levels of CSF heparan sulfate after 26 or 52 weeks of weekly intravenous enzyme replacement therapy.

We also ran a correlation, again, by linear regression of CSF heparan sulfate and serum heparan sulfate. And there was a relationship between those two values.

And so we wondered about a couple of different potential hypotheses. The most likely hypothesis that we thought was that the intravenous enzyme replacement therapy was crossing into the blood-brain barrier, entering the brain in some small amount, but enough to potentially lower heparan sulfate in the brain. And that was maybe why CSF heparan sulfate was going down.

The other thought was could there be some interesting science where CSF heparan sulfate might not reflect brain, and maybe that CSF heparan sulfate that we're seeing, some reflecting what is happening in the bloodstream.

And so we designed a experiment to potentially test this hypothesis. For this we turned to a methodology that Mark Sands' lab had developed in evaluating membrane-tethered enzymes as a way to restrict cross-correction when doing different experiments.

So here he took galactocerebrosidase, the enzyme that is deficient in the lysosomal disease, CRAB-A disease, or globoid cell leukodystrophy. And he transfected cells with lentiviral GALC, or the lentiviral GALC which is tethered to the lysosomal membrane using the transmembrane domain of lysosomal-associated membrane protein 1 or LAMP1.

So he first showed that doing this doesn't reduce or destroy the activity of the GALC. When you express this construct in the cells the intracellular activities is excellent. But then he looked at the media, the secreted media, and showed that the cells that are transfected with the membrane-tethered GALC did not secrete that GALC into the media. So the tether was working to keep that enzyme into the cells. It was enzymatically active against substrate, as shown by psychosine levels being reduced in both the GALC and the GALC LAMP-treated cells.

So at this point we were working in the MPS Sanfilippo B syndrome, or MPS IIIB. And the enzyme deficient in that is NAGLU. So we generated a membrane-tethered NAGLU using Mark Sands' construct approach with the transmembrane domain of LAMP1.

We transfected cells with the lentiviral NAGLU-LAMP1, and showed, again, that the same thing, you see intracellular enzyme but no secretion into media. We also looked at beta-hexosaminidase, which is a marker of lysosomal storage. It's elevated in the cells just to show that we think it's enzymatically active against substrate in the cells.

So then we looked at a way to deliver this to the MPS IIIB mice in a way that would treat the body and not the brain. So the AAV7 has been shown by others, when you give it intravenously, to treat the body but does not reach the brain, does not cross the blood-brain barrier, as you can see by this PET scan in mice and also by this graph looking at the vector copy numbers in the brain with the different viruses administered intravenously.

So we dosed Sanfilippo B mice with the intravenous AAV7 NAGLU-LAMP1 [inaudible 00:08:27] with a ubiquitous promoter. And then compared to untreated affected and carrier mice. We injected them by tail vein at four weeks of age and studied them at eight weeks of age.

And so you can see from the graph on the left that there is no NAGLU activity in the brain. There is good NAGLU activity in the systemic organs, so liver, heart. And no NAGLU activity in the serum, which we expect because the NAGLU doesn't get secreted when it's tethered to the lysosomal membrane.

We did the beta-hexosaminidase activity. Again, showing, it looks like, no treatment effect in the brain, but treatment effect in the other organs.

Then we sent serum CSF and brain samples to the UCSD GlycoAnalytics Core to measure total heparan sulfate by mass spec. And on the left you can see the serum levels of heparan sulfate in the carrier mice, the untreated affected mice, and the mice treated with the AAV7 NAGLU-LAMP. Showing that this treatment to the body reduced the serum heparan sulfate. However, the CSF heparan sulfate was not decreased in those mice despite the serum heparan sulfate going down. And as you can see also, the brain heparan sulfate was not reduced with the AAV7 NAGLU-LAMP treatment.

Next we wanted to see if it was possible to treat the brain and not the body. This was a little bit more challenging because, as Dr. Muenzer explained, anything you put into the CSF is going to enter the brain, is going to get out into the systemic circulation because of normal CSF turnover.

So for this we used the AAV9 viral vector, which we know will transduce brain very nicely, but we used a synapsin-1 promoter so that it would only express the transgene in neurons. We delivered it intra cerebral ventricularly to try to minimize exposure to the bloodstream and systemic circulation. And we treated the neonatal mice, so that we could try to maximize the distribution throughout the brain from that single injection point. So we treated the mice at postnatal day one or two, studied them at four weeks of age.

Shown here is the NAGLU enzyme activity showing that we were able to successfully confine the NAGLU activity to the brain. We did not see any NAGLU activity in the liver, heart, kidney, and importantly in the serum.

We did immunofluorescence to confirm that we had good distribution through the brain and that we were expressing the NAGLU in neurons. So shown here on the left is a coronal hemisection of mouse brain neocortex, showing the green as the NAGLU showing very good widespread distribution of this throughout the brain regions. And on the right here, this is a colocalization of NAGLU with neuN, [inaudible] nuclei. We did not see colocalization with microglia or astrocytes in these samples.

Again, we sent brain CSF and serum to the UCSD GlycoAnalytics Core for of heparan sulfate by mass spec. And in brain, as expected, we saw a reduction to carrier levels of heparan sulfate in the mice that were treated with the AAV9 synapsin-1 NAGLU-LAMP-I. In CSF we also saw a dramatic reduction in heparan sulfate in the treated mice, and there was no reduction in heparan sulfate in serum of these mice that were not... where the NAGLU-LAMP did not reach the bloodstream [inaudible 00:12:27].

So in summary with intravenous AAV NAGLU-LAMP-I, this was delivered systemically with a vector that does not cross the blood-brain barrier. We saw NAGLU activity in heart, liver, kidney and not serum or brain. And heparan sulfate was observed to be reduced in serum but not in CSF or brain.

With the intracerebroventricular AAV9 synapsin-I NAGLU-LAMP-I, this was delivered to the brain and expressed in neurons. We saw NAGLU-LAMP activity in the brain, but not the liver, heart, kidney or serum. Heparan sulfate of these mice was reduced in brain and CSF but not serum.

And thanks to the many people who did this experiment in our labs.

Susan Winckler: I'll just note that you continue our on-time performance of our speakers, no pressure Dr. Ellinwood. And, Dr. Dickson, we will see you again for the panel discussion after the next five speakers.

So Dr. Ellinwood, you are next up. And you are joining us as the Chief Scientific Officer with the National MPS Society. I'm going to step out of the way so that you can jump into your slides.

Dr. Matthew Ellinwood: Great, thank you. I'm very pleased to be here. I'd like to thank the Reagan-Udall Foundation for the opportunity to speak to you.

I am a comparative medical geneticist. I've been working in the field for a quarter of century, even though I'm now at the National MPS Society. That was after nearly a 20-year academic career working primarily on large animal models of these disorders.

These are my disclosures.

So there's an tremendous need for preclinical models for MPS IIIB and other Sanfilippo syndromes. That's been elucidated by our guests, and I won't spend too much time on it.

I did have an interesting conversation with a colleague who said, "SMA was able to get to an approval. How come Sanfilippo can't?" It is 10 times less frequent. It has a slowly or moderately progressive disease, with a difficult readout compared to neuromuscular events. All of these impact the ability for us to get to an easy approval.

In this context, large animal models become important. We don't do dog studies lightly and I think there is a strong ethical need to do so. And that prompted us to work in these disorders.

Dr. Muenzer, my colleague, talked to you about the diversity of neuropathic MPSs. There are seven large animal models of neuropathic MPSs in multiple species, or seven species. These are seven different loci, seven different species, two classes of enzymes, seven different kinds of non-reducing ends. All of them store heparan sulfate intra-lysosomally in the brain. They are all fatal neuropathological conditions. This has been proven as a biomarker of fatal neurodegenerative disease with the support of 640 million years of evolutionary time that separates us from avians.

Canine models of MPS III are all similar. Even though it's adult onset, it's a severe canine disease. They all suffer and have a fatal cerebellar ataxia. And the MPS IIIB model has been characterized both at the molecular and pathological level.

The clinical signs we see in the dogs, which begin at 24 months of age, are a wide stepping gait, hypermetria, truncal swaying, moving can start any time, a postural instability. They literally cannot stand, shake their head at the same time.

They also have an interesting reflex, when you hold their heads vertically they can't right it normally. They continue to fall to the ground at the end stages of disease. And we've used that reflex quantitatively to help prove therapy. You will see cerebellar rebound right here.

When we look at end stage, we see pronounced storage in neurons, a pronounced microgliosis and astrocytosis. And importantly, you will see that little structure at the base of the brain, the cerebellum is remarkably atrophied. And those folds of the cerebellum, they become so atrophied that cerebrospinal fluid can be imaged within them.

I'll talk about a study that is in support of a program at Allievex. The compound is called AX 250. It began as BN 250. It is now tralesinidase alfa. This is a prevention treatment model, dogs started with intraventricular or intracisternal infusions at approximately five months of age. They went out for 42 infusions every two weeks up to about 24 months of age. And the results were astounding.

This shows you the brain tissue GAGs as a result of the treatment dose, it was either vehicle 12 milligrams or 48 milligrams of the compound. We see normalization using the disaccharide heparan sulfate method as well as the non-reducing end method at 48 milligrams.

When we look at the CSF, we see the same result. Incredibly striking normalization using the NRE method specific for MPS IIIB. And not surprisingly, as Maria had shown, because this assay is validated we get virtually perfect correlations of these, with our values approaching 9.09 or 0.9.

We see over time a decrease in CSF heparan sulfate and non-reducing ends throughout the study, with near normalization at 48 milligrams within the first couple of administrations. We see improvements in staining for lysosomal volume using LAMP1, which is a marker for lysosomal membranes, in three regions in the brain, in the hippocampus cortex and cerebellum, with significant normalization in the cortex and cerebellum.

We see decreased neuroinflammation as noted in microglial activation in the cerebellum, and we also see a decrease in pathological astrocytosis.

Importantly, though, we need to be able to prevent the atrophy we see in this model. In the central panel is a T2-weighted image, and you can see the brighter images within those folds of the cerebellum. That's CSF. We can quantitate that and use it as an inverse proxy of atrophy.

And when we do that throughout the study, starting at about 12 months up to the end of the study, we see the affected animals, untreated animals, have a high level of CSF in the cerebellum indicating atrophy. And at the highest dose of 48 milligrams, we see virtually no atrophy compared to the normal animals.

And we can see this at the end of the study, a significant decrease between the untreated affected and the animals at 48 milligrams. And we also see a very striking correlation between the cerebellar volumes and the NREs in the cerebrospinal fluid.

It's important though to quantify this atrophy, and so we did a kinematic study evaluating that head bob effect. And we saw a difference in maximum angular velocity. The affected animals heads drop more slowly, because they have less control. You see the vehicle treated affected animals, very big difference. Whereas in the animals dosed at 12 and 48 milligrams, they were equivalent to the normal untreated animals.

We also wanted to evaluate behavior. We did this in something called a T-test reversal, where animals are taught a task and then asked to reverse that task. And it's based on baited rooms that they can go into on different sides of a T-arm. All arms are baited they just only have access to one, because dogs are very clever and they can smell, so we need to make sure we take care of that.

From sessions one to five the normal animals learn the task. And they did so in a statistical way. The affected animals that were treated with vehicle, they could not learn the task. And the animals that were treated with 12 and 48 milligrams of a drug performed equivalently to the normal unaffected animals.

So this is what we've been able to do in the largest and longest large animal study for a neuropathic MPS disorder. But this story is not isolated just to canine MPS IIIB, this has been replicated in other situations, including the MPS II mouse, the MPS IIIA mouse, involving four different enzymatic therapies. This is not under dispute, brain-targeted enzyme will decrease brain heparan sulfate, and we are able to measure that quantitatively in the cerebral spinal fluid. All of these images correlate brain tissue and cerebrospinal fluid heparan sulfate, and you can see near perfect correlation of these.

So in conclusion, comparative biology and 640 years of evolutionary biology confirm that heparan sulfate is the proximal and inciting cause of neuropathology in these seven disorders. That is not in dispute. And I think we've shown, using multiple modalities in a large animal model, that we can see improved tissue pathology, decreased neuroinflammation, prevention of CNS atrophy, and improved behavior.

And with that I end under time. Mark your calendars, I've never done this before. Thank you.

Susan Winckler: Dr. Ellinwood, thank you so much. We will see you later for the question and answer session.

So for our final rapid fire presentation, when we want to speak to animal models and what we are learning here, we're going to turn to Dr. Nidal Boulos. Sorry, Dr. Boulos, I was practicing and failed there.

But Dr. Boulos is the Director of Clinical Outcomes Research at Regenxbio, with a primary responsibility of managing outcomes that support translational medicine and biomarkers.

Take it away.

Dr. Nidal Boulos: Thank you. I'd like to start by thanking the Reagan-Udall Foundation for this workshop, and for the opportunity for me to be here today to present to you.

Okay, there we go. So what I'd like to do today is take you through the journey of bringing RGX-121 gene therapy as a candidate for the treatment of neuronopathic MPS II.

So RGX-121 is an AAV9 vector-based product that is designed to deliver a functioning copy of the IDS gene into the CNS, with a potential to restore I2S enzyme activity. An I2S enzyme is the enzyme that is missing in MPS II patients.

RGX-121 is currently being investigated in a clinical trial. We just completed enrollment in our pivotal study. And it is a one-time injection into the CNS that is designed to address the unmet need of CNS disease involvement in neuronopathic MPS II patients.

So the safety and the scientific rationale for RGX-121 were studied comprehensively in a biologically relevant mouse model of MPS II. RGX-121 was administered into the CSF via intracerebral ventricular injection into the mice.

And what you're seeing here are three cohorts of mice. You have wild-type mice, untreated MPS II mice, and MPS II mice that have been treated with RGX-121.

So when we looked at CNS I2S activity, we see that we are able to detect CNS I2S activity in the MPS II mice that have been treated with RGX-121 compared to the wild-type mice.

So then we then looked at GAG storage in these tissues. We looked at 12 regions of the brain and the spinal cord. And as you can see, the untreated MPS II mice store high levels of CNS GAG in all of the tissues. And we see a significant reduction in these GAG storage in the MPS II treated mice. And those levels are not significantly different than the levels in wild-type mice.

So we then looked at neurobehavioral assessment in these mice using the Barnes maze tool. The Barnes maze tool is a measure of spatial learning and memory in these mice. What you're seeing here is the average time that it takes the mice to escape a circular platform. It's measured over six consecutive days. And the concept is that the mice will get better at escaping the platform with every day as they become familiar with that platform.

And you can see that MPS II treated mice get better with every day at escaping the platform. Similarly, we see that with the wild-type mice. However, if you look at the untreated MPS II mice, you see that they do not get better between days three and six.

Although RGX-121 is administered into the CNS, we see that it does cross the blood-brain barrier and shows a systemic effect. So what we're seeing here is tissue GAGs from various tissues and organs within these mice. You can see high levels of GAGs that are stored in untreated MPS II mice. These are significantly reduced in mice that have been treated with RGX-121, and those levels are very similar to levels that are seen in wild-type mice.

Untreated MPS II mice also excrete large volumes of GAG in the urine. Again, we see normalization of urine excretion in treated MPS II mice, and these levels are very similar to levels that are seen in wild-type mice.

So we've heard earlier from Dr. Muenzer that neuronopathic forms of MPS II, they exhibit elevated levels of heparan sulfate. And this table here summarizes the various types of MPS. And you can see that those that manifest with neurologic symptoms do show heparan sulfate as the main GAG that is stored, so heparan sulfate is a key biomarker in neuronopathic MPS types.

So heparan sulfate is a long polysaccharide chain. In MPS II disease the absence of the I2S enzymes leads to accumulation of the sulfated end. And we've heard from Dr. Fuller earlier about the various methods to measure heparan sulfate.

So these 2-sulfated ends accumulate on the non-reducing terminals of the heparan sulfate chain. In our study we used the enzymatic digestion method to break down this heparan sulfate further into its basic subunits, which are the disaccharide subunits. We developed and validated a bioanalytical method that measures these specific disaccharides. And you can see here the various disaccharides that can form. I do want to point to D2S6, because it has that 2-sulfate that is specific for activity of the I2S enzyme.

This is a preclinical model that was published by another group, and where they tested a number of various treatment modalities in MPS II mice. Again, you can see that in MPS II mice there is high levels of heparan sulfate in the brain that accumulates. These levels normalize with their vector therapy that is targeted to enter the brain. In this study they also measured various disaccharides of heparan sulfate. And I do want to point out, again in red there, D2S6.

So what they have shown when looking at the percent contribution of each of those disaccharides, the total heparan sulfate, you see that there are about 31% of total heparan sulfate in the brain comes from heparan sulfate D2S6. Heparan sulfate D2S6 was also the disaccharide that was most responsive to treatment. And then these reductions in heparan sulfate D2S6 associated with corrections and disease parameters that include neuroinflammation and astrocytosis. And we also saw normalization in neurocognitive behavior in these mice.

What I'd like to do for the next part of this presentation is really walk you through how we took these preclinical findings and translated them to a human application. During our RRGX-121 clinical development program, we were able to access a human CSF from neuronopathic MPS II patients, from attenuated MPS II patients, and we were also able to access CSF from healthy individuals. We used our bioanalytically validated method to measure specific disaccharides within the heparan sulfate chain.

And the graph there shows you the specific, the four disaccharides that we measure, and the contribution of each of those disaccharides to total heparan sulfate within the CSF.

And you can see again there highlighted in red, that when we look at the percent contribution of each of those disaccharides to total heparan sulfate, we see that about 30% of total heparan sulfate is made in the neuronopathic MPS II patients comes from heparan sulfate D2S6. And that's higher than what we see in attenuated and in normal. You also see that heparan sulfate D2S6 was elevated in neuronopathic MPS II compared to normal attenuated MPS II.

So when we look at the concentration levels of total heparan sulfate in the CSF samples, we, as expected, see that there are increasingly high levels of total heparan sulfate in neuronopathic samples when compared to attenuated and when compared to normal.

However, when we specifically look at heparan sulfate D2S6, not only do we see that those levels are really high in neuronopathic CSF samples, we also see that those levels distinguish between phenotypes, between attenuated and between neuronopathic phenotypes. So heparan sulfate D2S6 is reflective of disease pathology and can distinguish between disease phenotypes.

So as part of our RGX-121 clinical trial, we are using heparan sulfate D2S6 as a surrogate endpoint that is reasonably likely to predict clinical benefit in neuronopathic MPS II.

And the reason for that is we're tracking it more closely because it makes sense for our trial, it makes sense for MPS II. We know that it has the 2-sulfate on the non-reducing end, that is very specific for the I2S enzyme. We've shown that it correlates with total heparan sulfate, and preclinical mouse models have shown that it correlates with other disease parameters.

And the graph on the right shows data from our pivotal trial. So we see very early responses in heparan sulfate D2S6, as early as week 16 post-treatment in neuronopathic MPS II patients. Majority of these patients at week 16 have levels of heparan sulfate D2S6 that are below the maximum level that is seen in attenuated patients. And we have a number of patients that have shown normalized levels within heparan sulfate D2S6.

So to summarize, heparan sulfate is a surrogate endpoint that is reasonably likely to predict clinical benefit. HS accumulation results from a missing enzyme, so it is a mechanistic tie there. Heparan sulfate is the metabolite that causes disease pathology in neuronopathic MPS. And heparan sulfate D2S6 disaccharide in the CSF is reflective of disease pathology, and shows distinct concentration levels that differentiate between neuronopathic and non-neuronopathic MPS II.

So disease models that reflect aspects of clinical pathology, gene therapy that expresses a missing enzyme have been successful in restoring enzyme activity in relevant tissues. This restoration of enzyme activity has associated with normalization of the pathologic substrate, which in this case is heparan sulfate GAG. And we also see improved neurocognitive performance in mice as assessed by behavioral therapy. So in translating RGX-121 to the treatment of children with neuropathic MPS II, we have validated and developed an accurate and a validated method to measure CSF heparan sulfate D2S6. We have shown significant reductions in heparin sulfate D2S6 in the CSF with levels approaching normal in the pivotal study. Therefore, accurate and sensitive measurements of CSF heparan sulfate, including heparan sulfate D2S6 do have the potential to be considered as surrogate endpoints that are reasonably likely to predict clinical

benefits. And I'll stop here and thank you for listening.

Case Study: Relationship Between Cerebrospinal HS Levels and Clinical Outcomes

Simon Jones, MBChB, Consultant, Paediatric Inherited Metabolic Diseases, St. Mary's Hospital
Heather Lau, MD, MS, Executive Director, Global Clinical Development, Ultragenyx
Eric Zanelli, PhD, Co-Founder, Allievex

Susan Winckler: But let's move now to just recapping, right? We learned about MPS, we learned about measuring heparan sulfate, we just talked through the animal model component, and now we want to focus on the relationship between cerebral spinal heparan sulfate levels and clinical outcomes. I'll note there are a number of questions about this in the chat that I'm confident are going to be answered with these presentations.

So for our first speaker, we will welcome Simon Jones, who serves as a consultant in pediatric inherited metabolic diseases at the Willink Unit in genomic medicine at Saint Mary's Hospital in Manchester, in the UK. In addition to being a consultant, Dr. Simon is a professor and a medical director at the National Institute for Health Research. And Dr. Jones, I will call you Dr. Jones instead of Dr. Simon, at least this time. So Dr. Jones, take it away.

Simon Jones: Thank you very much. It is great to be here. Thank you for inviting a non US person, as well as Dr. Fuller, of course. So yeah, it's great to be here. And I'm going to try and talk about the experience that we've had in Manchester where we've been looking after patients with MPS II and III for many decades now. And I've been personally involved in both clinical care and research of these patients for the last 18 years. And we've had a real interest in trying to solve some of the problems of Sanfilippo, and I'll talk about our successes and failures, perhaps more failures than successes. So I'll try and be honest here.

We have one of the largest clinics for MPS children in Europe, and we do a lot of early phase trials. So I have put a question mark at the end of that title, but hopefully we'll answer it, and this is being answered as the day goes on. So I'm going to start with a graph that you've seen before. This is the famous Elsa Shapiro's MPS IIIA Natural History Study, looking at development... This is the violent and adaptive behavior scale looking at the development of children with MPS IIIA. So of course, all of these children entered a natural history study, did not get treatment. So when we talk about sacrifice, we hear about these parents subjected or allowed their children to have lumbar punctures multiple times over a two-year period, as well as all of the very detailed assessments.

The first thing when we think about and we look at this graph, you see children developing initially in the normal range, then plateauing and then decreasing. So losing skills, and we've heard this repeatedly in descriptions of this disease. The first thing we see from a clinical trial perspective is what you want in your trial population is homogeneity. They've all got to be the same. And so those lined in blue are all of the slowly progressing children. So they start at a higher level, so

they gain more skills and then they decline much more slowly. So they should be much better treatment candidates, okay? Much greater window for intervention.

But what you see from this graph is they're very heterogeneous. They each follow their own path. So, I'm sorry, from a clinical trial perspective, they're out already. So we've got a rare disease population that's already shrunk because they're not homogeneous enough, and our best patients have already been excluded. So we look at this classical or rapidly progressive phenotype here, and we see that whilst it's more homogeneous, actually there's a fair bit of variation, especially at some certain ages that, and we heard earlier about the typical diagnostic age of these children being between about three and five years of age, where actually if you look here, this is months along the bottom, that's where the significant heterogeneity is, even in this classic or rapidly progressive phenotype.

So we're thinking about our perfect MPS IIIA trial, and being in a unit that has been trying to develop a therapy for this disease for, as I said, maybe nearly 20 years now, we did sit down and think, "What was the perfect MPS IIIA trial? What would we do?" Well, it made some sense to start treatment early, so under the age of two because they're still in the normal developmental curve. So if we want to get a really ideal top result, you'd treat them really, really early while their development is normal. And then what you've just got to show is that you keep it normal. So that makes sense from lots of perspectives.

And we also thought about, "Well, what about later treatment?" So the advantage of later treatment than earlier treatment is that, well, the later treatment is where the patients are. This is where they are when they're being diagnosed. So if you want the prevalent patients, you want to be able to open your trial and recruit it all at once, then you take this group. And this group are actually as likely to respond and benefit as this group. The problem is determining what a response is and measuring that response.

If we treat kids in normal neurodevelopment and follow them for many, many years, and they're still in normal neurodevelopment and you've probably got a good treatment outcome, if you take children in this messy, difficult, symptomatic age, they may well show dramatic benefit because, remember, they're not declining yet. If you could stop them declining, then you could achieve dramatic benefit. But how you measure that benefit is profoundly difficult because what we're talking about is modification of a vector, and there are multiple competing vectors, the progression of the disease, the advancement of normal development, and the treatment effect.

So what that looks like, what a good result, what success is in that age group is actually really difficult to pin down and no one's been able to quite define it in advance, which, as you will all know from clinical trials, is somewhat difficult. If you don't know what you're aiming for, how do you measure it? And our testing of neurocognitive outcomes is very good, very accurate, but the main

manifestation of the patient in this group is behavior. That's what my patients tell me in clinic. "How the hell do we manage the behavioral aspects?" And we've almost no good way that I can see of measuring that aspect. And so we're stuck with this important yet difficult in terms of a clinical trial outcome.

So the real challenge of going early, well, one of the real challenges is that, actually, it's really hard to find patients. So yes, we've done a trial like this, but we estimated looking back on our lab's diagnosis of MPS IIIA under the age of two. We looked back on 15 years of that diagnosis and only 10% of patients were picked up in that age group, sometimes because of an older sibling, sometimes just dumb luck really. I'm a clinician. I can say that. Yeah, we rely sometimes on dumb luck. So it's really difficult to find patients.

But the other challenge here is that if we treat at the age of one or 18 months, how long does it take before these patients clearly diverge from the natural history of the disease? Well, you're talking that they need to be five or six years to be clearly different from those natural history populations, and that's pretty challenging. I have to say, having run trials that are not like this and run trials that are like this on an academic grant or even with commercial funding, it's very, very difficult to do this, almost impossible. So we've got a real challenge here with clinical trials.

I want to talk about a tale of three trials that I was a PI in. First of all, a commercial trial. We've heard these mentioned before with intrathecal enzyme replacement therapy, no longer continued. A trial we did as an academic unit of a nutraceutical that was being used by the majority of MPS III families worldwide, and then an ongoing academic/commercial trial of gene therapy at the moment. And I think Joe mentioned this trial earlier on. There were similar trials from Shire looking at intrathecal enzyme administration in both MPS II and MPS IIIA, mostly starting at around the same kind of time.

This is from one of our posters at the time showing a really dramatic reduction in CSF heparan sulfate. And as Joe mentioned, this was nearly 15 years ago when this trial started. And so the early CSF markers, or the early CSF GAG marker or heparan sulfate, as we say it is, was based on a relatively poor methodology and so suggested that we had almost complete clearance of those CSF GAGs. And so this made it really difficult to choose the correct dose. So we treated patients in Manchester for six years on this study every month.

Looking back at the re-analysis of those CSF samples with the more modern techniques that Maria Fuller described to us, actually the CSF reduction in heparan sulfate reduction in MPS IIIA was 40 to 60%, in MPS II less than that. And the doses that we're using 45 to 90 milligrams once a month and even less than that in MPS II, when we compare those with the approved enzyme replacement therapy for CLN2 where we give 300 milligrams of enzyme every other week to the ventricles, well, we were probably one or two logs out, actually, in the dosing. And that's not a criticism of the work at the time. This was pioneering work that had never been tried before. But this led to a

discontinuation of this program despite the fact that almost certainly patients have benefited. I still follow them up, these patients, eight or nine years after the study stopped. So, difficult.

This is an example of a relatively poor old-fashioned CSF heparan sulfate assay that led to wrong dosing decisions that led to a study failing. Another study, this one an academic study. This compound, genistein. It's a soy derivative, and there was some nice work in patient fibroblasts and in our animal model of MPS IIIA and B showing that this reduced heparan sulfate. And so because of this, and because this was available over the internet, about half the patients in the world were taking it. Some of them are spending really quite large amounts of money. And so we tried to run an academic trial to answer the question of whether this actually worked or not and whether this was meaningful. And we got all of our funding from the patient organizations, the UK and the National MPS Societies. And because we ran this study in the UK, we spoke... Am I allowed to say this? We spoke to the MHRA, who are the UK regulator, and we came to them and said, "Look, this is really difficult. We've only got so much funding. We've got a window of opportunity to do this study."

And so there were already some other trials recruited in the very young patients, and so what we were left with recruited onto the study was the prevalent patients, most of whom were already near the floor of most of those neurocognitive tests. So we knew, and because we could only afford to run this study for one or two years, we knew that we couldn't use in those patients a neurocognitive outcome measure. We had to use something else. And so we went to the MHRA and said, "Look, the CSF heparan sulfate is the only thing we can use that will actually give us a readout. Would you accept us using this as a primary endpoint in a phase three trial?" And they said yes, and we were surprised that they said yes, but they said yes on the grounds that, actually, if they stopped...

This was the only way to run a study. If we didn't run the study, we hadn't kept people safe because people were already taking this drug. So simply preventing us from doing the trial didn't keep patients any safer. So it was actually safer to run the trial, and so we did. We recruited 20 patients with MPS III, and what we could see was with this drug, we only reduced the CSF heparan sulfate by five percent 5.5%. This was a more modern CSF HS method that is reliable. And whilst we did a whole pile of neurocognitive and behavioral and other outcome measures, we knew that they were not going to, in the short time period, in these quite advanced patients, tell us what we needed to know.

But the fact that we could only lower the CSF HS by this amount made us feel very confident to say, "Okay, this hasn't worked. This is important. A negative result. We've been able to show that this treatment doesn't make enough of a difference to have a clinically meaningful effect on these children." And so we were able to, I hope, draw a line under this at this point. It only took us 10 years to do this study, draw a line under it and move on because I think it's important

to, if you've not got an effective treatment, to fail fast, realize you're not working, and move on to the next thing. So we moved on to the next thing.

Here's our current trial. It's an MPS IIIA lentiviral stem cell gene therapy study. So this is similar to the lenti ex vivo stem cell gene therapies for metachromatic leukodystrophy and for X-linked adrenoleukodystrophy. We take stem cells from a patient, we modify them in the lab, put the gene back in, and over expressing that gene. So we make 100 to 1,000 times more enzyme than with an allogeneic transplant. And so we see in this study, we have five patients all recruited under the age of two, and we follow them up for three years now that we've got a dramatic reduction almost to the lower limit of detection of CSF heparan sulfate, and we've been following these kids for three years now, but we had to treat them so young. And this is what the issues were that I was trying to highlight earlier.

Although we've got four out of five children here developing within the normal range, we're still only seeing just about separation from the natural history of this disease. To be really clear, we'd need another one or two years, maybe more. And we've been in this study four or five months from bankruptcy the whole way through, and we've seen many biotechs be in exactly the same scenario. So this kind of study, whilst maybe giving you the purest answer in the long run is almost impossible for us to do. I will summarize.

Susan Winckler: I know you will.

Simon Jones: So I hope I've shown you, as all of our other speakers have, that the trial design and choice of trial design is incredibly challenging due to the natural history and the nature of the outcome measures we have to use in neuronopathic MPS disorders. And I would suggest that the perfect or the purest study of early treatment with a very long followup, plus a placebo group with large numbers, is financially impossible and ethically entirely inappropriate.

So we have to find a different way. We cannot keep failing, as I have done multiple times in this disease, for these patients. CSF heparan sulfate can be closely linked to cognitive benefit. Of course, you have to have caveats to that, thinking about the age of treatment. But if we are to have actual therapies for neuronopathic MPS disorders, I think we must approach clinical trials very differently to how we currently do. Thank you.

Susan Winckler: I'll take that is your last moment. Thank you. And thank you, Dr. Jones. You owe the other two speakers two minutes. Next up we have Dr. Eric Zanelli, who co-founded Allievex Corporation and was its head of research for the last five years. Dr. Zanelli, would you take us on our next step in this tour?

Dr. Eric Zanelli: Sure. Well, first of all, thank you for the foundation for inviting me today. I'm going to talk to you about the efficacy of tralesinidase alfa, also known as AX 250, for the treatment of MPS IIIB, and I'm going to talk to you about the

importance of heparan sulfate as a predictor of clinical efficacy. So actually, I'm not even sure I have much to add from all the great presentation we heard until now, especially thank you, Dr. Jones, for your presentation because I'm pretty much going to say the same thing in a different way.

So just to remind you, actually, Dr. Ellinwood already talked to you about AX 250 and dog data that we published some years ago. Just as a reminder, AX 250 is a trimer fusion protein made of recombinant human NAGLU fused with a truncated version of IGF2. So this protein is capable of entering the cells through the mannose 6-phosphate receptor, and the compound is delivered by ICV administrations once a week at 300 milligrams per dose.

So this is an overview of our clinical development, which by the way, started back in 2016. So some of its subjects have been treated now for eight years. So we have first a natural history study. It was called 250-901, where subjects were observed for about one year. Most of the subjects ended up in our interventional study, 250-201, and they were treated for another year. And then eventually there was an extensions for 240 weeks, which means, again, that in some cases, some of these children have been treated by now for more than six years. We also had escalation dose arms called 250 part I where these subjects were treated with 30, 100, or 300 milligrams of AX 250 weekly.

So I'm going to talk to you about cognition as a primary endpoint because it's an endpoint that has been approved by the agency as a primary endpoint in our confirmatory studies. We also talk a little bit about the adaptive behavior using the Vineland Scales. And in terms of surrogate markers, I will talk to you about cortical gray matter volumes and CSF and plasma HS-NRE as measured by an LC-MS-MS method, which are, again, as mentioned several times already during the day. The way we are measuring these heparan sulfate are disease specific.

So this first data slide is to demonstrate to you what we call in drug development to target engagement, because what happened is that you have children who have abnormal level of heparan sulfate both in the CSF and plasma at baseline. We treat those children for three, four weeks, and within three, four weeks, we normalize the heparan sulfate in both CSF and plasma. And as you can see on these slides, in some cases we have been sustaining normalization of heparan sulfate for more than five years.

The reason that we know that it is the normalization of heparan sulfate is due to the treatment and nothing else is for two reasons. Number one, as you can see in red, we have some children who did not receive treatment for various reasons, and these children did not normalize heparan sulfate, and we have also the case of one particular subject who had the device. The reservoir was removed for a few months because of technical issues. And during the time that the treatment was interrupted, you can see that the heparan sulfate level went above normal again, and as soon as we started the treatment, we re-normalized heparan sulfate. So there's clearly a target engagement, and the normalization of heparan sulfate is due to AX 250 and nothing else.

So here on this slide we are shifting a little bit here. We're talking about cortical gray matter volumes. We and others have shown in the past and publish that in all the brain regions, the cortical gray matter volume is particularly affected very early in the children with MPS IIIB. So the natural history of the disease I've shown on the left with the gray dot is that in a normal disease development, past the age of eight or nine at the latest, children with the most aggressive forms of MPS IIIB will have cortical gray matter volume below normal development. And on average, it happens around the age of five.

As a strong contrast, when we treat these children with AX 250, what you can see is an initial drop in the cortical gray matter volumes, which we believe result from the eliminations of the heparan sulfate that has been accumulating for years in the brain of these children. So there's an initial drop, but past this drop, there is stabilizations of cortical gray volume. Even in some cases, the cortical gray matter volumes rebounds and the volume actually increase. And what is remarkable is that, in particular, we have five children who have been treated for more than six years, and by now these children are at the age of 10 or 12 years of age, and they still have normal cortical gray matter volumes.

On the right, what you see is a very strong, very significant correlation between the change in cortical gray matter volumes over treatment and the cognitive age equivalence scores at the last visit, meaning that the protections, the preservation of cortical gray matter volumes predict cognitive efficacy in these children. So here on this slide, as has been mentioned several times today, obviously everybody knows that when you look at cognitions, you need to treat early to maximize clinical efficacy.

So in this particular slide, we have 22 children that have been treated in our clinical trials. I'm just showing you the data for eight of these children, because these eight particular subjects had all of them normal cortical gray matter volumes at the time of treatment initiations. And what you can see on the left is the gray dots is a natural history of the disease. So what we know in MPS IIIB is that, on average, children with MPS IIIB achieve an age equivalent scores of about 24 months at the age of four. And after that, in most cases, the cognitions decline.

What you can see here is that the children that were treated with AX 250, some of them for more than six years, have a positive change in cortical in cognitions. They definitely are at minimum stable, and in some cases definitely improving. And obviously, one child we always stuck in particular is what we call 9006, who has been our champion. 9006 started the treatment when she was two years of age. By now, I believe she must be eight and a half. She more or less has a normal cognitive development, which is obviously totally unexpected for children with MPS IIIB.

On the right, you can see that there is a correlation between the AQ cognitive scores and the average level of HS-NRE, or heparan sulfate in the CSF. So again, as you will expect, the children who are doing the best are the ones who have

normalized heparan sulfate, and on the extreme right to see these particular children, 9002, 9022, has been doing very poorly, who actually withdrew from the study years ago because, for various reasons, she was not treated with the compounds. And clearly, this child had very abnormal level of heparan sulfate.

So again, we've been talking a lot about cognitions because, clearly, the FDA has recognized cognition as a primary endpoint. I think what you heard this morning several times is that cognition is obviously only one aspect of the disease. I mean, the parents, the caregivers are always telling us that they are looking at a lot of other things than improvement in cognitions. Improvement in quality of life, improvement in sleep patterns, improvement in the way these kids are communicating.

So in this particular case, I'm showing you one example, which is one particular subdomain called self-caring within the Vineland Scale. And what you can see on the left is that the children who have been treated with AX 250 for at least three years, are doing a lot better in terms of adaptive behavioral and self-caring than natural history children. And what you can see on the right is that in terms of biomarkers, if you combine CSF HS-NRE with change in cortical gray matter volumes, what this figure is telling you is that the six children who are doing a lot better than expected from natural history are the six children who have both normalizations of CSF heparan sulfate and preservations of brain volume.

So here I believe is my last slide, which is a summary of what you heard today, is that, again, if cognitions is the only acceptable primary endpoint by the FDA, we will have to treat only children very early on, at latest at three years of age, to be able to demonstrate cognitive benefits because obviously once children's have lost cortical gray matter volumes, it's going to be very difficult to prove benefit with AX 250 or any kind of treatment.

So my last slide is just to remind you that I think when we talk about the [inaudible] marker that is reasonably likely to predict clinical efficacy, we have to keep in mind that the statement depends on age at baseline, preservation of brain volumes, route of administrations, and clinical outcome assessment. We do believe that AX 250 is a great treatment for children with MPS IIIB in other ways than cognitions. And we have plenty of data to demonstrate that these children are improving in terms of quality of life, in terms of sleep patterns, in terms of communications. But the agency has to accept that these clinical outcome assessments are as meaningful as cognitions for the parents and the caregivers. And obviously, I'd like to thank all the patients, their parents, and all the clinical sites around the world that have been involved with this clinical trial for the last eight years. Thank you.

Susan Winckler: Fabulous. Thank you, Dr. Zanelli. All right. To round out what will be our last slide presentation of the day, we will turn now to Dr. Heather Lau, who currently serves as the executive director of Global Clinical Development at Ultragenyx Pharmaceuticals, where she leads teams in developing therapies for

pediatric patients with rare genetic diseases. Dr. Lau, let's turn to your presentation.

Dr. Heather Lau: Thank you. Thank you for inviting me here. In addition to my role in clinical development at Ultragenyx, prior to joining industry, I, in fact, ran the NYU Lysosomal Program for nine plus years, and I was trained under Ed Kolodny. I'm a pediatric neurologist and I've treated every subtype of MPS over the years. So I'm honored to be here to talk about our program in MPS IIIA, and we're showing a reduction of CSF HS exposure and correlating that to clinical outcomes.

So you've seen this earlier by Dr. Jones and others. It's important to understand that this single enzyme defect leading to the deficiency of sulfatase leads to this triphasic course that Hughes explained, and I want to focus in on this positive developmental slope in those first two years where, again, it's hard to differentiate from children who are not affected. And then we start to see that arrest of development starting around 24 months and going into 48 months. Beyond 48 months, we start to see a negative developmental trajectory, and that's regression, heralding loss of skills in all domains, not just cognition, but motor and language as well. And we'll come back to that when we talk about our data.

And again, so we're talking today about CSF HS as a primary disease activity biomarker for neuronopathic MPS. There are other biomarkers that are supportive of this primary marker, and it's important to understand that there is somewhat of a sequence to these events. There was a question earlier posed today about the downstream effects. We know that there's a whole cascade of derangement going on in the south, but it starts with the first, which is HS accumulation within that lysosome, and that goes on to cause secondary storage of gangliosides, and then further injury to neurons. And we can measure that with neurofilament. And then, to start to see the impact on brain volumes, which you heard by my colleagues here today. And in fact, we see a progressive degeneration over time, and those volumes are shrinking. And so, those are sequential, but HS is occurring early in that process. And we're able to measure it in the CSF. So UX111 is designed to target the underlying sulfamidase deficiency. Its expression leads to expression of a functional enzyme to clear that toxic HS. This is an AAV9 in vivo gene therapy, that is administered intravenously. It delivers a full length copy of a functional sulfamidase gene, and this is under the control of a ubiquitous promoter. So we are transducing variety of cell types, not just brain cells.

And we do rely on both direct transduction, as well as cross correction. Again, that is something that we've leveraged in ERT for other therapies. And this therapy is under investigation for children with MPS IIIA. Okay, so our clinical development program, and I will say, we took this over from Abeona and moved forward with this. Our initial trial is a dose escalation open label trial. They had three different doses, but our most recent iteration focused in on a target population. It was a younger population, under two years old, or over two with

a developmental quotient of at least 60 or greater. For those patients, we have now treated 17 patients under that protocol. And what I really just want to show you here is that there is that first 24 month trial, but that rolls into a longer term follow-up. Because of course, we need to understand not only the long-term safety, but the full clinical benefit, not just on cognition, but motor and language and other domains.

And so, as of our last data snapshot, we have treated 28 patients. Of these are the 17 in our mITT and 15 of these 17 patients have it reached at least 30 months of age. Six of 17 have now reached age five or beyond. So we have long-term data. And our mean duration of follow-up was anywhere from 11 to 60 months, with a median duration of 28. And so, as I'm showing with others, we see a rapid reduction in CSF HS within the first month post-administration. We have a further nadir at six months and an overall reduction of 50%, of greater than 50%. And so, looking at the use of secondary biomarkers, this is telling us that the threshold that we've achieved with CSF HS reduction is adequate, because we're starting to see the secondary storage markers come down as well. This is the GM2 and GM3.

And so, that is sufficient to say that we are restoring lysosomal function, that we have had target engagement in the brain, because CSF gangliosides are also coming down. Now, what you saw was a percent change from baseline, but there's another way of quantifying the toxic effects of HS. And that's looking at exposure over time, just like in other disorders, like Phe, Phenylalanine, that you heard today from Dr. Dickson. It's that accumulation of that toxic metabolite that really impacts cognitive and neurodevelopment, and it takes time to see that impact. Today's elevation does not translate to today's cognition. It's accumulation over time. So we are using a time normalized area under the curve to measure our CSF HS exposure. And this uses all available CSF HS levels after treatment and not just that first and last one, to get a sense of the cumulative reduction in exposure. And here, we're starting to see, at a group level, a median exposure reduction of 63.3%, over a followup of two years. And the table below is one patient's calculation of this time normalized area under the curve.

Okay, so let's move to cognition. We have been following these patients now almost through five years and beyond. We are showing that, on this graph, we have our treated patients in green and our natural history, again, leveraging item level data from the Shapiro study in blue. And as others had pointed out, it's really hard to see a treatment effect between zero and 24 months. However, at 24 months and beyond, we start to see a divergence between the treated and untreated. And so, we are seeing either stabilization of cognition or improvement, while the patients in the untreated cohort are declining. By 60 months, we are seeing a statistically significant difference, but it takes years to see this. So when we look at starting from 24 months to 60 months, in our treated group, we're seeing an average of 23 point mean increase in our cognitive raw scores. This is in cognition, so this is pretty significant. But again, it took time to see. This is only one aspect. We are measuring, again, expressive in

a receptive language. You're not seeing that today. And other aspects of the disease are improving.

So now, let's put this together. Is there a correlation between CSF HS reduction and clinical outcomes? And so, what we're showing here is that there is. So the upper left corner is the clustering of our patients. And so, if you had a sufficient reduction of CSF HS exposure and continued gain in cognitive points on the Bayleys, you'd be up in that upper left. So 15 of our 17 patients are simultaneously achieving a CSF HS exposure reduction of greater than 50% and continuing to have a positive estimated yearly change in their cognitive raw scores. They're gaining skills. There are two outliers. Who are those outliers? So I have time, let's go back and show you.

There is one patient in our treated cohort, that is clearly declining, and this patient is actually heralding another issue. What happened here is that the patient had a rebound in their CSF HS. You saw our median levels, there was a little uptick. Some of our patients were developing an immune response. And so, what we see here is, one year prior to the decline in cognition, we started to see the rebound in the CSF HS. That was telling us that there's something wrong. And that led us to look further and find that there was, in fact, an anti-SGSH enzyme response, which is not unheard of in our enzyme replacement therapies. Correct? And so, we saw a loss of biochemical efficacy, preceding the loss of cognitive efficacy, by over a year. So in fact, yes, it's not correlating together up, but this case unfortunately is proving the point.

Our CSF HS is telling us that there's something wrong. We have one other patient who is an outlier. And right now, they're losing early biochemical efficacy again to developing these anti-SGSH antibodies. But the child has not yet declined, and we are intervening. So let me go forward. All right, so the late biomarker, this is my categorization, it's temporarily related a little bit, but thinking about preservation of brain volumes, as you heard my colleagues talk about, it takes years to say that we're stabilizing brain volume. It is a goal, but it's a later goal. We still have to go out to five years to show that we're not declining like the untreated patients in blue. And our patients here are also showing a slight dip and then, a stabilization within the normal healthy control range. And this is sustained, but the data is early, the population is still maturing.

This is males. This is females. And so, I would say that this is reassuring, along with the gangliosides, that our therapy is having a sustained response, and we still have to follow it forward. Our safety profile, just for completeness, we are seeing very mild to moderate elevations in LFTs, which is the class effect of gene therapy in general and only one grade three. So overall, today, in this very quick pace, we showed a correlation between the CSF HS reduction, that primary disease activity marker is rapidly reduced and sustained, and that leads to a correlation to improved cognitive outcomes over the long term. And this is supported by secondary and tertiary markers. And overall, we are showing promising interim results, suggesting a favorable benefit risk profile of our

patients with treatment of UX111. All right, as the last speaker, I'm going to use one second.

Speaker 1: You're fine.

Dr. Heather Lau: Okay, good. So it's been a wonderful day hearing my colleagues, my mentors, and Joe Muenzer, and others in this field really go into and educate the public about neuronopathic MPS. It has been a tall order to go from systemic treatments to crossing that blood-brain barrier. We're starting to do that. And with the advent of validated and high precision assays, we are able to measure HS. And it provides that dynamic range, the specificity and reliability to allow the use of CSF HS as a predictive biomarker, in contrast to those less specific older GAG assays, which I remember as well, because I was trained on those. The changes in CSF HS are dynamic and rapid, and it's telling us that we are achieving our goal. We're achieving and crossing the blood-brain barrier. And as you saw from Dr. Jones, it helps us understand if we're achieving biochemical efficacy or failure and allows us to fail fast.

And that informs the clinical development program. In contrast, the clinical outcomes, which are critical to parents and caregivers, they really do want to see an impact on motor language behavior. But it takes years to fully realize. It also depends on the age of intervention. I showed you a target population, but we're looking at our entire population and pulling the data to understand the true effect. Now, again, greater effect earlier you treat, but there is still an impact if we stabilize this fatal disease. And that is important to our parents and caregivers. So the totality of evidence provided today, both preclinically and clinically, really does support the role of CSF HS as a biomarker reasonably likely to predict clinical outcomes. And pursuing an accelerated pathway using this HS as this endpoint is critical to really move forward the development of lifesaving therapies for these groups of diseases. So with that, I want to say thank you to my team and to the parents and caregivers of our patients. Okay.

Q&A Session with Afternoon Case Study Presenters

Nidal Boulos, PhD, CCRP, Director, Clinical Outcomes Research, REGENXBIO Inc.
Patricia Dickson, MD, Professor, Washington University School of Medicine, St. Louis
Matthew Ellinwood, DVM, PhD, Chief Scientific Officer, National MPS Society
Simon Jones, MBChB, Consultant, Paediatric Inherited Metabolic Diseases, St. Mary's Hospital
Heather Lau, MD, MS, Executive Director, Global Clinical Development, Ultragenyx
Eric Zanelli, PhD, Co-Founder, Allievex

Susan Winckler: So I have a few that are discrete for speakers, although you should obviously feel free to chime in if you'd like, but some of them are very specific and then, others are more open-ended. But Dr. Boulos, there was a discrete one to you. There was a discrete question about what method was used for heparan sulfate measurement in the work that you presented.

Dr. Nidal Boulos: It's an LCMS method.

Susan Winckler: Okay. Did we get that? Could you hear her? Yeah, go ahead, if you just repeat it.

Dr. Nidal Boulos: It was an LCMS-based method.

Susan Winckler: Okay, great. Then there was one other one that was very specific, well, rather specific. So Dr. Zanelli, thinking about your best performer in your study, what would you say about the very early age and whether that was a contributing factor?

Dr. Eric Zanelli: Oh yeah, definitely, she was [inaudible] in the study. She started a treatment at two years of age. There's no doubt that, if we had started the treatment later, she would've done much less well.

Susan Winckler: Okay, very helpful. Dr. Dickson, welcome. I will say you should just unmute and jump in the same as our other panelists. And yes, you can see that you appear above all of them, so you have equal standing on the stage. So to Dr. Ellinwood, do the dogs show the behavior changes seen in children? And are the therapies ever used to help the dogs?

Dr. Matthew Ellinwood: Interesting question. A lot of the literature describes children as being violent, aggressive, et cetera. I don't think those are accurate. I think they have difficulty with impulse control and frustration and will be destructive, et cetera, because of that. We've seen none of that in the dogs. They are super chill and very friendly. Because they're social species, they always get housed with roommates. The only thing I've ever seen as affected roommates, if you took one away to do something, they got very agitated. They love their buddies, and they want to be reunited with them. But we saw no aggression. We don't treat the dogs, but by identifying the disease, we can test for them. And this particular disease in Schipperkes was found to have a carrier rate of 20%, and it has basically been eliminated.

Susan Winckler: Excellent. Thank you. Dr. Dickson, one for you, does your experiment confirm that CSF HS changes are due to changes in the brain and do not reflect changes in the periphery?

Dr. Patricia Dickson: So what we were able to observe is that, when we administered treatment that corrected the systemic compartment, to the point where we observed a reduction in serum heparan sulfate, we did not also observe a reduction in CSF heparan sulfate, and vice versa. If we treated brain neurons, we did observe a reduction in both brain and CSF heparan sulfate and did not observe a reduction in serum heparan sulfate. So it would point to a conclusion such as that, so that would be about as far as what I can say our data show.

Susan Winckler: All right, thank you. Let me make sure that I am hitting everyone with a specific question. And then, we'll go to some of the broader ones. Dr. Jones, could you expand on the point that the patient that did not respond in the trial... Just

expand on the point that I think there was one patient who had a CSF HS level that did not then correlate to cognitive development.

Simon Jones: Yeah, that's a fair point. So there's one patient who hasn't shown normal cognitive development in our lentiviral stem cells gene therapy trial. Interestingly, yet they had the same characteristics, we couldn't find any different characteristics. They were treated at the right time. There weren't higher antibodies. The vector copy number was similar. Interestingly, when we've looked at the brain volumes, which I didn't show, that her brain volume was maintained just the same as the other children. And what she shows is a really quite autistic behavioral phenotype. And now, many people say that Sanfilippo children have autistic life behaviors, but that's only an approximation of the behavioral deficit in Sanfilippo.

The parents of this child actually have an older child with Sanfilippo, who's been untreated, and they say that the two children are completely different. And so, we see this also in a number of MPS1 and MPS2 children who've had bone marrow transplant. Some of them developed a profound autistic feature or phenotype. So I think that's a disease related manifestation. And the CSF heparan sulfate correlates well with the maintenance brain volume and with the prevention of regression. The problem is that the autistic behavioral phenotype means that we cannot measure her cognition in a way that would be helpful. I think that's our current interpretation.

Susan Winckler: I saw a head nod. Did anybody want to add anything there?

Dr. Heather Lau: Simon and I talked about this, the cognition is a high bar to measure in children. So if they're not able to comply with the assessment, then you might have a falsely sense of false low. But I think the critical aspect here is that this child is acting differently than their sibling, their older sibling. And so, you can't expect a child to have every single domain respond potentially. And maybe you're holding them in that steady without... Regression or the lack of regression is a goal in a therapy, in a treatment for a neurodegenerative disease. That is the goal. It'd be interesting to follow forward.

Susan Winckler: Yeah, go ahead.

Dr. Matthew Ellinwood: Picking up off on the theme of siblings, I wanted to ask Eric, were there any siblings in your study that entered treatment at different ages? If there were, do you know about them? And can you comment on their differential responses potentially?

Dr. Eric Zanelli: Yes. We have one case actually. So 9006 or so-called Champion. She has a brother that has been treated also in our studies, but the treatment started a year later in age equivalence. And clearly, he has been doing a lot better than you would expect from the natural history, but he's definitely not doing as well as his younger sister.

Susan Winckler: Okay. Dr. Lau, one for you, you used a phrase of primary disease activity biomarker, but those are not the typical way to describe, at least in a regulatory perspective, response biomarker or surrogate endpoint. Did you mean something else? Or tell us how those might connect.

Dr. Heather Lau: I feel like we were all using that term today, the proximal disease.

Susan Winckler: I know. I heard it on yours and saw it on the slide.

Dr. Heather Lau: So I think the concept of early and late, it's relative. It's not exact timing, but it's sequential. So when we think about heparan sulfate, especially in IIIA, B, C, and D, they only accumulate HS. And so, HS is the most proximal or primary to the genetic defect, right? So the genetic defect causes the enzyme deficiency, leads to HS storage, then a whole host of downstream events. So that's what I'm using as a primary disease activity. If you start targeting and monitoring neuroinflammatory markers, that could be confounded by other treatments, such as immunosuppression in the therapy, that are co-administered. So really and truly, if I can affect HS, then I'm affecting the primary disease state. If I'm treating neuroinflammation, as a neurologist, I can actually temporarily treat neuroinflammation with a whole host of medications, but I'm not getting to the root cause. And the root cause here is a single enzyme defect with substrate deposition. So forgive me, I'm not a regulatory person.

Susan Winckler: No, I think it was for clarity, just in the...

Dr. Heather Lau: Yeah, that's how it...

Susan Winckler: As we know in the FDA space, there are a lot of people who are trained as lawyers. I'm one of them. And then, so there's magic language. So that was a magic language question in needing the connection of the words there. So this may be then somewhat related, so this is to any of you, but speaking specifically on the gene therapy or the intrathecal ERTs, any thoughts on how immunogenicity to products might be affecting cerebrospinal HS levels and, in turn, efficacy?

Simon Jones: So I've seen that in both enzyme trials and in other gene therapy trials, so I think antibodies can be an issue. I think what we've learned from intravenous ERT is, if you wait for a clinical outcome or an attenuated clinical response, due to antibodies, then you may wait five to 10 years to see that and know for sure, which of course, is completely too late, if you want to actually manage that response. I think we have many tools not only to manage an immune response. I think we shouldn't be scared of talking about it. It's a natural thing.

We should expect it, and we should be striving to make every child respond to our therapy. I think that's deeply important. We've got a small in in our trials, and we've got difficult outcome measures and difficult timing. So we have to make sure that we give every child the best chance to respond as fully as they

possibly can, which for some children, may mean we have to use immune modulatory strategies, as Heather has mentioned. I don't think we should be afraid or indeed apologize for that. I think we need to do whatever we need to do to get kids to respond.

Susan Winckler: Yeah. Very helpful answer. Yeah, go ahead,

Dr. Eric Zanelli: Yeah, maybe I can add, so in our case, we do see antibodies formations in most of the kids. There's no evidence that the antibodies are interfering on the efficacy. And I would say that probably what's happening is that, after a while, there is a kind of an immune tolerance, so the antibody titers tend to decrease.

Susan Winckler: Okay.

Dr. Heather Lau: I'd like to follow up. So for that case that I showed in our program, that child looking back probably had something called CRIM status, a CRIM status, that was CRIM negative, right? So in lysosomal world, we understand that CRIM status is very important in understanding antibody mediated loss of efficacy. And so, that's something that's mitigated by immune suppression. So CRIM status in that patient, their titers were in the 3 million. So that was heralding a response by losing the enzyme and then, leading to reaccumulation of HS. CSF HS is not directly being taken out of circulation by antibodies or affected by the... It's a marker that the enzyme is being attacked in our case. But we do see CRIM status as important to understand when you're embarking on gene therapy and other therapies.

Dr. Matthew Ellinwood: Two points, most of the dogs developed peripheral antibodies to the compound that we studied, but it did not seem to impact the efficacy in the CNS. And correct me if I'm wrong, Simon, but the study that you and Milan have conducted on ex vivo gene therapy for MPS1, involving autologous transplant and [inaudible 01:29:29] T therapy, actually removed the antibody response that children had had if they'd been previously put on ERT. Is that correct?

Simon Jones: Yeah, that's correct. And rituximab was used in everybody as a kind of prophylactic immune response, because most of them were sensitized by initially enzyme therapy.

Dr. Matthew Ellinwood: And post-therapy, that was gone?

Simon Jones: That settled on, yeah.

Dr. Matthew Ellinwood: Thank you

Susan Winckler: Dr. Dickson, I saw your hand raise. Yes, go ahead.

Dr. Patricia Dickson: In our preclinical studies, mainly the MPS1 dogs, we do see a reduction in efficacy in the animals that developed antibodies against the enzyme. However,

it didn't eliminate efficacy, and they were still better treated, just the ones that didn't have antibodies had an additional benefit, if you want to think about it that way, compared to those that did.

Susan Winckler: Okay. Anything else on that one?

Dr. Heather Lau: Well, the goal is tolerization, let's just highlight that. And that's what we're seeing as well in some patients. So your immune system can calm down, and you start to tolerize to that. So that's what we're probably seeing as well.

Susan Winckler: All right. Now, this one is specific on the gene therapy study. What do you hypothesize studies or discussion of gene therapies rather, what do you hypothesize regarding durability of response? And if the clinical effect wanes, could ERT be used thereafter?

Dr. Nidal Boulos: I think we can draw from hemophilia studies. I think hemophilia have shown the longest durability in terms of gene therapy. So expectation are, of course, in our specific gene therapies, we have to follow them long-term, but the expectations are that, with it being pediatric patients, that there should be some carryover for expression in long-term. But our studies are still young and mature, but if we draw from hemophilia, I think we have hope that they would be durable.

Dr. Heather Lau: From a neurologist perspective, neurons don't divide. We essentially are born with the same compliment of neurons that we go on. There is some neurogenesis over time, and most of the remodeling occurs in synapse formation. So if we're targeting neurons, hopefully, we would see durability. But I would have to caveat that we've only followed up for five years. So hopefully, unlike other high turnover cells, cells that are highly turning over, we hope to have durability in the brain. Simon, do you have any... You have a different modality.

Simon Jones: I think the in vivo and ex vivo approaches are quite different. We deliberately target, in ex vivo, rapidly dividing cells, but we target the stem cells knowing that, and we integrate to the genome, knowing that that should then allow us to express in a lifelong way. But of course, we're all still learning, and the longest lenti kids are, not in our study, but in other diseases, are 15 years out.

Dr. Matthew Ellinwood: I think the lessons from primates, where they've treated animals with AAV targeting the neuroretina, non-dividing neural tissue, those persist for out to eight years, which is the longest I think they've been studied.

Susan Winckler: Now, there's about 50 questions there, so that's a good thing. So how do you tell if the patients with clinical improvement are secondary to treatment? Or is it because they have slowly progressive disease?

Simon Jones: Well, I think everyone's tackling this slightly differently. On our lentiviral trial, we, as part of our inclusion criteria, had the patients had to be under one year,

but we also had an independent expert, who would review the patient's case history and genotype. And we had to be absolutely sure that they were of a severe or rapidly progressive phenotype before we could include them. And we rejected some patients on the basis that they weren't part of that. So yeah, obviously, if you get them very, very young, they're oligo or pre-symptomatic. So you have to have another way of predicting their phenotype. So that was our approach.

Dr. Eric Zanelli: Well, I would say, in our case, number one, in some cases, we followed [inaudible 01:33:37] for so many years that, if we still see an improvement, I believe it has to be a deviation from natural history. And the second thing is, obviously, as I show you, is that, in some cases, we know that, if the child is not getting treatment, he or she doesn't normalize heparan sulfate and he start losing brain volume. So clearly, I have to believe that the children's with normalized heparan sulfate, preservation of brain volumes, and improving cognitions are the result of treatment and nothing else.

Dr. Heather Lau: It's not a perfect correlation. But we did also exclude some attenuated phenotypes that are known or genotypes that are known for MPS IIIA. But again, it is difficult. But as you could see, the main is rapid progressors. We've enriched for the rapid progressors, but it doesn't mean that slow progressors, who are slower, would benefit or would not benefit. It just might be different. And so, the HS at baseline is what is important, if we're following the metabolite then and we see preservation over time, but again, that would take years.

Susan Winckler: Right. A specific question, Dr. Zanelli, how frequently did you measure heparan sulfate in the cerebrospinal fluid? And did you see a correlation between the decrease in the biomarker and the frequency of the infusions?

Dr. Eric Zanelli: That's a very good question. I could talk about it for the next two hours.

Susan Winckler: Yeah, we don't have that.

Dr. Eric Zanelli: So no, the short answer is that, so the way we do it is that, every week, when the subject come to the clinic for treatment, we have to remove 10 milliliter of CSF. So I can tell you that, for each child, I've been [inaudible 01:35:31] for eight years, we have a lot of CSF. So if we want, we could measure every week. So I can tell you, we have thousands of data points. And so, to the second part of the question, yes, it is interesting. That's why we believe that, after a few year, after actually one year of treatment, we can go to every other week dosing or even less. Because we do know that, after a while, when you've been able to sustain normalization of heparan sulfate, if the child doesn't get treatment for a few weeks, he or she still maintain normalization of heparan sulfate. It takes a few weeks before you start seeing a rebound.

Susan Winckler: Okay. At least one of you mentioned SMA in comparison to MPS. So to extend that comparison, what can we learn from SMA as to what drug approval could mean to MPS and similar disorders?

Dr. Matthew Ellinwood: I don't know about the others. I know I mentioned SMA. So SMA was approved for therapy in 2016. Within two years, we had it listed on the federal Recommended Uniform Screening Panel for newborn screening. That was in the summer of 2018. This January, we got to 100% of the United States screening for this disorder in newborns. So in a very short time, we've gone from a drug approval to universal screening in this United States, and we now have three approved therapies for SMA. So there is benefit systematically to the whole drug development landscape and diagnostic landscape, from just one approval, that could accrue to many of these disorders.

Dr. Heather Lau: SMA is different though?

Dr. Matthew Ellinwood: Yes, agree.

Dr. Heather Lau: Werdnig-Hoffmann is an early infantile disease that has rapid progression to death, right? So we're talking rapid progression and slow progression. In MPS, it's relative. We're talking years, decades, which is still too fast for our families, but it's different than the early infantile diseases that are rapid progression. And so, you'll see difficulties with the more attenuated phenotypes of SMA, but the SMA that it was based on, their endpoints are faster. They come to this faster.

Dr. Matthew Ellinwood: But from a public health standpoint, getting an approval opens up newborn screening. That will recruit more patients. That creates a better drug development landscape, if new competitors want to come in, et cetera, additionally, from getting kids diagnosed and treated.

Susan Winckler: Yeah. There's a question here now on measuring cognition, and Heather, it's tagged to you, but that doesn't mean that you need to take it. But when measuring cognition, what are you using after patients get to 42 months? And how do you transition between the Bayley and something else and measure cognitive growth as a continuum across that age?

Dr. Heather Lau: Oh, I'll start, but I think Dr. Zanelli can talk about this as well. So obviously, it's a wonderful problem to deal with, if our children are reaching the ceiling of the Bayleys, for example, and then, they'll bridge over to the Kaufmans. But that is the part of the lack of flexibility we have here is that, when we're showing that children are excelling or achieving higher and higher cognitive milestones, we can't use those interchangeably according to the FDA currently. I'm being delicate here, but as a neurologist, if a child is walking and talking, it doesn't matter the measurement. The child is walking and talking and they're not declining. We need help in understanding how to bridge that. And Eric, do you want to talk a little bit about your program?

Dr. Eric Zanelli: Sure. Our colleague from the FDA in the room know that the agency wanted us to use raw score instead of age equivalent. The point with raw score is that the raw score for Bailey and Kaufman are totally different. So to Heather point, the point is that when a child achieve a score of 88 on the Bailey scale, then we are stuck, for lack of better word. So all we can do is to keep the maximum score as a reference or try to switch to age equivalent. But then because when there is an equivalence between the Bailey and the Kaufman scales, or my overall favorite topic or discussion is to use the violence scale because of violence, you can use the raw score for the whole child regardless of age.

Susan Winckler: Okay. You gave me an artful metaphor that when the child jumps over... it's appeared that they've got over the high jump but then we stopped measuring how high they could jump. They're far, far, over.

Dr. Eric Zanelli: Yeah, exactly.

Susan Winckler: Yeah. Yeah. Back to animal model to make sure that we don't lose that. To what degree are the animal models able to recapitulate the human MPS disease? For instance, the MPS III dogs.

Dr. Matthew Ellinwood: So the MPS III dogs have a fatal neurodegenerative disease. In that regard, I would say they are great models. They show atrophy of a major component of the central nervous system, the cerebellum. It is different in that is early adult onset. It is not a model of attenuated disease, it's severe canine disease, and it is primarily cerebellar instead of cerebral. With those caveats, I think it's an excellent model. It's the same basic neuropathology in terms of heparin sulfate causing fatal neurodegenerative disease. It is a large sulcated brain, only one order of magnitude the size of humans versus three orders of magnitude smaller in the mouse. I think it's an excellent model. For some of these diseases where large animal models like this exist, I would propose that the FDA consider animal-only rules for this.

Simon Jones: Can I just say as well actually even the mice have a really good correlation with human disease. Obviously when you're scaling up, it's better to use a dog but the mice have it with IIIA and IIIB, have a behavioral phenotype that mirrors the patient... and IIIC, Jill. Yes.

Dr. Matthew Ellinwood: And D.

Simon Jones: It really mirrors the... okay. And D. It mirrors the patients that we spent a long time showing that the mice, just like the patients, have a defected circadian rhythm. They don't sleep when they should be sleeping, they don't have a sense of danger when they should have a sense of danger, and they have overactivity like the patients. So the animal models for this disease are really, really good, actually.

Dr. Matthew Ellinwood: I mentioned it earlier, even inus die from a fatal spinal cerebellar ataxia. These compounds kill every large vertebrate that stores it.

Susan Winckler: I think that the power of your videos is what's driving the dog questions, but they're very helpful. Dr. Zanelli, a discreet question. There was just a question about what's the status of your current program?

Dr. Eric Zanelli: We're not here to discuss about business. All I can tell you very practically speaking that we have a meeting with the FDA on March 15th, so we'll see. I will tell you on March 16th where we are.

Dr. Matthew Ellinwood: Since we have no parents up here and I've spoken to some recently, this program cessation has been just gut-wrenching and devastating. They are looking at consigning their childrens to a long, slow death if this does not resume.

Susan Winckler: Which I promised I would ask. Thank you. And I will have a yes or no question that we had someone tee up for us, but we'll hold that for the last one. So as a group, I don't think that any of you mentioned this, but if you are aware of FDA's new genetic metabolic diseases advisory committee, which I imagine you are, any thoughts on how that might have a role in this case study? It's okay to say no thoughts, although Matthew you are just...

Dr. Heather Lau: Say something.

Susan Winckler: Let me know if you want me to save you and move on, and I will.

Dr. Matthew Ellinwood: I think that this new advisory committee is just perfectly set up to address this kind of issue. I feel for the FDA. This is an organization with people of great goodwill, but 10,000 rare diseases? How do you wrap your hand around all of those? And having a committee that can come to the table and say, "Actually, this is a pretty easy call or this is complex, we need some help here," getting clinical expertise that can address the variety of these different disorders, that's going to be so hugely helpful I think for all of these review committees. And I am sympathetic. If you haven't spent a quarter of a century or more in these diseases, it could be difficult to figure it out, so this committee can bridge that.

Dr. Eric Zanelli: Very good answer. I like that.

Susan Winckler: All right, so you have a thumbs up from the panel here. Let's talk a little bit about accelerated approval, and a component that that is also then tied to a requirement of confirming clinical benefit post-approval. So what do you think that might look like given the various challenges you've all shared with designing clinical trials and some of the components, and is there confidence that a well-designed trial that cannot be done pre-approval could be done post-approval?

Simon Jones: Thank you.

Susan: You're sitting closest to me, so you get to jump on that one.

Simon Jones: No, I think it's a really important question. If there were more accelerated approvals in this disease area, then it's absolutely critical for us to be able to do trials that post-approval can answer the questions. And believe me, I'm a clinician primarily before a researcher, and so I need the questions to be answered as well as the FDA or anybody else, the patients. We all want the questions to be answered. It's important for all of us. So I think there's no doubt that some of the disease registries that were post-marketing pharmacovigilance requirements in the past weren't done with the aim of answering questions.

They were not in the scientific method, if you like. They were open-ended, observational, they just collected data without setting up a hypothesis and structuring the program to answer or solve that hypothesis. So I think we need to change the mentality around post-marketing studies and make them proper studies that can actually answer those questions. I think the advent of more numbers, which you will get in a post-marketing situation and a longer time period, allow you to ask those questions in a very different way. So I think it's absolutely possible.

Dr. Heather Lau: I'll add to that. So again, as a clinician first and someone who followed these patients and met with them yearly to see how they're responding to their ERT, whatever disease state, I took care of a lot of different types of lysosomal storage disorders. And for one case the registries are retrospective, they're limited. So I was involved first as a PI for MEPSEVII for MPS VII and a disease monitoring program. And so again, you're able to do this... collect clinical trial grade data information over time, and do that in larger numbers because now more children are having access to therapy and we are committed to following up especially in gene therapy for safety, long-term safety, five, 10 years.

So it's not just about not having the right tools, it's that the tools that we have right now can't measure in two years. We need to see changes not only on cognition but motor behavior, understanding item level, like looking at the different items that are... how the children are performing at that subdomain level on a cognitive scale. Are they maintaining certain activities of daily living? But you can do that. We are committed to a confirmatory study to follow up and to get clinical trial grade information. I've published off of registries. They are important. I did that for a variety of diseases out there. But that data is limited. So if we can prospectively define it and agree on it, it can be done and you'll get the numbers because now other children are getting treated in the meantime. Our limitations are the small end now waiting before we can enroll more, right?

Susan Winckler: So that's a key difference in the preclinical and the post-clinical?

Dr. Heather Lau: That's the barrier, is that we can't continue dosing patients pre-approval. It's prohibitive. We need that post-marketing ability to follow and to treat others so they're not waiting. These children are dying. They are sustaining irreversible

brain damage while we're trying to prove the confirmatory. So accelerated pathway, my understanding, is that we show that there's a biochemical engagement in HS dropped, and that we're going to come back and show you over the ensuing 5, 6, 7 years. I don't don't know if anyone else can add to that.

Dr. Eric Zanelli: Well I mean, in all case, I think we've been very clear. We agree with the agency that if we get a path to accelerated approval, we will initiate the recruitment of subject in our confirmatory study as soon as possible. And by the time we have accelerated approval, the recruitment should be completed.

Dr. Matthew Ellinwood: I think it's critical that any labeling must address the ability of a drug to both prevent and treat signs of disease, and it should be broad in terms of age similar to what's been done recently for ERT and mannosidosis, and not narrow for some of the recent drug approvals for Duchenne muscular dystrophy. We've got to have the ability to recruit those preclinical children, especially when we get newborn screening. It may make the statistical evaluation of the outcomes more complex, but you can use mixed-model approaches, et cetera. But we do need that broad approval as well as for indication and age as well as accelerated approval.

Susan Winckler: Okay. I have a discreet question for Dr. Dixon, and then I'm going to go to the yes and no as our last question. So Dr. Dixon, does the reduction of CSFHS in patient's brain in your 2010 study suggest that intravenous enzyme therapy does in fact cross the blood-brain barrier, at least in MPS I?

Dr. Patricia Dickson: So there was a... I just want to make sure that we're talking about the same thing. So there was a 2010 study looking at canine brain...

Susan Winckler: Yeah, I think they mistyped. Sorry. Yes, go ahead.

Dr. Patricia Dickson: Okay. Just want to make sure. And then there was a 2020 study looking at CSF heparan sulfate in the original patients treated with intravenous enzyme replacement therapy. So my interpretation of the data, and again, could be correct or not correct, my interpretation of the data is that it does cross the blood-brain barrier, but that the levels are very small, on the order of what we've measured in the brain is about 2% to 4% of normal in the animal studies. That amount may not be sufficient for full clinical impact. Is there any clinical impact? I think there probably is, to be honest, but is that the ideal clinical impact? No.

Susan Winckler: Very helpful. Now to the yes/no question, which has five parts. So there are a lot of caveats in this question.

Dr. Heather Lau: Can't be a yes/no.

Susan Winckler: It is a... well...

Dr. Matthew Ellinwood: It's a serial.

Susan Winckler: It just has five caveats, and that the request is for everyone to have a yes or no. And it gets to whether reduction of HS and CSF is reasonably likely to predict stabilization of cognitive decline. So now you know where I'm headed. If started before age two, so first condition, is reduction of HS and CSF reasonably likely to predict stabilization of cognitive decline in greater than 80% of patients for three to five years or more in MPS III? And you could choose to answer yes or no to the first part of the question and leave off the 80% if you so choose. Thoughts?

Simon Jones: Well, I...

Susan Winckler: You're stuck. Now everyone knows not to sit in this chair.

Simon Jones: Based on the data we have, yeah, I would say yes, it's reasonably likely to predict and there are of course multiple caveats, but yeah, I would say yes.

Susan Winckler: All right. Yes, with asterisks which is perfectly acceptable.

Dr. Eric Zanelli: I'd say if the endpoint is cognitions, the answer is yes. If you start early, you normalize CSFHS, you will achieve [inaudible].

Dr. Matthew Ellinwood: Based on the model data and the clinical data from my colleagues, without any doubt, yes.

Dr. Nidal Boulos: Yes, absolutely. We know heparin sulfate is there, we know it's not going to go away. So we know it will be predictive.

Dr. Heather Lau: Yeah, and with those caveats, as well, I agree.

Susan Winckler: Dr. Dickson, you get the final word.

Dr. Patricia Dickson: I think in the spirit of which that question is asked and what we think it probably means, yes.

Susan Winckler: All right. Anytime you can introduce even more asterisks, it's okay because we know we're still exploring, right? We are still learning, we are still exploring. But I hope we know from this discussion that we are learning more and making advances. So with that, let's thank our speakers for this afternoon.

Panel Discussion: Challenges in Qualifying Biomarkers to Support Rare Disease Approvals

Moderator: Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA
John Crowley, JD, MBA, Executive Chairman, Amicus Therapeutics, Inc./Incoming President & CEO, Biotechnology Innovation Organization
Cherie Fathy, MD, MPH, Medical Officer, Office of Therapeutic Products, Center for Biologics Evaluation and Research, FDA
Carole Ho, MD, Chief Medical Officer & Head of Department, Denali Therapeutics, Inc.
Gavin Imperato, MD, PhD, Chief of General Medicine Branch 4, Office of Therapeutic Products, Center for Biologics Evaluation and Research, FDA
Edward Neilan, MD, PhD, Chief Medical & Scientific Officer, National Organization of Rare Diseases
Cara O'Neill, MD, Chief Scientific Officer & Co-Founder, Cure Sanfilippo Foundation
James Wilson, MD, PhD, Rose H. Weiss Professor and Director, Orphan Disease Center, Professor of Medicine and Pediatrics, Director, Gene Therapy Program, Perelman School of Medicine, University of Pennsylvania

Susan Winckler: So as I noted, we are shifting from slides. We are now moving from slides to panel discussion among this august group here. So we are turning to this group to help us synthesize what we've heard today and move us back toward that larger inquiry of biomarkers. And let's say hello to our panelists who are joining us. We have, as I come down this way, John Crowley with Amicus Therapeutics, and soon to be BIO.

John Crowley: 12 more days, yes.

Susan Winckler: All right, soon to be BIO. Dr. Cara O'Neill with the Cure Sanfilippo Foundation. Dr. Cherie Fathy... I got it right, right?

Dr. Cherie Fathy: Cherie, but it's okay.

Susan Winckler: Cherie. That's right.

Dr. Cherie Fathy: That's okay.

Susan Winckler: So Cherie Fathy from FDA's Center for Biologics Evaluation and Research. Then next to me here is Dr. Edward Neilan from the National Organization of Rare Disorders. And then we turn to Dr. Carole Ho with Denali Therapeutics and Dr. James Wilson from the University of Pennsylvania. And then we should have... do we have our remote? And he's in front of me. There we go. Dr. Imperato, would you like to say hello? And it's Imperato? I practiced it four times.

Dr. Gavin Imperato: No worries. Hi everyone.

Susan Winckler: All right. Thank you for joining us remotely and keeping your respiratory virus to yourself. We understand the importance of doing that. So we want to talk about challenges in qualifying biomarkers to support rare disease approvals, although I have to say we've heard quite a lot of that today. But let's step out from the case study and have each of our panelists provide some reflections on the

discussions and help us think about where we should focus our attention. Dr. Wilson, I'm going to turn to you and ask you if you reflect on your research and experience in rare genetic diseases, would you kick us off by providing your thoughts and experience in qualifying biomarkers to support approval of interventions to treat rare disease?

Dr. James Wilson: Sure. Well, happy to. And again, thank you for being here. I run the Orphan Disease Center at Penn and I've worked in the area of gene therapy for 40 years. Made the decision about 15 years ago after we had discovered a new family of vectors for CNS disease that storage diseases may be the easiest to treat and the ones that we focused on. And what we have been developing, and something that we may want to consider, is not only MPS diseases in this context, but consider how we can leverage this experience for other diseases. And that's what we've tried to do in putting together a platform where we use basically the same capsid at the same route of administration and the same manufacturing. And back 15 years ago, I met a number of you in the field, ML and Mark and others, and we made the decision we would start at MPS diseases in terms of the larger group of storage diseases.

And the reason was, reflecting on what Matt and Patty had said, is there were some very good large animal models of these diseases. That was really important for us to validate dosing and also pharmacology and toxicology. And the other one was the hope that there could be a biomarker for all of them. So that was 15 years ago, so I'm pretty excited to be here and I hope that decision was right. But then, considered moving the platform through those diseases into other storage diseases. So we founded the company Regenix Bio and did the work to support an application, this platform for MPS I. We heard the great data in MPS II and then founded a company, Passage Bio, to take on ganglia cytosis storage diseases, early infantile very severe diseases, GM1, CREBA, and MLD. Worked with Amicus on MPS IIIA and IIIB.

So we now have brought four of those into the clinic. We have 11 preclinical data sets, and I thought it'd be useful just to sort of share our experience in terms of whether there's any read through from preclinical to clinical and then across programs, and we talk about animal models and generally animal models are not very good. But what was really surprising here is how good animal models are, not only cats and dogs, but mice in terms of scaling and also in terms of correlation of biomarkers, pathology, and survival. Now what you can do in an animal model is you can get statistics, you can look at clinical, and you can correlate biomarkers with histology as well.

And that seems to read through to what is being seen in the clinic. The most complete data sets are MPS I, MPS II, and GM1, and one patient dosed for CREBA. So I'll just end with some final comments about reflecting on that experience is what, is a playbook? As I think about it, and for MPS diseases, the benefit which I hope we can all realize is having a common biomarker. And that would be enormous in terms of us taking a platform through all of these diseases. The others are bespoke, but they're all substrates. And it turns out

that when there is a defect, an accumulation of substrate has been really a pretty good predictor preclinically of what you'd see from a clinical perspective. I also think that we've completely thought about preclinical data in drug development. We used to think about animal studies as IND enabling. I don't know if anyone's heard that, that allow a support of an ID.

We now talk about them as BLA enabling. So in other words, how can we structure those preclinical studies, which may mean just slight modifications of what you measure, so that when you complete those studies, you not only have safe to proceed to get into the clinic, but you position the program so that when you get to the point where, "Wow, this is really looking well," that you could leverage the animal studies to support that this biomarker would predict clinical benefit. Matt was as bold to say that animal data may be sufficient, but I think that's the kind of spirit there. Correlation of biomarkers with disease severity, we saw that with MPS II and absolutely critical and I know many of those involved in the patient advocacy groups, we really need to get our act together and consolidate natural history data not only from one center but from others so that we can proceed with an open label study and as best as we can, despite the fact there's heterogeneity, convince ourselves FDA and others for an accelerated approval pathway.

One final comment, and so I'm a scientists, I've been at Penn, but there's another concern that I'd like... it'd be great to talk about once we get through the speakers. And that is, let's say we do succeed and we get accelerated approval on these diseases based on biomarkers. At the end of the day, this has to be a successful business model and for it to be a successful business model, I think where the war is going to be won, it's not with health authorities, it's with those that reimburse. So if we come forward with an FDA approval and say, "Aha, we have this biomarker correction," are the payers are going to say, "Okay, we're going to pay?" And maybe this goes beyond our remit here, but I'm sure Peter Marks and his colleagues at FDA don't have anything to say about that and maybe we need to bring them into the room, but then at that point we'd be all dressed up and nowhere to go. So that's a thought that maybe later on we can talk about.

Susan Winckler: Right, and it is a reality of... with the promise of getting to that, that there's the regulator decision, which is the first... well, the major gatekeeper, but then there's a dynamic beyond that. So any thoughts and reaction to the commentary about an animal model being BLA enabling or the components as it relates to natural history that any of the panelists want to jump in on?

Dr. Carole Ho: Yeah, sure. I'd love to just add to that because I think particularly in these disease areas where the biology is very simple and very well understood, animal models can be actually very good at understanding the relationship between these biomarkers in different compartments of the animals, such as looking at the CSF, looking at the brain, and looking at the periphery, where you can make these very clear correlations that in humans, you cannot do that. So it is ethically not acceptable to take biopsies of the brain, which is one of the major

challenges I think we've had in this area in demonstrating, for example, biomarkers that can be collected in CSF or in the periphery are reflecting what's happening in the brain.

But I think what we heard today is that there is consensus that there are biomarkers, CSFHS, that can be measured in the CSF and do reflect what's in the brain. And that is very much supported by the animal model data. I think the animal model data can also correlate those biomarker changes with clinical outcomes in the animals, which are very helpful for dose selection when we go into the clinic, so that we can make sure that we're going into the clinic with a dose that makes sense because as we heard, patients are waiting and these trials take a long time.

John Crowley: And Susan, maybe I'll just emphasize the second point of what Jim discussed and that's the importance of natural history studies. If we're going to be doing these studies where placebo controls are impractical or oftentimes largely unethical, we're going to need to have robust natural history studies. When parents and families call me and they ask, "What can we do?" particularly in these diseases where there is very little research in an advanced stage going on, I always tell them two things.

One, educate the community, find more people like you. Find more children, more people living with this disease. You're going to help them, you're going to educate them, and you'll help we as drug developers enable the studies that we need to do. And then the second thing is, work with your communities, your key opinion leaders, researchers, the whole ecosystem to build those natural history studies because that's what ultimately I think is going to be an incredibly powerful tool for us doing these studies.

Susan Winckler: All right. Let me turn now. Dr. Neilan at the National Organization for Rare Disorders, you and your colleagues are thinking about these issues for all rare diseases, so you have a bit more of a landscape view of the topic. How should we think about that broader perspective when discussing biomarker qualification?

Dr. Edward Neilan: All right, thanks Susan, and I will get to some things that we talked about in a prep call, but having listened to this delightful meeting, I think I'm going to start with a little more general commentary.

Susan Winckler: Absolutely.

Dr. Edward Neilan: I was thinking there's two things that I am not that might be useful. I am not a world-class expert on mucopolysaccharidosis such as our earlier speakers. I'm not a world-class expert on FDA regulation, but I've dabbled in both and I now work at NORD where our mission is to try to improve the health and wellbeing of all patients affected by rare diseases and-

Susan Winckler: Which is why you're here.

Dr. Edward Neilan: Yes. And I told Susan on a prep call that I think we would look at it from a point of view that's already been anticipated by some of the earlier comments, including Jim's, that while there's understandably a desire to get a first drug approved, some kind of treatment approved for disease no matter what on some level, that accelerated approval has been under threat.

Susan Winckler: Quite a bit.

Dr. Edward Neilan: And looking across the scope of the rare diseases, it's important to NORD and it's long active now 41-year-old public policy team to try to protect accelerated approval. And I might point you all to look back about two years, I think in December of 2021, NORD's public policy team put out about a 30-page report on accelerated approval. And again, I'm not the policy expert. I wear that hat for a moment. And point out that one of the things that kind of did was review the progress of the accelerated approval pathway up to that time.

And it's a little bit difficult to judge that based on the fraction of things that received accelerated approval that have already been fully or traditionally approved because that conversion is difficult, as has already been mentioned, and some of them are behind. That doesn't mean they won't get there, but only 6.3% of the drugs that had been approved by accelerated approval had been withdrawn. So fundamentally as I think it was who said this earlier, Mark... Dan, when he said, "The system is working, we just have to let the system work," and that resonated with me because fundamentally, if 84% have been left on the market and FDA is comfortable with that, the system is basically working. You do have periodically something that the payers refuse to pay for or that has a confirmatory trial that fails and voices come up, "Why do we have this accelerated approval?"

And what NORD on a public policy front wants to defend is the idea that an FDA approval is an FDA approval and payers should pay for it, they shouldn't be second guessing the FDA. That works for everybody's benefit. But then the balancing thing is we have to try to make sure that sponsors design studies that use biomarkers and approaches that are as careful as the ones we heard about today. That's the other opening point I wanted to make, again, as a generalist. For about 12 years, I was the principal doctor at Boston Children's Hospital doing enzyme replacement therapies. And I got involved in a number of different clinical trials, but it was never the focus of my own research. I had a lab that did more basic science things and that's why I was dabbling in that area. But gosh, what was I going to say?

Susan Winckler: That's all right.

Dr. Edward Neilan: You probably know where I was headed, right?

Susan Winckler: I think so. But let's lead you to the right place.

Dr. Edward Neilan: Yeah.

Susan Winckler: So in acknowledge... I think you were speaking to also the collaboration in the scientific community here, right? That you had strong clinical trials? Yep.

Dr. Edward Neilan: I'm jumping... I know what I was getting back to. No, what I was going to get back to was the general point. Having listened to the whole day's session and coming from someone who's a laboratory scientist, a clinical investigator, a patient advocate, a practicing physician still, I, for one, became convinced of the things that we heard today about how the CSF heparin sulfate would fulfill, I think, those criteria that Peter Marks started us off with for a good biomarker to be used in this fashion with accelerated approval as a goal, and also was convinced after today's discussion that in fact it would be likely to predict clinical benefit. And so don't let the cautionary note that not every biomarker is suitable take away from the fact that today's discussion, I think, puts this particular group of disorders, the neuropathic MPS disorders, on what seems like a good platform to move forward.

Susan Winckler: So you found yourself by the information shared?

Dr. Edward Neilan: I did.

Susan Winckler: All right. That... it's more clear now. If there's no thoughts on that, I want to turn... let's talk a little bit about the drug developer perspective. And I'm going to go first to you, John, and then I'll come back to you, Dr. Ho. As we mentioned you joining our stage from both Amicus Therapeutics and your incoming role at Bio, what lessons have you learned today and then in decades of experience in the biomarker qualification space, and what would you identify as challenges that we still need to overcome?

John Crowley: Yeah, Susan, it's interesting. When you listen to the discussion today and you see the data on what's happened now in MPS and with the cerebral spinal fluid and HS as a marker, I think it's overwhelmingly clear, with these products in this disease, with this biomarker, it is reasonably likely to predict clinical benefit and should be, as we've discussed, subject to the accelerated approval pathway. It's interesting when you look at the accelerator approval pathway itself, the legislation is very clear and it's very unique that they put an adjective and an adverb in there: reasonably likely. And papers have been written about it. What does that actually mean? It's somewhere over 50% that it's reasonably likely, and it also means we're going to make mistakes. And it may not necessarily be the ultimate drug. It oftentimes is not going to be, but it's going to be a very important tool in the arsenal as we see in MPS3, in a disease where you've seen nothing but suffering for generations, for as long as we've known in medicine.

So I think that's very important in this disease, but it raises a bigger issue, and that's where are we in rare disease drug development broadly? We've come a long way. We've come a long way since the Orphan Drug Act, but we've got a long, long way to go. And I think we're finally at this inflection point where we have so many now of the tools of science to offer hope, hope tempered with reality, of the challenges of drug development. And now the challenge is how do we make sure that we're achieving the gold standard of safety and efficacy grounded in key science? And to do that, we've got so many of these challenges. Biomarkers are one tool that the regulators have, that we as drug developers, that experts have in determining safety and efficacy. It may take a lot of work to use it as a biomarker, as we've seen with the MPS disorders now, but also it can be helpful in determining dose or biologic activity. It's a tool and it can be a regulatory tool.

But we're at this inflection point, and frankly I think it's a crisis in the world of rare diseases, and we've seen this now where so many programs have been delayed or stopped or threatened to be delayed or stopped. And not because the science just doesn't work. Sometimes that's the case, but the whole ecosystem isn't working the way it needs to for this next generation of therapies. At Amicus, we've developed, we've had now approved, two medicines, one for people living with Fabry Disease and a next-generation medicine for people living with Pompe Disease. And we've spent a lot of time and a lot of resources looking at these fatal brain diseases in children as well, and some with Jim, a number of different programs in gene therapy, some that we had licensed out of Nationwide Children's Hospital.

When we announced that, and I'll just give a little framework here, when we announced our programs in the Batten diseases, so 14 different subtypes of Batten disease, similar to some of the neurologic diseases we've talked about today, there was a lot of hope, a lot of great science. We actually went in the clinic in CLN6. We went in CLN3. Again, just devastating brain diseases where children again lose the ability to walk, to talk, to think, to eat, and ultimately die. So we know what the outcome is going to be and it's going to vary by child and severity and ultimately when they might succumb, when they might die from the disease. But we went in the clinic and we did years of work, hundreds of millions of dollars. And in addition, we invested a lot of resources in preclinical work. And when we started that, about a year later in the fall of 2019, I got an email from a mom who had adopted a child from Africa with CLN1 Batten Disease.

And she just had a lot of questions, she flew out from the West Coast, came to see us as we've done, and so many of us have all done with these families, and we finally gave her some hope and we had research and we had scientists working on it. Well, fast-forward, and we've now had to discontinue all those programs and give them all back, as we did with Jim and the MPS programs as we did with Nationwide and the Batten's programs. And we're a reasonably successful company now with our two approved products. And I had to explain yesterday, I had a call with that same mom, and she just asked, just gut-

wrenching, "How could you do this? How could you stop these programs?" I said, "Look, let me tell you where gene therapy is and let me tell you where biotech is, and give you at least my perspective."

And there were three things I shared with her. The first is, look, the economy and the rise in interest rates has been tough for biotech and long data. I explained that it raises the bar for investors, which means they require a higher degree of certainty. Secondly, the diseases and the technologies are hard, harder than we even thought four or five years ago, including the manufacturing. But then the third thing we talked about... First, out of our control with a macroeconomy and interest rates. The second, somewhat in our control, in science and drug development, manufacturing, what we need to do to make sure that these are safe and effective medicines. But the third was regulatory science. And the example I gave was in one of those Batten's programs where we had done a pilot study and four children and we saw clear separation from the natural history. The guidance that we received, we've talked about this was great, now go do a five-year placebo controlled study. It just went down. It was an unfeasible study to do.

And so for that and all those different reasons, we had to pivot, and I hope someday Amicus can come back to it. But the industry broadly now, we have more than at least 200 rare disease programs that we've identified that have stopped in the last several years for all of those and many, many more reasons. So for me, as we think about it, we're on the dawn of this golden age of medicine. We've got so much hope and promise and we're getting in our own way. People think, for me as a parent or patient advocates or entrepreneurs, well, we will take any risk. We'll do anything. And that's not right. That's nonsense. We will take smart risks, but we need to think about it. And what we do at Amicus is ask everybody to think, if you had the disease or you were the mom or a dad of a child with the disease, what would you do? When would you start a program? When would you stop it? How far would you push?

Because time and money and all those resources are limited for parents and foundations and companies. And we've got to think about that in a practical world and it means, in partnership with regulators, we need to think of each drug and each disease uniquely and think about the risk benefit assessment uniquely. And that's where biomarkers have to be an incredibly important tool. And I think it was years back, AML had given a talk and shown that of the, I think then, maybe seven or 8,000 rare diseases, at the pace that we were going, it was going to take 150 years to treat half of them. That doesn't work, so let's find a way to make it work and let's take smart risks where and when we can and let's work together as a community.

Susan Winckler: I'm struck, John, the foundation was created to help advance regulatory science because Congress recognized that there's a lot of science. You have the evolution of science, great people working on great things, but the regulator has to keep pace with that. And it's really challenging.

John Crowley: It is, just like we as innovators and academic researchers, NIH, the whole ecosystem, this virtuous circle of what it takes to make a medicine is really, really hard. And that's where we need to work together to make sure that regulatory science is progressing in lockstep with what we're doing in the clinic, in the benches, in our companies, our universities. So when we think about that, biomarkers are an important tool, as are natural history studies, Bayesian statistics, adaptive designs. And in the rare diseases, the whole notion of pick an endpoint, in muscle diseases, pick a six-minute walk and do a great big large study and roll the dice. And if you hit a P of 0.05, you win. If you don't, you're probably going to lose. That doesn't make any sense as well.

Think about it as a physician or a parent deciding whether to have a child treated. You'd look at a whole range of risks and benefits, a heat map. They did this. FDA did this very effectively with Ultragenyx and Mepsevii when they looked at the multi-domain responder index, and as we ultimately did with our Pompe program, and it just lit up green. You knew it was working, and this isn't easier. It's not a lower bar. I really, really don't like the word or the words regulatory flexibility. It unnecessarily implies a lower standard, and it's not. When we're bringing all these tools to bear, it's actually a higher regulatory science that we're asking for and that we need, and that's what we need in rare diseases, and now's the time that we need it.

Susan Winckler: Which helps us. That's, I think, a more helpful lens in thinking about the advancement of science and the sharing of information.

John Crowley: Absolutely.

Susan Winckler: That's part of what's needed.

Dr. Edward Neilan: Can I put a question to John?

Susan Winckler: Absolutely.

Dr. Edward Neilan: Sorry. I'm guessing, John, you might prefer preponderance of the evidence over...

Susan Winckler: Well, we can't change the statute.

John Crowley: Yes, we're not going to change the statute. No. You want the gold standard, right? You want safety and efficacy, but how you judge that is going to be different. Each molecule, each disease. The risk you're willing to assume, the evidence generated that you need for substantial evidence of efficacy to support approval has got to be different in each disease. And that's what we really need.

Susan Winckler: So let me turn, Dr. Ho, to you. You're a neurologist and a drug developer for both rare and broad indications, and have the focused lens coming from Denali Therapeutics. What would you highlight?

Dr. Carole Ho: Yeah, great. Thanks Susan. So I just first want to say I'm just very grateful to be here with this community. I think just starting broad, I've worked in drug development in therapeutic areas, include adult neurodegenerative disease ophthalmology. And I think in those areas, we have seen the use of biomarkers, the use of anatomical endpoints to potentially support approval. And so I think that this has been done for larger indications. And now as we think about what we have in front of us here today in addressing these MPS disorders, we have really great science that you all heard today. So, why are we here today? We have a huge unmet medical need, and there's an urgency to this. Patients are dying because they have accumulation of this toxic substance in the brain that is leading to irreversible brain damage. We have a community here where we are coming together to build consensus, and it was wonderful to hear the talks today where I think there's alignment across our academic colleagues, our industry colleagues, physician scientists, that CSF HS is a suitable biomarker that is likely to predict clinical benefit.

I think what's very important right now about the science is that the science is emerging and is progressing. And I want to applaud our FDA colleagues who we've seen them recently at the world meeting, learning about the science. That's really important. We need to embrace that science. But I'll also just note that the science is not that new. The accumulation of heparin sulfate and glycosaminoglycans, this has been used to support approvals in peripheral disease. It is the way that now you've heard diseases are diagnosed. This is how they track progress. This is how they make sure that the patients are taking their medicine and it's followed when patients even, for example, need to take a vacation and they miss a dose, well, they're following those urinary gags to make sure that they know when the patient needs to come back. This is really not that new science, but what is new is really understanding how this science can be measured in the brain.

With all of this, we need the FDA to move faster, and I think you've heard the challenges that we've had in clinical development looking and relying on clinical endpoints. It's extremely challenging. We heard from Dr. Muenzer, we heard from Dr. Jones, we heard from Mr. Dant on the challenges of looking at clinical endpoints, and now we actually have science that has progressed that we don't have to do that. These clinical endpoints in these rare diseases with low prevalence take a long time, eight to 10 years from start to finish, particularly when you're looking at neurologic endpoints. That's really important because these programs are taking longer than they did for development of peripheral enzyme replacement therapy. This costs upwards of $500 million to develop these programs over eight to 10 years. And most importantly, patients are asked to wait for eight to 10 years. That essentially means that you're impacting a generation of patients and a generation of families to try to understand if these medicines work.

I was very struck by the point that several made about the fact that the ethics are questioned on doing randomized placebo controlled trials. As a drug developer, I'm finding myself in a really challenging position because we are asked to do those randomized double-blind trials, and we have engaged with the community to understand the acceptability of that. And while we've heard today that the ethics are questioned, we've also been told, "Well, if that's the only way you can bring a medicine to our diseases, then that is what you need to do." And so we have done that.

I think as we look at the science and we look at where we are today, we are ready to use this pathway for accelerated approval, and we need to apply this and we need to move right away. The FDA understands this, and there is a guidance that a draft guidance started in 2018 for single enzyme rare diseases that have accumulation of substrates. Sounds exactly like what we're talking about. In 2020, that guidance was made a final guidance, but that has not been applied yet to these therapies. And maybe there are a number of questions why. A question might be, well, with CSF HS, is that reflecting brain HS?

I think we heard very clearly from our speakers today, from Patty Dixon, from others, that there is clearly a relationship that we can clearly define between CSF HS and brain HS [inaudible 02:26:48], which showed very nice data across a number of programs showing that we have the assays. I think Maria Fuller really addressed a lot of the questions that Peter Marks brought up around the assay level of qualification and analytical validation that's required. We have these highly sensitive mass spec assays and now we have a pathway forward with this guidance, so we need to apply this guidance. And the question I think as we leave this workshop today, is not whether CSF HS is a suitable biomarker, but how do we use this and what is the threshold that's required to support accelerated approval? I think all the programs you've heard today need an action plan with the FDA to move forward, to evaluate these for accelerated approval. And the reason is that patients are waiting, and as you also heard today, they don't have time.

Susan Winckler: Thank you, Carole. You summed up my recap. I don't have to give it at the end of the meeting now because you captured much of that. Well, Dr. Fathy, we've been talking about regulators all day, and now you can step to the microphone along with your colleague, but as you sit at CBER, share with us the agency's thoughts on using biomarkers to support development and review of treatments for rare diseases. So taking it up a level, but thinking through that. We will just put it to you, is the agency open to the use of accelerated approval in the rare disease space?

Dr. Cherie Fathy: Yeah. So first of all, thank you so much for having this discussion, for having me. I've really enjoyed listening to the panels today and the discussion topics. So I think Dr. Marks summed it up quite well. We do really support the use of appropriate biomarkers in rare diseases. At CBER, our goal is actually to advance the public health by ensuring that patients have products that are safe and effective available to them. We also recognize that for too many patients, we

need better treatments than what's currently available today. And we also all know that sometimes the pace of drug development is much slower than what patients and families can afford. And so for that reason, we see tools like biomarkers and accelerated approval as critical tools for getting patients access to new, safe, and effective medications in a timely manner.

And so we actually encourage our sponsors to evaluate for potential biomarkers throughout the course of drug development. And we also recognize that it's especially important and helpful when the disease course is rare or the progression is quite slow or variable, it can be a very important tool in these diseases. But we also recognize that biomarker qualification is a significant undertaking, and so we support collaboration in this space with us. That means communicating with us early and often so that we can be on the same page and support biomarker development as much as possible. It also means working with our partners in this space, so NIH, academia, sponsors, patient support groups, the nonprofit sector, because we work better when we all work together. We also want to emphasize that we are, and we recognize that we will have to collate multiple sources of evidence when we come to evaluate a biomarker. So that can range from an awareness of the scientific community's consensus on the utility and appropriateness of biomarker for its context of use to what the preclinical data is showing, like animal models, to genetic in vitro data.

Later on, we'll look at pharmacodynamic and mechanistic evidence. And even potentially, when appropriate and possible, the integration of real-world data and real-world evidence. I also think it's important, we oftentimes talk about, when we think about biomarkers, we think about those that are likely or reasonably likely to predict a surrogate endpoint, but we actually recognize a multitude of biomarkers, and that ranges from those that can improve the ease and accuracy with which we can identify patient populations to those that support trial enrichment, like identifying patients who are most likely to benefit from a drug to, later on, those that can enhance patient safety by identifying toxicities earlier. And then of course, surrogate endpoints. Those are likely that our predict clinical benefit or reasonably likely. When we're assessing these biomarkers, we want to make sure we have a really good understanding of how this biomarker is going to fulfill an unmet medical need, how it's going to benefit our patients.

And we also want to very importantly make sure that we understand the risk of a biomarker not working. Dr. Marks brought this up this morning. We want to know what are the potential consequences of a false positive or a false negative. These are really critical for us to understand as we're qualifying biomarkers. And we have lots of resources available for sponsors as they come to evaluate a biomarker, to develop a biomarker. So everything from individual meetings with us to CDER's biomarker qualification program. We have a guidance document on biomarker qualification, looking at the evidentiary framework for developing a biomarker. We have the best resource online. We have even guidance documents specific to rare diseases, looking at drug

development considerations and biological products. So, that's specific to biomarkers.

And when it comes to accelerated approval, like I said earlier, we see it as a really important pathway for expediting access to treatments for serious diseases that don't have meaningly efficacious treatment available. And so we recognize that when it comes to patients and family members, when there's an unmet medical need, they may be willing to consider an increase or unknown risk if it means that they'll get a meaningful treatment benefit. And our job at the FDA is to really help identify and elucidate those risks as much as we can relative to the disease progression and support the development of safe and effective drugs. Sorry to use the term, but this is our way of regulatory flexibility in that we can support the development of products that are safe and also that there's substantial evidence of effectiveness through adequate and well controlled trials.

And I think you can see our commitment to this space by looking at how many programs we have available to support the acceleration of rare disease drugs. So we have Dr. Marks's the START pilot program, which is akin to Operation Warp Speed for vaccines, but in the rare disease space. So when we can work nimbly, can we support sponsors getting to the finish line faster? We have, and I'm sure I'm going to mess up the allocation of the words here, but we have CDER's Rare Disease Cures Accelerator, which is-

Susan Winckler: Close enough.

Dr. Cherie Fathy: Something like that. It's available online, which is a centralized platform or infrastructure for characterizing rare diseases, developing endpoints and trial conduct. We work with organizations like the Critical Path Institute to further characterize the natural history of diseases. And for biomarker development, we have the Rare Disease Advancement Endpoint Program, and we also have funding opportunities. Like right now, there's grant opportunities available for rare neurodegenerative diseases to support the studies that look at natural history and can qualify biomarkers in that space. And we hope to continue to be able to do that.

Susan Winckler: So I hear the extent of the activity, which also then tells me that in fact, while many don't recognize that the agency is, you want the dialogue and to better understand working within the... You are a regulator, and so you have certain constraints, but there's interest in conversation and collaboration.

Dr. Cherie Fathy: Absolutely. From a personal perspective as an ophthalmologist, it's very exciting for me to see any sort of advancement in this space. And so my hope and why I joined the FDA, one of the many reasons why I joined is that we can be part of this important conversation and we can support really important programs getting to the finish line with the best science possible.

Susan Winckler: So Dr. Imperato, thank you again for joining us, and I hope you're feeling well enough to answer this question. If not, you can toss it back to Cherie. So as you think about using biomarkers for regulatory action, Dr. Fathy just reminded us of really the scope, a significant extent of opportunities that are available, and yet we recognize there's a need for more. But what challenges do you think in using biomarkers for regulatory action? Because that's a question that only regulators can answer. So how do you think about that? And then do those challenges end? We actually know they don't, but do they end after? How do you think about navigating those challenges in the post-approval period?

Dr. Gavin Imperato: Sure. Happy to answer the question. Are you able to hear me okay?

Susan Winckler: We can hear you.

Dr. Gavin Imperato: Okay, great. First of all, apologies that I wasn't able to join in person. I have COVID. Fortunately, it's relatively mild. I managed to avoid getting it for four years, but my luck ran out, so it was great to listen in virtually on the presentations earlier in the day and want to thank all the presenters. It was really helpful and illuminating, and I really appreciated hearing the presentations and walkthrough of all the data that was presented.

So there are a number of challenges, and these are obviously well-known to this audience. I'm happy to provide some insight into how we see this from within the walls of the agency. And I want to reference a comment that Mr. [inaudible] made in his presentation this morning, and I'm loosely paraphrasing. Essentially, the essence was that our regulatory system must evolve to reflect advancing science. And we at the agency absolutely agree with that.

That is precisely the reason that we are leaning into these tools like biomarkers and accelerated approval because they are readily available to us in our regulatory toolbox, and they can really move the needle in delivering novel therapies to patients in need. And as Dr. Fathy mentioned, we have a whole slew of programs and avenues for interaction at the agency that are all in some way geared towards accelerating, enhancing, promoting, lowering the Delta G for interactions that are going to be substantive and productive with regard to rare disease drug development. So really, there are a lot of challenges clearly, but a lot of opportunities as well. As I heard the presentations today, I was thinking about how do we make sense of what these challenges actually are and what are the different sub-set of components, because it's nice to step back and think about the big picture and then ultimately come down and think about how do we operationalize this on a day-to-day basis within review divisions at the FDA where the rubber meets the road?

And I was thinking that the challenges fall into essentially three categories: evolution, collaboration, and communication. And I think there's an internal and an external component to all of those. With regards to evolution, and thinking back to Mr. [inaudible] comment, there's been an explosion in basic science over the past many years. That explosion in knowledge has been rapidly

translated to the clinic in the setting of many diseases, and that's great news. It presents a challenge from the regulatory standpoint because that advance has happened so quickly. And so reflexively, from the standpoint of a regulator, how do we deal with the unique regulatory challenges that are presented by advances that are wonderful, products that clearly have potential by virtue of available data, but don't fit squarely into a known regulatory paradigm? And so this really segues into the second big bucket, and these are all overlapping, and that is collaboration.

So it's clear to us, it has been for some time now, that engaging all of the stakeholders in the drug development ecosystem is critical. First and foremost, the patients. We gain so much by interacting with patients and listening to patients and caregivers because when all is said and done, the drug is for the patient. And we really want to make sure that all of the decision-making that occurs from the regulatory standpoint, from A to Z, centers the needs of the patient, so it was really helpful to hear some of these patient stories earlier in the day because that comes to tremendous benefit for FDA staff because we can easily lose sight of the fact that there's a human behind charts and graphs and data. And that's a really, really critical thing to recognize.

So continuing with this collaboration component, so there's the external component. Settings like this are super valuable to us. All of the forms or interaction that Dr. Fathy mentioned, particularly for rare diseases. And I also want to emphasize the collaboration that happens within the walls of the FDA. We have, simply for logistical purposes, a highly structured organization with regard to the disciplines. So for any individual drug development program, there's a chemistry, manufacturing and controls team. There's a pharmacology toxicology team, there's a clinical team, there's a clinical pharmacology team, there's a biostatistics team, and the list goes on depending on the complexity of the submission. What we've recognized relatively recently is that because the evidentiary framework for biomarkers and accelerated approval is obligately holistic, that interactions among those different disciplines is not a nice to have. It's absolutely essential, particularly because we recognize that, speaking specifically from the clinical perspective, so many of the questions that we would ideally want answered in a particular format, like a clinical study, we may not be able to answer in the form of a clinical study.

And so it's essential for physicians, clinical reviewers to understand and engage with pharmacology, toxicology colleagues who are evaluating data from disease-relevant animal models. And that is something that I have seen really come into full bloom recently at the agency. It's not something that an external audience would be privy to because it's part of our day-to-day workflow. But it's something that I think is important for patients, caregivers, advocates, and sponsors to know, that we are really operationalizing the commitment to patients and to evaluating totality of evidence by virtue of all of these interactions and efforts to enhance internal collaboration. Central to that obviously is open communication, so we really are making efforts to do that internally. And in addition, the communication piece with our sponsors is really

prominent. It's part and parcel of these programs that we have in place to accelerate rare disease drug development.

Even absent engagement in the context of one of those specific programs, all of our alphabet soup of formal meetings that we have with sponsors are where we ultimately work through these critical issues. So we're very fortunate in the Center for Biologics and in the Office of Therapeutic Products to have a very positive culture when it comes to collaboration and communication. It's something that Dr. Marks and Dr. Verdun foster, and so it is definitely a focus to enhance the quality of our communication with our sponsors because we recognize that these are difficult issues to wade through, and communication is essential. It's difficult to overcommunicate in settings where there are so many possible points of miscommunication. And so we have, of course, limited time and limited resources. I would love to be able to pick up the phone whenever there is a quick issue you'd like to have resolved by speaking to a sponsor. We're bound by the formality of our interactions. But we are looking for opportunities wherever possible to enhance the closeness and the quality of those communications with sponsors. So I totally understand the frustration that's been expressed in various ways.

I don't know that this will come as any degree of reassurance, but regulatory review is a human enterprise. We haven't been replaced by robots yet, and so we do approach drug development and regulation in this space with a tremendous degree of empathy. And it is really very, very challenging. I would say the most electric day at FDA bar none is when we announce a novel product approval. It is so exciting.

So the review teams at the agency are so excited about delivering novel products to patients, and as Dr. Marks highlighted earlier this morning, accelerated approval and biomarkers are really, really powerful tools. We've used them. We're going to continue to use them, and I think the future is very, very bright and I'm very excited about what's to come, and I'm fundamentally most excited for what this is going to mean for patients and their families.

Susan Winckler: You're capturing the evolution, the collaboration, and the communication. I was struck that your collaboration was both outside the agency, and then within the agency, and that was a question that came up quite a bit earlier in the day. But I want to make sure that we turn to Dr. O'Neill to think through, as we said, and we heard powerfully today that top of mind in discussion in rare and ultra-rare disease is the voice of the patient and their caregiver.

You've been described as a powerful and candid advocate for accelerated approval, and I want to make sure I get this right if I paraphrase it, but the preference for the uncertainty of promising performance and potential risks versus the certainty of a painful life. What would you want to make sure that we think through as we are talking about opportunities in the ecosystem in rare disease development and this framework that Dr. Imperato, Gavin, I'm going to

get it right, not today because I have them all in my head, but on evolution, collaboration, and communication.

Dr. Cara O'Neill: Yeah, thank you Susan. It's really an honor to be here with literally the experts in the space. The discussion has been incredible. The information shared I think has taken us all to a new level. And so it's the end of the day and much has been said, but I'll share my perspective where I come from, which is really kind of a blended perspective, that of a pediatrician who's been able to become a patient advocate and author papers on clinical management guidelines and caregiver preference for treatments for Sanfilippo Syndrome. But the reason I'm here is because our personal life was shattered by a diagnosis of my daughter, Eliza, 11 years ago.

And over that time, if I take this view back, the cycle that we see in repetition, which John described is this. A company comes into the space, yay, we're excited, there's hope. The science is excellent. There's a lot of promise. The company engages with the agency. There's dialogue, there is challenge in clarity about what that path forward is, I think on everyone's part. And the company comes back, there's adjustments, there's changing of the bar, there's a lot of back and forth with long timelines in between. And so we have now the timeline has been drawn out, the monetary costs have gone through the roof and the company ends up either shelving the program or going out of business trying to make it work. Either way, our children are abandoned. Whatever the reason, this is the result and our kids are the people who pay the price for it. You can rinse and repeat that for every neurologic MPS disease and so many other diseases.

We've heard a lot about this long timeline of the neurologic deterioration, and I think it's clear and evident that that does not allow neurologic MPS diseases to fit into a traditional drug development paradigm. We have been trying to force it into that model, and we have resulted in exactly zero approved therapies directed at neurologic component of MPS diseases over the past years, including no treatments of any kind ever for the most prevalent form of neurologic MPS, which is Sanfilippo Syndrome.

So clearly we are stuck, we are all stuck, and I think we are all trying to figure out how to get unstuck. But there really is a regulatory path. The accelerated approval path is here for us, and I think this has allowed us a chance to really talk about how we can move forward in that. You asked about uncertainty because in accelerated approval, naturally uncertainty is going to be a component of that, but I think we take a step back and understand what we do know for certain because there's a lot more that we do know than we don't know.

And what we do know is that this disease causes unrelenting losses of every skill. And you saw that in the videos this morning. Our kids go from singing their ABCs to utterances, stuttering, and then silence. From enjoying their birthday cake to being fed through a gastrostomy tube in their stomach. Running wildly

on the beach through the streets where you can barely keep a hold of them to being unable to move and even roll over in bed. They lose the ability to engage with us and the people that love them most. Our children become locked in and lost to us even though they are right there in front of us. And after their words are gone, we're left to become detectives trying to quell the frequent periods of screaming and distress that we live with every day.

We know our kids die early, but one parent said to me, "You know what? I know what's coming, but I fear my child's suffering more than I fear her death." And that is true. Living longer is important and we want our kids here, but we want them to have a decent quality of life and that means something different to all of us. What I just described is the reality of no treatment, and that is a very real risk. Sanfilippo and neurologic MPS disease itself causes catastrophic irreversible brain injury and harm to every single person who has this disease. And logically parents weigh these facts and risks heavily in their risk-benefit considerations. And we ask that regulators also meaningfully incorporate this weighting into the regulatory decisions they make as part of their PDUFA mandate.

We also know that withholding treatment in the face of likely beneficial therapies known to address that primary substrate, that toxic heparin sulfate, causes harm. And we should be thinking about this. We've heard today about children being subjected to randomized trials, and that is a real risk that I think we are overlooking. Former acting commissioner, Janet Woodcock spoke about this when she was reflecting on the use of placebo controlled trials in rare serious disease. And she said, people say that they want placebo controlled trials, but I always ask them, "Would you be willing to die for a P value?"

And in this case, specifically in our context, I would say, would you be willing to let your infant or toddler during the period of maximum cognitive vulnerability and critical neurodevelopmental windows to be enrolled in a study where they will be allowed to develop irreversible brain injury? I mean, we have got to think very hard about this and find a more humane and ethical way forward. I know that our science with these biomarkers will allow us to make a more creative pathway. When we think about safety, that's one of those risks. That's one of those uncertain factors, but really by the time we arrive at considering accelerated approval, safety is no longer a hypothetical kind of amorphous thing. We have already gathered so much information from the Phase 1, 2 safety studies, and when doctors talk with patients about a drug that may be approved by accelerated approval, they will have that information. And as John said, we make smart decisions. We are not willy-nilly throwing our kids to the wind. We want the information. We need the information, and that needs to be made on an individual basis with our healthcare team.

We really see these risk-benefit calculations play out with the actions of patients in the clinical trials though. And that's going to give us a real world example of what is the risk tolerance for these populations? Well, it's playing out before us in those patients that have been coming into the clinic year after year, getting

weekly infusions into a port in their brain, going into the ventricle of their brain. Or being sedated or held down for monthly spinal fluid infusions as in Cole's case. And those really reflect the risk-benefit profile and their tolerance for uncertainty around long-term clinical outcomes. Families are not always steeped in the science and the details of that, but they do rely on their doctors and they do understand the meaningfulness of heparin sulfate's impact upon their child very clearly. And from the moment of diagnosis, they know the heparin sulfate in excess is the problem.

It is the disease. It's what defines it. It's what was used to make their diagnosis, and it's what drives the pathology. So they appreciate when they understand that, yes, this treatment reduces heparin sulfate. That's a very accessible piece of scientific information in their decision making. So what residual uncertainty are we left with? Obviously we will need lengthy follow-up of patients to fully elucidate the clinical effect of any treatment. That's required. That's desired by patients as well as everyone else. So we absolutely want that to happen. We've heard today about treating the ideal patient, this very young presymptomatic patient, and absolutely that's ideal, but we live in the real world. And the reality is that those patients are identified exceedingly rarely, and usually because of a sibling. 99% of the identified population is symptomatic, and those patients too can have significant and meaningful benefit from treatments. It will take longer to see it, to see it diverge from the natural history, but that's the right thing to do. We can't leave a whole generation of kids behind just because we would like to see a large magnitude effect.

And those things really are only going to happen in a post-marketing situation. So I think our community's tolerance for uncertainty is quite well understood and respectfully, we ask that the FDA, and I think we're hearing this, that this robust discussion, hearing the advancing science, looking at this large body of evidence that they'll take that back and help open the door to equitable access to this really important regulatory pathway, which is accelerated approval. We have safety information, we have a valid biomarker, and we have treatments that are really right here about to be lost that are reasonably likely to help children. So we need now. We need now. We always need now, right? But we truly do need now or we're going to lose another generation of our kids.

Susan Winckler: I was waiting because I was pretty sure there was going to be applause there.

So you are helping in the ecosystem that we were talking about, right? And the challenges in the ecosystem. I think, John, you talked about it, Dr. Wilson, you did as well, that we've got to think through what do we know? What don't we know? How do we apply it? It's difficult space, but there's a reason to do the difficult work, and that's important for us to think through. Dr. Wilson, I noted that you said you wanted to come back to something. Do you remember what it was?

Dr. James Wilson: I can't remember what it is, but I do have a thought.

Susan Winckler: That's all right. Share that.

Dr. James Wilson: When I was talking to some of the panelists beforehand about this meeting, it was described in various ways, but some brought it up as a watershed moment. I've been doing this for a long, long time, and there's something different. I feel something different. The science has evolved like science does, faster than probably we would've ever expected, and health authorities are engaged. It's different now than it was before, but since I run the Orphan Disease Center, I think the one thing that really has changed is the patient advocacy groups have educated themselves and become powered. And maybe it's just timing, but I think the time is right now where people are coming together and I would argue that all of us come together and let's try to look forward rather than backwards, but hold each of us accountable to one another in this moment that this is, and I think this is the moment.

Susan Winckler: I think then you set us up perhaps. Somehow we have gone through nearly all of our time with insights from the people who said we needed to collaborate. I think this matches a bit the list that you laid out for us earlier today, Mark, in making sure that we had the clinicians, the drug developers, the patients, the industry, and the regulators coming through. I want to give you each, I'm not going to ask you a yes-no question, but I do want to give you each a minute to say something about this space. It would be great if you want to say what's most helpful in navigating the challenges of qualifying biomarkers. If it's what's the one thing you think we'd like to see in addressing rare diseases. You get one minute and one shot here. And Carole, you're first, so I'll tee you up. We'll go Dr. Ho, Dr. Wilson. Dr. Fathy.

Dr. Carole Ho: Yeah. So I want to just go back to why we're here today. And I think you've heard there's an urgent need. You've heard from Cara. You've heard from Mark, and there are other moms of children in the audience here, and we have a path. The science really is breaking open for understanding these neurologic diseases and also what is downstream, the disease process that's discussed in the 2020 guidance. If you can understand the disease process, then it's appropriate to use this accumulated substrate as a surrogate biomarker to support accelerated approval.

We want to see that happen, and we understand that there are a lot of processes in place, and this isn't something that can happen overnight, but this is a problem that as Cara really outlined, we've been facing over a number of years. While the science is accelerating, we need to accelerate our regulatory pathway to get these medicines approved. And that's what I really hope that today serves really as a catalyst for the community to come together for academia, for industry, for our patient advocacy, to come together to unify on a path forward and work collaboratively with the FDA across both the CDER and the CBER division of the FDA, to have a unified path that's clear for all of our companies to come forward with our promising medications with a path for review and approval.

Susan Winckler: Dr. Wilson.

Dr. James Wilson: So aspirationally, what I also suggest we think about as we come forward here in the United States is that genetic diseases are global and the need is global. And there are unique challenges, but also unique opportunities. And I think the advocacy groups often bring those communities together. Social media helps. And I was delighted to see that FDA has brought forward a program to try to harmonize. Let's get this done, but let's then take on the world.

Susan Winckler: Right. Dr. Fathy, Dr. Imperato, Dr. O'Neill, I'm pointing in the wrong direction. So Cherie.

Dr. Cherie Fathy: So again, thanks again for allowing us to have this conversation. I think it's easy also to see the FDA as kind of a faceless organization, and hopefully situations like this allow us to really emphasize that we join the FDA because we do want to support our patients in our field to get access to treatments that are safe and effective for them. I really think we have very talented people at the FDA pushing the boundaries of regulatory science to really get us promising new ways to look at how we can answer these tough questions in a very sound and safe manner.

Susan Winckler: Great. Gavin, then Cara, then John. Gavin.

Dr. Gavin Imperato: Thanks. Yeah, I certainly echo that sentiment. And I would add that there's a tremendous amount of enthusiasm at FDA about bringing novel products to patients in need. There really is. And I think that as many have highlighted in today's workshop, we're living through a paradigm shift. And that's naturally going to be challenging. It's going to be painful, but the only way to get through it is together. So I think the collaboration and communication are really going to be essential. And the other point I wanted to highlight is that Mr. Crowley had mentioned this, we at the agency cannot be or cannot function as though the broader ecosystem of drug development does not exist.

It's a key part of our mission to facilitate the availability of novel products for patients in need. And we can only do that if we have drug developers who are actively engaged in the space. And so there's a responsibility, I think, for the agency in that regard. And I think leveraging these tools that we have, biomarkers and accelerated approval, will really be critical to demonstrate that there is a path forward for products in this space, that they are ultimately going to get to patients, because that's such a critical part of our mission. It's fundamentally our job and it is congressionally mandated. It's the law. We are with some degree of interpretability and flexibility delivering what we can through our statutory authorities to meet unmet needs. So thanks so much again. This was really, really, really productive and appreciate everyone sharing their perspectives.

Susan Winckler: Fabulous. Cara, John, Ed. Kara.

Dr. Cara O'Neill: Gavin, I really appreciated your commentary about the collaboration piece and the communication piece, and I think absolutely that's the key. So much of things we're guessing, we're trying to mind read, we're trying to anticipate and prepare. And so when questions come up that are related to the patient experience, risk-benefit, things like that, being able to hear from the agency what those are, instead of trying to maybe guess what those are and develop materials and understanding around those would be incredibly helpful moving forward. I think the fact that there are so many of you here and online is a signal about what you know needs needs to move forward and the goodwill to do that. And I'm just very encouraged by that and thankful.

Susan Winckler: Fabulous. John. Ed. The clock is ticking.

John Crowley: I'll just say, like Jim I'm also very enthusiastic. I do think there is a lot of history here. Some of it's very good, some of it very challenging over many years. But now is the time, and this is the moment I think, as we look forward. So I'm very enthusiastic about what we see and we talk about collaboration, communication. It also means resources and leadership that come along with that. Obviously from the great leadership of Dr. Marks to so many great people at the FDA. And we need to not only collaborate, but empower each other. I'm an advocate of bringing this together under a center for rare diseases. I think now is the time. You saw how it transformed the world of cancer and oncology. So to reduce the inconsistencies across CDER and CBER to bring more resources, to bear greater leadership, I think that could be a very effective tool and a discussion we should have as we look forward.

The last point I'll leave you with is one of time, and Cara, you so eloquently and passionately and emotionally appropriately described that, for all of us in this room to think about that, is time. When we look at what we as developers or parents or regulators think, what is substantial evidence of efficacy and what is sufficient for safety and efficacy to think about time to bring that in. Because if we start with the assumption, what you also said, Cara, that we could be dooming another generation children in these diseases of neurodegeneration specifically. If we start with the assumption that that's not acceptable, so how do we then begin to think about what do we do? And what tools do we bring to bear? What mindset do we bring? Because delay and denial we know will lead to suffering and death, and we all agree that's not acceptable. So now's the time.

Susan Winckler: Dr. Neilan.

Dr. Edward Neilan: Yeah. So I want to reiterate something that's already been touched on today, which is that for the rare genetic diseases where, unlike common things like headaches or asthma which we still don't fully understand, we do know exactly what the underlying cause was, and especially for the metabolic disorders, we also know the next few steps towards the pathogenesis. And this really seems like a prime area to use biomarkers and accelerated approval and get it right many more times than you get it wrong. And I hope that the careful work that

has gone into this meeting and sort of the dissection of the current state of affairs for neuropathic MPS may not only lead to good decisions coming for those diseases, but perhaps be another demonstration of this more broadly.

Closing Remarks

Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler: With that, we'll take your enthusiasm. We'll close you out. I am sorry that we are three minutes over. We strive to not do that, but we also had to give voice to these extraordinary panelists. So join me in thanking all of our panelists.