Dr. Ozlem Goker-Alpan:

Hi. Good morning everyone. Thank you for coming. That's bright eye, bushy tail, it's 6:45 here. So I would like to actually welcome you to the satellite symposium that we are hosting in conjunction, LDRTC is hosting in conjunction with World 2025 with Affinity CE as a CME symposium. So this section is going to be on early treatment and we're going to talk about what we mean by early treatment. We want to transform the lives of these infants and children that are diagnosed either early screening or through newborn screening. So I just want to have a very brief introduction. And so if you look at the graph and the road, the road goes to somewhere non-return. So we want to decide what is the non-return in a disease process.

Unfortunately in our medical education, we are taught to identify the diseases when they present with symptomatology. So that includes organ dysfunction and organ complications. Like in Fabry disease, Gaucher disease, the signs of symptoms of disease actually are point of no return. So when the point of no return occurs, there are pathological changes already. Neuronal death, bone destruction, and even at that time you can intervene by decreasing the substrate levels, refolding the protein, so on and so forth. The process will continue to progress despite any intervention that is made. So this is the most important process we need to remember while we see these infants or very young children and when to decide to to not to reach that point of no return.

So once structural and functional damage is established, therapy may only slow the progression, but it will never be able to restore the normalcy. So at this time and at 21st century, we need to expect normalcy from treatment, not improvement. And I want to actually compare a longer standing, delayed diagnosis, and delayed therapy to actually higher disease load with a shorter duration of therapy. So all these kids that are diagnosed through newborn screening, I'm going to give examples with GD actually in the next slide. They are actually mildly symptomatic, which means that the disease already started. So they have a higher disease load to present that early. But I want to actually make you pay attention to the graph.

So these are 13 children that we treated less than one, some of them were less than two, and then we were able to decrease the substrate levels. Lyso-Gb1, these are all cohort of nGD less than six months to almost acceptable or normal levels, which is 20 or below. And these children came with Lyso-Gb1 at about 80-90, so on and so forth. Very, very high levels. If you take an adult with 90 of Lyso-Gb1 with complications, you're never going to be able to achieve this ever. So I want to actually attract your attention and take the other speaker's presentation with this context. With this time, I want to introduce the invited speakers, David Kronn, Elizabeth Jalezo, and Uma Ramaswami.

Unfortunately, Dr. Jalezo had to attend the patients back in North Carolina, so Lindsay Torres will be presenting her slides. Thank you David.

David Kronn:

Thank you. Good morning and thank you for joining us this morning at this early hour. So I'm David Kronn, I'm the head of Genetics and Metabolism at Westchester Medical Center. So my experience is initially as a pediatrician and my early training and what we did at Westchester was actually to establish a newborn screening referral center. I started off with the lens of newborn screening before we actually saw any patients with Pompe disease. The idea of pre-symptomatic diagnosis was something that we really knew about before we actually saw any patients with Pompe disease. So we've had quite a bit of experience. This is nearly 30 years of experience with newborn screening and I've been pretty involved with the expansion of newborn screening in New York and also the expansion of screening in New York of Pompe disease screening.

So we're going to talk about a little bit of the spectrum of Pompe disease, how things have changed with early diagnosis through newborn screening, how the patients are actually doing and some of the lessons learned. So just a little bit about Pompe disease itself. It was first described in 1932 by Johannes Pompe, who was a Dutch pathologist. He described Pompe disease in a seven-month-old baby who died with severe idiopathic cardiomyopathy. And he saw the initial findings of glycogen on the slides when he did the autopsy. The enzyme also known as acid maltase or aglucosidase alpha was first described in 1963 and the gene was cloned in 1991. I put in yellow the key point is in 2006 when the first ERT for Pompe disease was approved, aglucosidase alpha.

And that was approved for the use in IOPD and LOPD. Initial experience showed improvement, but we knew that patients diagnosed symptomatically were not doing as well. And so there was initial... That was the initial period of understanding how patients would do and how they weren't doing as well and maybe some parts of the disease were not reversible. So that was when there was a pilot program in Taiwan to start the idea of doing newborn screening for Pompe disease. And that was very successful and we have a little bit of slides of that. And based on that success, newborn screening was expanded to the US and nearly every state does newborn screening. We started in 2014 in New York state. So we have about 10 years of experience.

In 2015, Pompe disease was added to the RUSP and we now have two additional therapies, two additional improvements in therapy over the initial Myozyme and Lumizyme. And so that adds to armamentarium and we've learned more about other modalities during this conference. So we all know about Pompe disease. I'm going to go over these quickly. The thing about it is that it's quite a spectrum of disease. So we have the severe infantile onset Pompe disease and then we have a later onset LOPD. But in between there's quite a spectrum. And as we're starting to do newborn screening, we're getting to see that there's actually differences between IOPD patients as well.

Not all patients present with cardiomyopathy at birth and there are some patients who present early with LOPD in the first maybe about a year of age. So there's quite a long spectrum. And so we're starting to understand the differences between patients. So again, early diagnosis is very important and we'll talk about that. And just a little bit prior to 2006, the survival in IOPD was very poor. Most patients did not survive beyond two years of age. And so really not doing well. What's also important, and I think something I learned from pediatrics was the Mercedes principle, go for the money. So once Pompe disease became a treatable disease, people started looking for the Pompe disease and we started adding it to molecular testing.

We would do enzymatic analysis more frequently. So we started seeing patients already in 2007. So it was sort of like before we thought before that we hadn't seen any patients and now at 2007 suddenly we started seeing many patients and so we built up a cohort of IOPD who were diagnosed symptomatically and then we moved on to newborn screening since 2014. We also know that there are delays in diagnosis and people are aware of this slide. And so patients with IOPD were only diagnosed when they became symptomatic and they did not respond so well to the therapy. And also we know that the long latency in diagnosis for LOPD, which occurred before 2006. People are much more aware of the diagnosis.

And so patients with muscle weakness now will have molecular testing done much earlier. So hopefully that will lead to a lot of earlier diagnosis for patients who are beyond the newborn screening age. So here's a little bit of a problem with Pompe disease. So what is Pompe disease? So we have to confirm that there is a GAA deficiency. We would love to have biallelic pathogenic GAA variants. And this is quite a problem because it seems that there are a lot of private mutations in patients with Pompe disease. So the genotype phenotype correlation is not very well-defined. There are some patients who have severe

phenotypes and they end up with IOPD. And we know patients with a splice site mutation are more likely to have LOPD.

But there's a huge variation between, so it's not clear that every patient who's picked up early will actually go on to be clinically symptomatic. And so with newborn screening, we're picking up patients who are not symptomatic, they're in the presymptomatic phase of the disorder. Also, there are some biomarkers, elevated CPK Hex4, which may be useful, but we probably need better biomarkers and that's something that's being worked on at this time. Also, the classification of Pompe diseases is quite difficult. I mean we're all aware of IOPD, LOPD, and then we're now seeing a larger spectrum of variant patients, patients who present later who don't have cardiomyopathy at birth with IOPD and patients with LOPD who present early.

We also have coined the classification of at risk for LOPD for patients we pick up on the newborn screening with LOPD who may be at risk for developing it over time. We do not know at this time whether all patients who are diagnosed with newborn screening will actually become symptomatic. And that's something that we have to follow. And we have a cohort of patients now who are approaching one, they're about 10 years old now, but we have only a few patients that have received treatment since they were diagnosed with newborn screening. So the initial Taiwan experience in 2005 and 2007, they had diagnosed, they divided the island into two and half the island was screened and half the island were picked up clinically.

The patients who were picked up through newborn screening, there were six patients, they all survived. They're all doing pretty well compared to the patients who are picked up clinically. They had a much worse outcome. In fact, in patients who are diagnosed with LOPD after six months of age, the prognosis is still quite poor even if they're started on treatment. It was added to the RUSP in 2015. One thing that is important to be aware is that the method of screening is different between states and that can affect the time at which the patient is referred to your center. In New York, we're very lucky in that they do have molecular testing so we would see a patient at about five to six days of age after newborn screening is done at 24 to 48 hours of age.

It also turns out that the incidence of IOPD is somewhere between 1:100,000 and 1:200,000. But the incidence of LOPD based on newborn screening is closer to one in 20,000, which is much higher than was expected from clinical patients. So that's something that we need to follow and see whether all these patients who are at risk will actually develop the disease. This is from the Taiwan study and you'll see here that the patients who were diagnosed through newborn screening were doing very well, whereas the patients who were diagnosed clinically had a much worse prognosis. So following the screening for newborn screening for Pompe disease has now expanded to nearly every state. It's a little bit slow.

There was a sort of a fall off during Covid and it took a while before every state started screening. So it's now nearly every state but not quite everybody. So when we see a patient, we're pretty primed to seeing patients. We actually see the patients and we also arrange for them to see cardiology on the first day of their visit to the newborn screening center. We send repeat enzyme assay, we do molecular diagnostics to confirm the diagnosis. And then we also review the initial molecular data on the CRIM status based on the Erasmus database. And that's very important to help us if we need to make treatment decisions early, if the patient has evidence of cardiomyopathy that the patient will be sent into the hospital and will be initiating treatment pretty soon.

And that's something that we're always considering. And also at that point, the CRIM status is very important to decide what type of immunomodulation will be done for the patient. Whether we do a full immunomodulation or modified immunomodulation with methotrexate. The patients who are diagnosed or considered to be at risk for LOPD will go into follow-up. And we follow the patients quite

closely in the first year because sometimes when we think it's maybe an LOPD patient, it actually has turned out to be an atypical IOPD patient. So we want to be quite vigilant in the first year of life because the cardiomyopathy in a patient with IOPD may not occur at birth but may occur at two to three months of age.

And that's something that we've seen in some patients. And so we're more vigilant now than we initially thought we'd have to be for these patients. So that's something you should be aware of when you see a patient with newborn screening. The patients who are followed through LOPD will do sequential evaluations. After the first year we don't continue to do cardiac evaluations at this time unless there's any concern. And we continue to follow CPK and Hex4 levels every six months. And then as patients progress and they're clinically stable, we may lengthen that to a year and we partner with their local pediatrician. One of the things we don't want to do is over medicalize patients who are at risk for LOPD.

There is a concern that patients will be lost to follow up. And that's something that we're very concerned about, that they don't come back, they don't believe that this is a possible diagnosis. So we want to engage the family and make sure that they continue on follow up so that we don't miss an opportunity to treat the patient. So these are the decisions that have to be made in sort of what we do with the patient, the CRIM status of course, that we've already gone over this and then the starting dose and frequency. So of course with patients with IOPD, we start at a higher dose and we are now considering the treatment options. And of course you've learned about some of these today during the conference.

The LOPD of course, patients who are at risk are more complicated. We have to follow them quite closely. So we have patients who have gone on for many evaluations. When they get older, we start PFTs and more systematic physical therapy evaluations and then we consider how they're doing. The CRIM negative patients and this is something that we worked with Dr. Kishnani early on and we knew from early treatment of these patients that these patients did not do well with just ERT alone. And so we now have this significant immunomodulation protocol with rituximab, methotrexate, and IVIG. And we've done this for several patients now and we're very happy that this has been really well tolerated.

And so we're now 10 years out with some of the patients and they don't have any sequelae of the effects. And in some patients we've actually done the regimen two and three times. So it is well tolerated. So we just have to support the patients during the time at which they're doing the immunomodulation. But it has had clear benefits for patients, especially if they're CRIM negative. So I just want to... Before this talk, I went and reviewed the patients we have at our center in Westchester. So we have actually eight patients with IOPD who are diagnosed since April 2014. As we concur with the data from Taiwan, they're all doing pretty well, I mean they're all walking, they're all ambulatory. Their respiratory status is pretty good except the CRIM negative patient has the need for CPAP at night.

So there has been some changes. There are some things that have changed with the patients. So we do see evolving hearing loss in these patients. A lot of them have speech delay, so that's something that we have to be concerned about and we're concerned about some of them having developmental issues and this is something that is evolving in some of these patients. And actually we saw a poster from Argentina where there was significant MRI changes noted on one of the patients with IOPD. So this is something we need to be aware of. And of course when Dr. Kishnani mentioned yesterday on the GI side effects that are becoming more apparent, so it is an evolving phenotype.

So they do show some progression even though they're pretty stable. So it's something that we have to monitor quite closely. So there is a need for a better therapy of course, something that perhaps crosses the blood brain barrier and that's something that has been considered and presented during this conference. So in the patients with LOPD or at risk for LOPD, as long as they do not have evidence of cardiac effects, we follow up at three months, we continue to do sequential monitoring of CPK and Hex4

and then this is done again at six months, nine months, and 12 months. And then after the first year, if things are sort of stable, there's no evidence of a rising Hex4.

If it was rising, we may see the patients more frequently and do biomarkers more frequently and do a more intensive PT evaluation to decide if they need to go into therapy. But after 12 months, we may go to six months and we do it every six months till about three years of age and that we continue yearly and we partner with the local pediatrician to make sure the patient is being followed closely. So we don't want to miss an opportunity and we try to work with the patients, we spend some time with the families to make sure that they're aware of what to look for as the patients get older. So when do we start a patient who is asymptomatic or showing minimal symptoms? Obviously if they're showing rising biomarkers, that's a red flag.

Any evidence of muscle weakness on sequential exam is a concern. And failure to meet milestones, of course that's a major concern. Head lag, worsening PT evaluation, abnormal PFTs in some of the older patients. This becomes a negotiation with the family because a lot of families do not want to have a child have ERT every two weeks. So we have to discuss this with the family. And if there's a concern, we may see the patient more frequently, shorter interval of visit to make sure that they're aware this is happening and this gets buy-in. We need to have buy-in because we want to make sure that there is a very good compliance with treatment because it is a significant burden on the family to start ERT.

So I think we've already talked about this. So as the patients get older, we're actually starting doing more formal PT evaluations and pulmonary function tests because they're able to do the actual evaluation. So that's something that we're quite keen on getting done. So the lessons learned. So previously, we had thought of two diseases, LOPD and IOPD. There was no effective treatment prior to 2006. The outcomes of IOPD were suboptimal with clinical diagnosis and that's something that was very significant and something that really led the impetus to develop newborn screening. For LOPD there was previously long delays in diagnosis. What we've learned is Pompe disease is very heterogeneous even within IOPD.

There are variations in presentations. Not all newborns have cardiomyopathy at the time of the initial evaluation. And even patients we're seeing picked up clinically have quite variable phenotypes in terms of LOPD. There is no clear genotype-phenotype correlation in a lot of patients and that is a concern and it makes it difficult to make clinical decisions and management decisions. Hopefully that will improve as we have more data from the follow-up of the patients at risk for LOPD. Of course we're quite aware now and the benefit of early treatment of IOPD with newborns diagnosed after newborn screening. So that's clearly a benefit and clearly one of the major benefits of newborn screening.

So what's in the horizon? We've learned more about new treatments and possible treatments that cross the blood brain barrier will be important to look at. And the long-term outcome for patients diagnosed at risk for LOPD is not clearly understood at this point. Most of the patients that we're following at risk do not have symptoms of disease. So they're doing well, but we need to maintain their in follow-up and continue to follow them. Thank you very much. Within time.

Lindsay Torres:

Good morning. Excuse me. I'm Lindsay Torres here to present for Dr. Liz Jalezo. I'm a pediatric nurse practitioner at UNC Chapel Hill and have worked with the MPS team there for the past several years. Today we'll be discussing optimizing outcomes in MPS 1 and MPS 2, the role of early diagnosis and therapy. Our objectives are to identify the common presenting symptoms of MPS 1 and MPS 2. Recognize the spectrum of clinical manifestations associated with these disorders and identify the limitations of current enzyme replacement therapy approaches. MPS 1, mucopolysaccharidosis 1 is

typically referred to as Hurler or Hurler-Scheie syndrome. This is a progressive multi-system disorder resulting from the loss of alpha-iduronidase enzyme with features ranging over a continuum of severity.

We've historically referred to it as across three subtypes. Hurler syndrome referring to the severe or neuropathic form, Scheie syndrome, referring to the attenuated or non-neuropathic form, and Hurler-Scheie encompassing all of the individuals in between. Symptoms can include corneal clouding, joint contractions, hernias, hepatomegaly kyphosis, and cognitive impairment in the severe form. However, it's interesting to note that Kubaski reported in 2020 that while individuals identified with the attenuated phenotype under six years of age will have normal IQs, there is a significant portion of individuals who are thought to have the attenuated phenotype but show evidence of cognitive decline between six and 25 years old.

Allogenic hematopoietic stem cell transplant is considered the gold standard of therapy for those with the severe form of MPS 1 or Hurler syndrome. It can alleviate disease symptoms and improve survival. However, the best outcomes are when it is done before two years of age or before the onset of neurological impairment, which is typically thought of as a DQ or developmental quotient of greater than 80 to 85. Stem cell transplant reduces facial coarseness, improves joint mobility, and improves sleep apnea, cardiac disease, and may have some impact on hearing loss. Survival, especially in the severe population is improved with hematopoietic stem cell transplant and when initiated early can stabilize neurocognitive decline.

However, early treatment is essential as we are much better at preventing progression of symptoms than reversing existing damage. Earlier transplant results in improved neurological outcome. And the figure here on the left, this gray line represents those who are either pre-transplant or untransplanted. And you see with IQ on the x-axis and chronological age on the y-axis that there is a steep drop in IQ as age advances. However, those who have undergone transplant show a stabilization of IQ over time with age. ERT, as I said, it does affect many somatic disease manifestations, but not all. It does not impact the eye disease and has limited impact on bone disease. However, it does help with pulmonary function, cardiac function, and cognitive function.

This pair of siblings who were identified early, the younger one was identified early, the female was identified at five years of age. Her brother was five months of age at the time of initiation of ERT. So they're a great example of looking at the improvements in early diagnosis. The older sibling experienced progression of her joint disease, developed carpal tunnel syndrome, shoulder stiffness, and temporomandibular joint dysfunction. She also had moderate bilateral hearing loss although her cardiac valve disease did stabilize with the advent of ERT. She continued to experience mild obstructive sleep apnea 18 years after starting treatment. The younger sibling shown in this picture at 18 years of age had no respiratory dysfunction, no large joint arthropathy, no hearing loss, and attained adult height of the 25th percentile.

However, both siblings did have progression of their corneal clouding. As mentioned, ERT does not have significant impact on the eye disease. This highlights the importance of early identification and also early intervention before the disease manifestations become irreversible. In MPS 2 or Hunter syndrome, this is due to a deficiency of the lysosomal enzyme iduronate-2-sulfatase. It is an X-linked recessive disorder and leads to the accumulation of GAG in nearly all cell types, tissues and organs. On the left we have a child with a severe form of MPS 2 at approximately two years of age. Can see the standard or hallmark coarse facial features, enlarged tongue, depressed nasal bridge, upturned nose, and macrocephaly. In the severe presentation it typically presents earlier with physical and developmental delays.

They go on to develop cognitive decline, airway involvement, cognitive disease, and without treatment, death is typically in the first or second decade of life. In the attenuated phenotype, physical symptoms may be just as significant and just as debilitating. However, attenuated in this case refers to the lack of

cognitive involvement. These individuals still go on to experience joint disease, airway and cardiac involvement. Rod dystrophy affecting their peripheral and night vision. However, they may survive into adulthood with normal cognition. Enzyme replacement therapy is the standard of care for MPS 2. Stem cell transplant has not typically been recommended for those with MPS 2 because of a lack of data, the efficacy.

However, ERT has positive influences on growth velocity and MPS 2 as shown in this figure where children who this height on the left-hand side age at the visit on the y-axis and in the normal population, they follow this gray line. Here you see that with... Starting ERT we see that the growth trajectory tends to follow the normal curve. The age of onset of symptoms in untreated children has been around one and a half years of age and four years of age for attenuated phenotypes. By the time they're coming to clinical suspicion, they already have symptoms that will not be reversed by starting ERT, which is why we'd like to intervene earlier. Here's a sibling report of MPS 2. On the left there is a twin who is unaffected.

On the right, the twin has MPS 2. ERT was initiated in the affected twin at three months of age. Three years later he has no evidence of coarse facial features, he has no joint disease, no organomegaly. His cardiac function has remained normal. No evidence of dysostosis multiplex. However, he did display mild developmental delays compared with his unaffected twin brother. In conclusion, MPS 1 and MPS 2 are multisystem progressive disorders with a phenotypic spectrum that ranges from mild to severe with early severe neuropathic disease to those who have no neuropathic disease. Earliest manifestations can be nonspecific but include umbilical hernia, protuberant abdomen, macrocephaly, coarse facial features.

They may or may not have developmental delays depending on the phenotype that is expected. Frequent upper respiratory infections and otitis media. Stem cell transplant is the standard of care for severe MPS 1, but it must be given early. And enzyme replacement therapy remains the standard of care for MPS 2 and for those with MPS 1 in the attenuated phenotype. Evidence suggests that earlier initiation of ERT results in improved clinical outcomes despite the known limitations of ERT. However, further therapeutic development is needed to target compartments such as the eye, the central nervous system and joint disease. And we do have evidence of improved outcomes with earlier intervention that supported RUSP nomination for the addition of MPS 1 and MPS 2 to newborn screening. MPS 1 in 2016 and MPS 2 in 2022. Thank you.

Uma Ramaswami:

I just wanted to first of all say thank you to Ozlem and to the organizing committee for inviting me. So my title is a little bit more difficult because I think with Pompe and MPS 2 there's sort of clear guidelines on newborn screening. So the task I've been given is other lysosomal disorders not included in RUSP, expanding early therapy for Fabry disease. So I'm sure the audience here knows that Fabry disease is a X-linked lysosomal disease like MPS 2, but I'd say it's quite different in that there is no neuropathic or early onset phenotype. And as far as I'm aware, Fabry is probably the only disease where there is no clear early infantile onset. And therefore it really becomes difficult and challenging when it comes to thinking about newborn screening.

But I'd like to say today that the disease burden starts very early on. And many of you may be aware that the early symptoms include pain, GI symptoms, hyperhidrosis and reduced quality of life that happens in the first decade, often unnoticed. In the end, organ failure. So the renal, the cardiac and central nervous system end organ disease really only happens much later on. But as Dr. Goker-Alpan had mentioned, I think the point of no return has probably been reached. And therefore early treatment really is important even if there is no infantile onset for this disease. So we also have disease therapies.

We have first-generation ERTs, agalsidase alpha and agalsidase beta. We now also have pegunigalsidase alpha for adults and in clinical trials for children.

We have an oral chaperone Migalastat, which is now licensed for children over 12 years of age with an amenable GLA variant. And we have other novel therapies that are currently under clinical trials. So I just wanted to remind ourselves, so the top left graph, this was something that we looked at, I think it's now nearly two decades ago in 2003 when I had my first patient with Fabry who had very severe symptoms, but the literature continuously said this is an adult onset disease. So we then looked at 22 children with Fabry disease and we recognized all of the symptoms that I mentioned previously. So we had our children presented with significant gastrointestinal symptoms, fatigue and tinnitus, which they were really not able to explain very clearly, but it was quite challenging for them in particularly at school.

Cornea verticillata whilst does not respond to treatments is really important for diagnosis. The median age at onset of pain, the graph on the left with the blue bars, the majority of the young classic male patients in particular had pain by the age of 10 years. We also did a study looking at cardiac involvement in children. And Havranek is from the Czech Republic who came to visit us as a clinical fellow. And you can see here that over time in our patients, particularly those with the classic variant, the blue part of the red bars are disease progression with left ventricular hypertrophy and very clearly showing that these children do progress in the adolescent age. And we also looked at the early onset of classic and cardiac variants.

And as would be expected, the patients, the children with the classic phenotype of Fabry disease, like the adults were progressing in their disease. So this is a more recent study from the Dutch group where they showed that early start of enzyme replacement therapy in a small number of pediatric patients clearly showed a disease attenuation. So these patients were started quite young, so they're all under the age of 16. And the data here is shown after 10 years of treatment. And these two graphs are on cardiac data. So this is left ventricular hypertrophy. On the x-axis you have the untreated and the treated group. And on the slide A is on echo and slide B is a cardiac MRI. And on the y-axis you've got the left ventricular mass shown in grams per meter squared.

And you can see clearly in the treated group that all of these patients continue to not develop left ventricular hypertrophy. Now one thing I would say in children, quite often if you do your echocardiogram or cardiac MRI, most of these patients will probably have left ventricular mass within the normal range. But what I would suggest to pediatricians here would be to follow up the percentile. So if your child had left ventricular mass within the 25th percentile on age appropriate charts, then you look at that progression and whether that crosses to the 50th to the 75th. So if that's happening then you know that there is progression even though your values may appear to be normal. So it's something that I've learned over many years of treating these patients.

And so their hypothesis is very similar to what Dr. Goker-Alpan has already shown. That the earlier you treat, so that's the light blue, if you treat before disease onsets of symptoms or very early onset of symptoms where you do not have the point of no return, then these patients are likely to be stabilized and not have the ongoing progression that you see even on disease modifying treatments. I'd also say that there are tests that we can do for newborn screening. It's not that we don't have it. So you have the first year test enzymatic assays, whether it's... Primarily it's either they do it on digital microfluidics or tandem mass spec, which is very common. And of course you can also do high molecular assays using the high resolution melting sense.

So it covers the 7 GLA exons, but it does have low sensitivity for exons 2 and 6. Second tier tests are also available. And of course in Fabry disease, the main issue we may identify, and I'm going to allude to some of the newborn screening programs we have already, is the variant of unknown significance.

Plasma lysoGb3 can be informative and particularly in males, but you can also see mild to moderately elevated values in late onset phenotypes. And we heard that very nicely from Dr. Balena yesterday. So I just wanted to share with you the number of newborn screening programs that have happened all over the world. So this is not for us to be reading the whole amount, but in Europe you've got several groups, but the Italians have led the way starting with Sparta.

And then there's been several other programs that have been involved in newborn screening for Fabry disease, Asia, Taiwan have led, and I'll touch upon the Taiwanese data in a minute. And also in the USA there have been a fair number of programs that have looked at newborn screening for Fabry disease. And also recently there has been a newborn screening pilot in Latin America. So how do I summarize all of that data that I showed you? In Europe, the prevalence of Fabry disease is one in 3,100 to one in 13,000. In Asia, particularly in Taiwan, 86% of their newborn screening babies had the later onset cardiac variant. And in the USA it's very variable as you can see. And of course Fabry disease is not on the RUSP program currently.

And again, newborn screening in Fabry disease advantages are you have available methods, tried and tested, you have approved treatments, improvement in early diagnosis is really important, better knowledge of the natural history and of course it's an X-linked disease. And offering family screening is important. With every family member or even every baby or an index case, you will identify three to four adults and three to four children in that same family. And so there's a big implication. Of course there are other disadvantages such as the variance of unknown significance and the later onset cardiac phenotypes and how do we manage them. And these are things that we should bear in mind and diagnostic management and presymptomatic of Fabry disease.

There is a very nice publication not too long ago from the Italian group showing how they manage these children. I won't go through all of it in detail, but I would say that this is a really nice publication that I would suggest you should refer to. In conclusion, classic Fabry disease is a progressive life-limiting disease and newborn screening incidence, if I put everything together, it's approximately one in 37,000 and not one in 117,000 that we know from the literature. The later onset Fabry disease is often misdiagnosed for years. Newborn screening incidence of late onset is even more prevalent as you can see there, up to one in 4,600. In the UK Biobank, the prevalence of likely pathogenic Fabry disease causing mutations is one in 5,700.

And you can see that again for both variants for classic and newborn, for the classic and the later onset, the prevalence is much more frequent than we anticipate. Disease progression occurs in all males and we know that whether they're classic or whether they're later onset. Disease progression is going to be in 100% of males with Fabry disease. In females, of course the disease progression can be variable, but we do in our experience have more than say, 70% of our females do progress particularly with their cardiac disease, less so with their renal. While approximately 60% of GLA variants are identified by newborn screening are late onset variants, this should not be a reason, in my view, to exclude Fabry disease in national newborn screening programs.

And I want to introduce a concept that I think of as reverse cascade testing. So if you identify a patient, a baby with a later onset cardiac variant, you have a mother or a father who's got that disease. You have identified that individual who might be in their early thirties who've actually not had the disease manifest or they don't know about it. So now immediately you have helped that baby by treating that father or the parent and also identifying other individual. I call this reverse cascade testing. We do this in familial hypercholesterolemia or at least we are trying to advocate it. And I'm going to advocate this as a new concept for you all to think about in Fabry disease.

And perhaps if you're looking at RUSP, that might be something you need to talk about because you're not just looking after the baby, you're looking after that baby's parents who may not be there for that

baby if you don't treat them. So that's just my thoughts. And the urgent unmet need is standardizing the protocol of how we manage these babies. You heard about not medicalizing them and I think that's something that we need to be looking at from a global community, not necessarily with individual countries. And my last slide really is I want to touch upon another completely different disease. This is just one slide and this is acid sphingomyelinase deficiency. And you have a real whole spectrum here.

So we know it's a deficiency of acid sphingomyelinase with variants in the SNPD1 gene. Type A being the more rapidly progressive disease presenting in the neonatal period and even very early on. And then you have the chronic visceral on the other hand, which is type B that presents a little bit later in childhood and adolescence. We know that by newborn screening both in the US and in Europe, the prevalence, the incidence is not very dissimilar. It's much less frequent than Fabry disease. But nevertheless, we have a treatment currently olipudase alfa, which we know works for this disease. So we have a treatment here. So if you want to look at the Wilson and Jungner criteria, ASMD will fit almost all of those.

And then of course you also have a really good biomarker here, I've just shown you the biomarker... To just go back. The biomarker. So it's the graph on the right-hand side that you see using lysosphingomyelin versus lysosphingomyelin 509, which is a carboxylated variant and there is a really nice correlation and we know that it distinguishes and picks up ASMD quite nicely on newborn screening. So we do have a biomarker and we can also use that for sort of disease progression and monitoring. The genotype-phenotype correlations, NPB, the chronic visceral very often has missense mutations with residual enzyme activities and the more severe acute neurovisceral are associated with frameshift and nonsense mutations with complete loss of enzyme function.

So I do think ASMD is another disease where newborn screening is really needed and is going to be beneficial. So with that I'm going to say thank you and hand over back to Ozlem.

Dr. Ozlem Goker-Alpan:

Thank you for this wonderful presentation. So I am opening this section for questions. We're going to do the good old microphone way. We have microphones here. Please, anybody who's coming, address your question and who's the question is addressed to. Thank you. Questions? No questions. I will...

Audience Member:

I had a question about MPS 2 and the role of transplantation. I know that there is old literature which suggests that it doesn't work, but I also know that there is suggestions that it could work. What is your take on the role of transplantation for MPS 2?

Lindsay Torres:

I think that it's something we need to investigate further and see as more families are choosing that option. I know there are a lot of families out there who have chosen the option of transplant that haven't been followed up to see how that has done. And so I think that's an important thing for us to investigate and see whether transplant is the appropriate option given that there isn't much right now for the younger children diagnosed early. With newborn screening, we may be able to try transplant earlier and see if that may be more beneficial.

Audience Member:

No, I think it's really important to look at the data from Asia and India and many parts of the world where it is standard of care and for us to maybe understand what is really going on there. Thank you.

Dr. Ozlem Goker-Alpan:

Any other questions?

Audience Member:

Thank you. I had a question for the last speaker. I was just curious about the incidents in the Fabry testing in the newborn screening from California to Washington state and there's a really big discrepancy. Is that due to their testing procedures or is it anything to do with the populations? It seemed like a really-

Uma Ramaswami:

I think that's a really good question and I haven't really looked at whether it could be the population. I'm not entirely sure with the testing because the testing was very similar for all of the states that I looked at in the US. So either the microfluidics or the tandem aspect was the initial. So I don't know if the demographics are different and maybe that's what's reflecting it. And also perhaps if you had a founder effect and then you had more classic patients in certain states. That's not something I'm aware of.

Dr. Ozlem Goker-Alpan:

I have a question actually for the speakers. So for [inaudible 00:47:18] David, so in a hypothetical scenario that you actually identify an infant with an attenuated mutation, what is your best biomarker for muscle damage and then continuation of that. So if there is a trend of increasing or abnormal or very high levels of that biomarker, when do you want to start this patient on treatment? When they become symptomatic, like hypotonia, this and that, or you want to intervene at that time?

David Kronn:

So we sequentially do CPK and Hex4 in the patients we find who are at risk of LOPD and we do track them. So if we start to see an elevation, we will do the testing more frequently. And if the patient's level moves into the abnormal range, then it becomes a discussion as to whether we start treatment. So I think we're trying to pick up patients before they actually manifest with any significant muscle weakness. And so if there's evidence of active disease and this continues with sequential monitoring, then we have a discussion with the family and we will start treatment.

Dr. Ozlem Goker-Alpan:

And one more question. So is there a data between when the kids were started when they show starting symptoms versus this preemptive treatment without the symptoms but based on biomarker, like very high biomarkers like CPK of a thousand, this and that?

David Kronn:

I don't know if that exists. This would be patients who are more clinically diagnosed, so patients who are diagnosed before newborn screening. But we do see those levels that are high in patients who have IOPD before they go on to treatment as well. So that's important and then we can track them as levels are high and then start to come down. So yes, it is seen in the IOPD patients.

Dr. Ozlem Goker-Alpan:

Any questions to the audience, Dr. Kishnani?

Audience Member:

I could just comment. We clearly have an emerging cohort of patients with LOPD, some with the common IVS, splice site variant, which if you look at the clinical literature, clinically identified cases also with this variant have been treated at two years of age. And so we now have this from newborn screening and I think David is fully aware of this data with earlier treatment, complete normalization of biomarkers. But that's not just all that we're treating also of PT, kinematics, postural and areas of involvement that you typically see in Pompe disease. And we have been using muscle ultrasound as a non-invasive biomarker as well to track disease.

David Kronn:

I mean we're very concerned because patients who have started to show clinical changes, muscle weakness, the success of treatment is always concerning because it's very hard to reverse findings of muscle weakness once the pathological changes are present in the muscle.

Dr. Ozlem Goker-Alpan:

Any questions?

Audience Member:

Mike West from Halifax, Canada. So my comment or question is for Dr. Ramaswami, and I agree with you that we need to be providing earlier treatment for Fabry patients including children. I would observe that within Canada, excuse me, we're probably undertreating children. We don't get a lot of patients being put forward for therapy. So I think they are being undertreated. I think our guidelines are probably very similar to yours and we would certainly want to treat patients that are showing increasing LVH even in the normal range.

Excuse me. So I think there is a need for increasing awareness amongst treating physicians who are following these children. We don't want to medicalize them, but we don't want to miss treatment opportunities. So how do you go about doing that? I don't deal with children so my pediatric colleagues probably don't want to listen to me yammering at them. So how do you ensure that there is that awareness?

Uma Ramaswami:

So I think that I agree completely with you and I also think it's a really good point you raised about increasing awareness. We heard yesterday about centers of excellence. For me personally, once we've made the diagnosis, I do think there is a need for centers where patients can be managed, where people have experience or gaining experience as it were. So if you have one patient in one hospital, it's very difficult for that individual clinician to be able to learn and gain experience. It could even be a hub and spoke. So you can have a center of excellence and you can have young people or babies or children being managed in the local hospitals and then you have a standardized way of investigating.

I absolutely think we don't need to be investigating every year and every child because the disease progression is slow. But the idea is knowing that if you have a child's echo, which was the left ventricular mass index was on the 25th percentile and two years later it's on the 75th with no other indications why that might be, then there's definitely disease progression, albeit within the normal range. It's the same with ECG changes as well looking at PR interval. So prolongation of PR interval happens very slowly and we know that a prolonged PR interval is abnormal in an adult. In children in the first few years of life that might be normal and then you have a shortening.

So it's about that increased awareness. So perhaps, I don't know, it's through colleges, it's through webinars and then also identifying young people, identifying babies by newborn screening and then following up. It's a difficult question, Mike, but I do think that we need to work together as a team globally and just have some kind of guidelines, which is what I was saying in regards to monitoring.

Audience Member:

Thank you. If I could make another comment, excuse me. I think there's one other advantage of starting children with Fabry disease on therapy is that when they get into the teens, older teens, younger adults, there's often great resistance to start therapy even despite progressive disease. So I think if you've already got them on in childhood, they're less likely to stop treatment when they get into the terrible teens at that point. Thank you.

Dr. Ozlem Goker-Alpan:

Thank you. There is another question here.

Audience Member:

A question, a comment from Taiwan. In Taiwan we have executed newborn screening for MPS type 2 for nine years. We have screened over 700,000 newborns and we have performed three patients of severe type of MPS 2 and they received HSCD and after all successful. After HSCD, we have quit ERT now for four years. We have regularly followed up their end activity and urine GAGs and they perform very well. So I think in Asian countries the MPS 2 takes the major part about 50% of all patients with MPS.

And as far as I know, the HSCD experience is relatively experienced in Asian countries, especially Japan and Taiwan. So as Dr. Priya just said, I think we should reference the experience of HSCD for MPS 2 in Asian countries because as you know, the successful experience of HSCD for MPS is very important for these families. Thank you.

Dr. Ozlem Goker-Alpan:

Actually, I'm going to continue that comment for you, Lucy. So what is the earliest consideration for bone marrow transplant? I mean we discussed two years and the neurocognitive changes, but we know these SCID babies, they get transplanted immediately. So is there any data, the early versus later transplant or they waited...

Lindsay Torres:

But there was some data that I showed where the earlier transplant did have better impact on outcomes. I think-

Dr. Ozlem Goker-Alpan:

What is the earliest here?

Lindsay Torres:

I don't know exactly what the earliest has been, but I think with MPS 1 we have seen we can transplant infants by six months of age and have seen even improved outcomes with them. I think one of the challenges with MPS 2 is that historically children have not been identified or diagnosed until they already have the presence of neurological or cognitive decline. And so at that point it's really too late potentially. And that may be why we haven't had as good outcomes with stem cell transplant in the US.

So the advent of newborn screening may help us see better outcomes because we'd be able to intervene earlier.

Uma Ramaswami:

I'll just comment on that as well. I think two years is too late for an MPS 2, so I think we should be really thinking about a very similar concept as MPS 1 and start it. And that's why newborn screening is really so important.

Dr. Ozlem Goker-Alpan:

And could you comment on the ERT to start with? Occasionally you start ERT and when they're not ready for bone marrow transplant, what is the data with that ERT versus bone marrow transplant versus BMT and ERT?

Lindsay Torres:

I think there are different institutions do that different. There has been evidence, as you know I showed that starting ERT seems to have similar effects. I think it's really institution dependent. And with MPS 2, I don't know that we have a lot of data in the US. I don't know if our Taiwanese colleagues can comment on whether they start ERT prior to stem cell transplant.

Audience Member:

We start ERT ASAP, as soon as possible and then we wait for the time to the donor match of HSCD. And then for our three successful transplant baby detected by newborn screen for MPS 2, they are before one year of age, they receive HSCD. And after HSCD for about three months, they quit ERT and then we observe their urine data and activity to see if the HSCD work well. Thank you.

Dr. Ozlem Goker-Alpan:

One question, maybe I can ask to the group and audience. So I want to get your opinion about the sex differences in the follow-up and treatment of girls and boys with Fabry disease. I think this is very important. The reason is I have symptomatic girls as early as three years of age. So just one word. Do we need to separate the ages for genders versus we need to start screening them all at the same age?

Uma Ramaswami:

I would screen them all at the same age.

Dr. Ozlem Goker-Alpan:

This actually concludes the session. Thank you very much for attending.