MPS I: Implementation Considerations

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Transcript

Laura Russell: Okay. We're going to go ahead and get started. First I just had a quick disclaimer. This webinar series was supported through cooperative agreements with HRSA and CDC. The contents of the presentations do not necessarily represent the official views of CDC, HRSA, the Department on Health and Human Services, or the U.S. government. With that I am going to turn it over to Dr. Gulamali-Majid for an introduction.

Dr. Gulamali-Majid: Good afternoon, everyone. It is my pleasure to welcome all of you to the first part of the three-part MPS I Webinar Series on implementation considerations, clinical aspects and available screening methods. This webinar series is co-sponsored by the APHL newborn screening Quality Assurance, Quality Control Subcommittee of the APHL Newborn Screening and Genetics in Public Health Committee and the NewSTEPs New Conditions Workgroup of the NewSTEPs Steering Committee.

Today's webinar will focus on implementation consideration for those who are currently planning to implement newborn screening for MPS I. Today's agenda will include fact finding and engaging stakeholders, resources needed and timeline considerations, follow-up considerations and education. After that, we'll receive the questions and answers and we'll try and get them answered.

I'd like to introduce our speaker. Our speaker today is Sarah Bradley who supervises follow-up of inherited, metabolic disorders in the New York State Newborn Screening Program. Prior to joining NSP, she worked as a clinical genetic counselor in a pediatric setting at Albany medical center and in an oncology setting. She received her Master's in genetic counseling from the University of Pittsburgh, and a Bachelor's of Science from Cornell University.

Sarah Bradley: Hi. Thank you for that introduction. Next slide please. As Dr. Gulamali-Majid said in her introduction, we're going to be talking through today really as the title says, Implementation Considerations. For states who are in the earlier stages of implementing or thinking about implementing screening for MPS I, these are some considerations. We'll start off with just some basic facts in talking about engaging with stakeholders and then we'll be talking about some resources that may be helpful, timeline considerations, follow-up considerations, which is my personal area of interest, as well as education considerations.

Next slide. Just to give a little bit if background, as Dr. Gulamali-Majid said, I'm a follow-up supervisor here with the New York State Newborn Screening Program. To give you a little bit of context, I'm not doing this presentation, I'm not coming to you as an expert on MPS I implementation. Because in New York State, we are doing a pilot study right now for MPS I, but it's with a limited population, with samples from a few hospitals. We're, like many of you, in our early stages of doing a statewide implementation.

I'm coming to you as somebody who is in the midst of picking through these challenges ourselves. When I came to the Newborn Screening Program four years ago, it was in the midst of when we were doing our ALD implementation, and soon after we then did our Pompe implementation. I'm definitely familiar with rolling out a new condition.

In New York we had been doing a pilot study with Dr. Melissa Wasserstein who is currently at Montefiore Medical Center in the Bronx for LSDS. This began in 2013 and it was initially for Fabry, Gaucher, Niemann-Pick and Pompe disease. We went live with Pompe screening in October 2014. In May of 2015, a few months later, we added MPS I to the pilot too. We've been doing the MPS I pilot for about two years now.

Our method that we used is MS/MS for the IDUA enzyme activity. For the pilot we are doing one tier only but we do plan to add a 2nd tier molecular test for MPS I when we eventually go live. Currently that is in the end stages of assay development. That's where the molecular tests [inaudible 00:05:50] right now. With our pilot, we have screened about 29,000 babies. We've had nine babies test positive, of which seven were babies that had pseudodeficiencies and two, we're still waiting to hear what the outcome was.

What's different with our pilot, or potentially different, is that Dr. Wasserstein handles all of the follow-up. We notify them of the abnormal test results, but their group handles notifying the pediatrician, notifying the family, doing all followup testing. It's, in that sense, hands-off for us at the Newborn Screening Program. Our hope is to go statewide with MPS I later this year.

Next slide. I'm going to ask everybody to think about the stakeholders that will be involved for screening for MPS I in your state, and use this as a framework as we think about, through the rest of the discussions today. Obviously the Newborn Screening Program, I think that's probably the majority of the audience today, but also certainly screening for MPS I is going to have an impact on the specialist in our state who will be seeing these babies and will be referring the babies too.

The pediatricians in the state certainly will have a stake in this, as well as the hospitals. Then also obviously this impacts the public and the parents of the kids who are screening positive, but just in general the parents of the kids who are being screened. Just to have that in the back of your mind as we're going through the rest of the presentation today.

Next slide. I don't mean to steal the thunder of Dr. Whitley who's going to be doing our second part of the webinar series on Monday. He's going to be talking about clinical aspects and diagnosis and management of Pompe disease. I don't mean to steal any thunder from him, but I just wanted to provide a little bit of background information for anybody who was not familiar with MPS I, just so we're all on the same page for today.

MPS I stands for mucopolysaccharidosis type I. That's one of a group of metabolic disorders that's caused by an absence or malfunction of a lysosomal enzyme that's needed to break down something called glycosaminoglycans which we'll call from now on GAGs. These are long chains of sugar carbohydrates that help build connective tissues.

As you can see, MPS I is a lysosomal storage disorder. It has been known in the past by different names than MPS I, which are listed here. What you'll most often hear is Hurler syndrome, or Hurler-Scheie syndrome, or Scheie syndrome. Those really represent a phenotypic spectrum where Hurler syndrome is the most severe end of the spectrum and Scheie is the less severe, more mild and Hurler-Scheie is really in the middle. Really MPS I is the preferred terminology, but again, you will still hear people say Hurler.

Next slide. MPS I is caused by mutations in the IDUA gene. That gene codes for an enzyme called alpha-L-iduronidase or IDUA. That breaks down two of those glycosaminoglycans called dermatan sulfate and heparan sulfate. When a child or an individual has MPS I, mutations in that IDUA gene cause the enzyme to either work poorly or not at all. That leads to a buildup of these GAGs in cells, and specifically within the lysosomes.

This disorder is inherited in an autosomal recessive manner, like many of the other conditions that we've screened for in Newborn Screening, such that in general two mutations will cause disease for a child or an infant. If somebody has just one mutation, they are carrier for the disorder, and don't usually have any symptoms.

Next slide. When we look at the phenotype, the clinical picture of MPS I, we see two basic subtypes. This is where some of the terminology can differ. The preferred terminology now is severe versus attenuated MPS I. The severe form is a little bit more common, with a prevalence of about 1:100,000 births. In this form infants appear normal initially at birth but usually develop signs and symptoms in the first couple of years or so of life.

Those symptoms can include a coarsening of their facial features, macroglossia which is an enlarged tongue, an enlarged head, a deep voice, sleep apnea, an enlarged liver and spleen, intellectual disability, hearing loss and skeletal abnormalities that can cause a lot of morbidity. The prognosis for children with the severe form of MPS I, unfortunately they in the past have often passed away before the age of 10.

The attenuated form of MPS I is more mild, with a little bit later age of onset, usually between age 3 to 10 years. The symptoms are, again, this facial coarsening, learning disabilities, hearing loss, heart disease, the skeletal abnormalities and respiratory disease. We tend not to see the cognitive ... The true intellectual disability tends to be less with this form and some of the other symptoms are less. The prognosis with the attenuated form can be quite variable.

Again, Dr. Whitley will go into, I'm sure, much more detail about this. Again, with terminology, the severe form in the past had been known as Hurler, and the attenuated names have been known as either Hurler-Scheie, or Scheie syndrome.

Next slide. The treatment options for MPS I, in the past it's always been supportive or symptomatic management, physical therapy, particularly with the skeletal abnormalities that the kids had, or even surgery. In more recent years stem cell transplant has become an option, as well as enzyme replacement therapy which when started it's done once a week for the rest of that individual's life.

The stem cell transplant is thought to be particularly a good option. Certainly not an easy option for anybody to go through, but an especially important option for children with the severe form because it can help stop or slow the cognitive decline that they face. ERT does not stop that cognitive decline because it doesn't cross the blood-brain barrier. Again, while we're screening for this, it's helpful to catch those kids early so that stem cell transplant can be an option for them possibly.

Next slide. The diagnosis of MPS I can be made. We do know that we can detect a low level of enzyme activity in peripheral blood leukocytes, in plasma or cultured fibroblasts. It can also be suspected if you have increased excretion of those glycosaminoglycans, the heparan and dermatan sulfate, in urine. Also molecular testing for the mutations in the IDUA gene. That is the only gene associated with MPS I. That is another approach as well.

We know that there are at least 100 known mutations in that gene. Although there are several commonly recurring ones, what makes MPS I a challenge in the same way that Pompe can be a challenge is that there are known pseudodeficiency alleles that can lower enzyme activity but not cause disease.

Next slide. For Newborn Screening we do know that the low enzyme activity can be detected in dried blood spots and that can be done via tandem mass spec, or digital microfluidics. The [inaudible 00:15:05] part of the webinar series will have a lot more information from [inaudible 00:15:10], Patrick Hopkins, about new different testing methodologies. If you're really interested in those specifics, stay tuned. Next week you'll hear more.

February 2015 is when the Discretionary Advisory Committee on Heritable Disorders in Newborn and Children voted to recommend that MPS I be added to the RUSP, and here we are today talking about it.

Next slide. Currently there are five states who are screening for MPS I statewide. Those are the ones here in green. These are Missouri, Illinois, Kentucky, Ohio, and Pennsylvania. I knew of three states, New York, North Carolina, and Georgia who were doing pilot studies for MPS I. That's currently to the best of my knowledge where screening stands right now.

Next slide. Now we're going to talk about some of the resources needed and the timeline considerations. Next slide. You'll keep in mind that we know that there are five states who have started screening statewide. In thinking about this presentation, my approach was to talk with the states who have been doing screening statewide, and to learn more about their experiences.

Fortunately Newborn Screening tends to be, in my experience, a very friendly community of people very willing to help each other out. I reached out to colleagues from the Illinois, Kentucky, Missouri, Pennsylvania and Ohio Newborn Screening Programs with a list of questions. They were kind enough to respond either via email or I spoke with some of them over the phone. These are the type of questions that I was just trying to get more information on.

Just for each of them I wanted to find out some background information, like when did they start screening, and to get some context of, was this voluntary or was it due to a mandate, some basic statistics about how many babies they had screened so far, how many positive they had had, how many true cases, what their testing methodology was and their testing process? Then some questions obviously about their implementation, so how long did that take approximately, were there any special timeline considerations, extra resources needed?

From a follow-up perspective, how much lead time do they give to their medical community? Did they involve any extra specialists besides geneticists? Did they have a diagnostic or follow-up algorithm? What education was done ahead of time? Then what I really wanted to know from all of them is, since they've gone through this processes, did they have any advice for other states just earlier in the process, or any do's or don'ts that they would recommend, now that they have the benefit of experience and being able to look back?

Next slide. Starting off with the first question for the, which was again about their screening background, what I found from talking with each of them, and I should say, this is all organized by question and by state. [inaudible 00:18:44] For Illinois their experience has been that for MPS I there was a legislative mandate that was passed in 2007. They began a pilot study in November 2013 and their statewide screening began in June 2014.

For Kentucky, their newborn screening law is written in such a way that they have to test for conditions on the RUSP. As it became clear that that's the direction that it was headed for MPS I, they had begun working towards implementation in anticipation of that. They were then ready to begin statewide screening in February of 2016.

Missouri's experience is different. They've been screening the longest of everybody. They had a legislative mandate screen for five other LSDs. The method that they were using at the time allowed for the addition of two more disorders. They worked with their state advisory group who suggested the addition of MPS I and MPS II. The MPS II didn't work out, but MPS I did. They began screening statewide in January of 2013.

Next slide. For Ohio, their legislative mandate was initially for Krabbe disease, but the method that they were using allowed for the addition of both Pompe and MPS I. Krabbe screening began in July of 2016. In Ohio they are screening for MPS I statewide, but they're not considering this technically live yet because it's not been reported on their newborn screen report. The testing is being done and they are acting on abnormal results and calling these out. They hope to be live this summer. I think there was a holdup with their LIMS vendor on the reporting issue on this one.

Pennsylvania, they had a legislative act in 2014 to add six LSDs to their mandatory screening panel. Pennsylvania has managed for its screening panel, as well as a supplemental screening panel. They had again a mandate to add six LSDs to their mandatory screening panel. That was implemented in February of 2016, but due to the initial funding availability and concerns about there being a 2nd tier test available, only Pompe was initially added to their mandatory panel. The other five LSDs were added to their supplemental panel. MPS I was added to the mandatory panel on February 1st of this year.

Next slide. Here are some very rough statewide screening statistics. [inaudible 00:21:47] there is a little asterisk here, for this little disclaimer on the bottom just really to caution everybody to be careful about making any direct comparisons with these screening statistics between states, because these are all based on different screening methods. Some of these states have 2nd tier testing available, some do not. Everybody has different cut-offs.

I guess I would caution you against making any direct comparisons from one state to the next. In Illinois, they reported that they had screened more than 330,000. Of those they had about 150 who were positive. A little bit of a breakdown of those is they had 12 babies that had variants of unknown significance, so they had phenotypes that were hard to figure out. They had 51 babies who had pseudodeficiencies only. They detected one case, one true case of severe MPS I, as well as eight babies who were carriers of MPS I.

In Kentucky they had screened a little more than 67,000 babies. Of those they had two positives. One turned out to be a carrier and one was a true case. In

Missouri more than 300,000 have been screened so far. This had 133 positives, of which there were two severe MPS I cases and two cases where the genotype was of unknown significance, ones that are still in a bit of a limbo.

Ohio has screened 140,000 babies. Of those they've had 16 positives, two with severe MPS I and eight had negative follow-up testing, two had been lost to follow-up, and then four were pending a diagnosis. In Pennsylvania who's, again, just been screening since February, they've so far screened over 21,000 babies. Of those, with their testing approach, ten have been sent for DNA, which is a 2nd tier. Of those three ended up having no disease, six are still pending and one was lost to follow-up.

Next slide. The methodology used for the different programs. In Illinois they're using an ultra-performance liquid chromatography. They're doing one tier only for the enzyme and they're using a 17-hour incubation is what they reported to us. In Kentucky their testing is contracted out to Mayo for all of the LSDs. Mayo is doing a flow injection analysis, tandem mass spec approach. In the two cases that they have had that were positive, Mayo did perform a 2nd tier testing of heparan sulfate and dermatan sulfate. Otherwise that 2nd tier is still under development, but again, they did do that approach for the two that were positive.

In Missouri they used digital microfluidics platform. They used one tier only for the enzyme and they get same day results. In Ohio they used, like Kentucky, flow injection analysis, tandem mass spec, one tier only. They are considering in Ohio using Mayo's collaborative laboratory integrated reporting, the tool from Dr. Piero Rinaldo, to help reduce their false positive rates. That's a tool that Dr. Rinaldo will be speaking about on the final webinar on this series. They're also considering possibly adding a 2nd tier molecular test.

In Pennsylvania, their testing is contracted out to Perkin Elmer. They're using the same methodology as Ohio and Kentucky. Their process is that if the enzyme is low on the initial sample, they ask for a repeat. Then if it's low on the repeat, then it is sent for DNA testing. They are doing DNA testing as a 2nd tier.

Their implementation experiences by state, Illinois reported that they had initially started off in their implementation with microfluidics assay but they ended up switching to tandem mass spec because at that time that offered a larger scale testing platform to accommodate the addition of other LSDs. They did say that they needed additional lab and follow-up staff to handle that increased workload.

They also reported frustration with working with their LIMS vendor to get the testing up and going. They described that as their rate-limiting step to be able to fully implement and go live with testing. Kentucky, for them, again, they sent their testing out to, it's contracted out to Mayo so the contract first had to go out to bid. It was then awarded. There were several back and forth until that contract was finalized. Then the follow-up group in Kentucky had to modify

contracts with the universities to provide the consultations and confirmatory testing.

In Kentucky again, a similar frustration that they had was working with their LIMS system vendor. They described that as a very slow process. Just something to keep in mind that these are just two out of five states but that's 40% of states doing screening for MPS I so far. That has been a very slow acceptance, working with the LIMS vendors. That might be something you'd want to initiate sooner rather than later, at least those discussions.

Next slide. Missouri again, they were the first to start screening. They had a one-year startup time for four LSDs, but they were the first in the country to do so. They had to develop the methodologies from scratch. Their mandate did include a mandatory startup date. There was not enough time, funding or lab space for them to use the tandem mass spec screening method. They did what was very helpful to them, is they created an LSD taskforce that included specialists from around the state. I believe there were parent advocates on that group. A lot of the stakeholders that I've asked you to think about in the back of your mind were present on that taskforce, and they helped guide their implementation.

What was a challenge for Missouri especially was that they had to get dry blood spots from confirmed MPS I cases. It's just something to think about. They had just hired in Missouri one full-time employee for the lab, and they also had to provide funding to the genetic referral sectors. That of course might vary from state to state.

In Ohio again, they reported that working with the LIMS vendor to configure the reports has been a timely process. I believe that's why they have not gone live with the reporting. They did have to add staff to accommodate the testing and to handle the weekend and holiday staffing. They also of course needed increased funding to purchase instruments and reagents, to add that staff member, to update their brochure and to update their LIMS system as well. That all unfortunately costs money.

Next slide. In Pennsylvania they reported that their implementation took quite a while, but only because there wasn't initially an agreement that MPS I should be on their mandatory screening panel. Once that was added to their mandatory panel, it took about three months for the lab to be ready for the implementation. Again, they've only been live since February, so they're in the still early stages and they have found that they are sending a higher volume than they had expected for DNA testing. Those that had finished the diagnostic process so far have been normal. They are already considering adjusting their cut-off values that they may be set too high possibly.

That's a summary of what this implementation experience has been for these five states. I just wanted to mention that of course if you have any more specific questions, or as you're getting started yourself, if you want any specific information about resources needed, like for example, how many staff or

instruments were utilized by these labs, I would consider contacting these labs directly because there are many factors individual to each labs that can affect this and they can definitely best explain their setup.

Next slide. For the advice that these states gave, I tried to group it generally in terms of theme. One theme was just the initial planning and the validation of their assays. Several of them advised to just consult with other states who are experienced and have been doing screening already. Here are five examples of states that you could reach out to. I can attest, they're all very friendly and willing to answer questions.

We were given the advice to not listen to rumors about screening methods, that you should really conduct your own investigation and take into consideration all the needs of your program. Try to go into it with an open mind and not think definitely that ... Be open to other screening methods, I guess. Once you do decide on what screening method you will do, they gave the advice to begin securing contracts with instrument and reagent vendors as soon as possible.

It was also advised that obviously you'll need to obtain bloodspots on true positive cases, on pseudodeficiency cases, babies that are carriers, also false positives. Those will all help you validate your screening method. Finding those cases, those true positive and positive controls, they're in high demand and they're in limited quantity. A possibility is being able to utilize the CDC's quality assurance materials, which again is another plug for next week's third webinar in the series. There will be a talk from individuals from the CDC about that program.

Once they had recommended that prior to going live, that you conduct a full population pilot phase where every baby is screened but normal LSD results are not reported. They also said, if you do this, please don't delay the start of that, because you might risk missing a baby in the meantime. Then there was also advice given that you may want to consider having your IRB review of your pilot phase plans ahead of time just to give a second set of eyes, or maybe more than one second set of eyes for consideration.

Next slide. For the test specific, we've seen this in New York but we've also been given the advice to expect possible seasonal changes in LSD enzyme activity levels due to summer heat humidity. I know that's something that we often experience with summer here in New York. Multiplexing with other LSDs to help identify poor quality samples and/or those that have low leukocyte counts. Again, we have found that to be helpful in New York where we're doing Krabbe and Pompe screening, you need some time to tell if the enzyme levels are low for everybody, that this is maybe just not a good quality sample.

Consider using a borderline abnormal reference range that requires a repeat to increase your detection sensitivity without overburdening your referral centers. Then again, explore the possibility of using the CLIR tools available through Mayo that we'll hear more about next week. If you can, the molecular testing is

very helpful, because of those pseudodeficiency alleles. They pose a significant challenge for interpreting results.

If you are not able to do 2nd tier molecular testing, this is for the states that are not doing it, that they advise working with the specialists in your state to develop a plan ahead of time for genetic testing. That might entail identifying a diagnostic lab that will be easy for the centers to work with, that might be willing to work with the families in terms of the cost of the testing. Just something to think about ahead of time as you're getting closer to going live.

Next slide. Then the last bits of advice. We heard from several states about issues related to their LIMS vendors. Reaching out to them far in advance of your start date was definitely what multiple states recommended doing. Then also you may have to add stuff to do the testing but several states had recommended at least initially when you go live, having some extra staff handy, particularly IT staff can be helpful because they can help troubleshoot any initial issues that pop up.

Next slide. Next what we're going to talk about are some follow-up considerations. Again, follow-up is the part of Newborn Screening that I work in. It's something that I've been thinking quite a lot about, and I'll share my thoughts with you.

Next slide. What has been helpful to us in New York, at least when we were going live with ALD and with Pompe was we created algorithms or flowcharts of what the testing process looks like. I know this seems basic but just to visualize, I've put together two very basic algorithms, one for labs doing MPS screening, but not doing the DNA 2nd tier, and then one with DNA in the 2nd tier.

Just as a basic approach, you'll have a baby that has low enzyme activity below that state's cutoff. This will then screen positive and get referred to a specialist within that state who will order the appropriate confirmatory testing which might include the DNA molecular testing. The confirmatory IDUA enzyme, as well as the urine GAGs. The possible outcomes of that could be, you might have babies that have no disease. They have pseudodeficiency alleles or it turns out maybe they're just a carrier or you have kids that have the severe form of MPS I, or the attenuated form.

Next slide. With DNA, it's a very similar approach, just that you have the babies who have the low enzyme activity. They then go for the molecular testing, but in-house at the Newborn Screening lab. That test that has the capability of weeding out these babies that have either no mutations or pseudodeficiency alleles, so then you're only referring to the specialist the babies who have at least one or more mutations in a variance of unknown significance. Then the specialist will then order the same confirmatory testing, minus the molecular of course, and then they can find different outcomes.

Maybe the baby doesn't have the disease or are a carrier. They might have an uncertain phenotype. I should have said actually that you could have an uncertain phenotype in states not doing molecular testing. That's an outcome that isn't always unfortunately possible. We see that a lot with out Pompe cases, where it's not clear these ones when the onset is, not in the initial newborn period. It's very hard to find out what the real phenotype is going to be for the baby.

Then you also will have babies that the initial testing makes it more clear that they either have a severe form of MPS I or the attenuated version.

Next slide. Just to give you a little bit of a jump start. I did do a little bit of research about what labs offer this confirmatory testing for MPS I. I'm not saying this is necessarily an exhaustive list, but this is what I was able to find. For the enzyme testing, Duke and Mayo are doing the enzyme. For the urine testing, Emory, the Greenwood Genetic Center, Mayo, and the University of Alabama are doing the urine.

The molecular testing, there are a lot of options for molecular, but I've only included the ones that are doing single-gene sequencing, or at least the only ones that I know of that are doing single-gene sequencing. The IDUA gene was offered on a lot of labs doing panel testing, but it seems like maybe that's how we need to do single-gene testing. Baylor, Emory, Mayo and Prevention Genetics are offering that testing. Again, this is not necessarily an exhaustive list. This is just what I was able to find quickly.

Next slide. Some considerations just from a follow-up perspective is that MPS I is a multisystemic disease, no matter if it's the sever form or the attenuated form. Initially we always tend to involve some geneticist in our state in the evaluation of these kids. I think that's still the appropriate probably way of managing these but realistically there will be several other specialists involved in the care, diagnosis and management of these kids. They'll include obviously genetic counselors, but also cardiologists, ophthalmologists, orthopedists, neurologists, otolaryngologists, pulmonologists, transplant specialists, plus the babies' pediatricians.

There's probably others that I haven't even considered, but just to make clear that this is something that affects multiple systems. There will be likely multiple specialists involved in the long term care of these kids. These are all people who are stakeholders in this process. It may be important, especially when we're having conversations with the geneticist, to also maybe have that help us facilitate discussions with these providers too.

Next slide. MPS I, and I've touched on this before, because we have a similar challenge sometimes with Pompe, but what can be a challenge is differentiating the phenotypes, so differentiating the severe, versus the attenuated phenotypes will certainly be a challenge at times with MPS I. There are treatment differences, so it actually is important to determine that. The severe

form, as I mentioned earlier, the [inaudible 00:42:36] transplant is recommended in that group. The attenuated form, the ERT, is appropriate. [inaudible 00:42:43] transplant can be done in the attenuated group as well but ERT is maybe a more standard approach.

What's challenging is that there may or may not be a symptomatic difference between these babies, especially during the neonatal period. That is definitely a challenge.

Next slide. What is really helpful when it comes to MPS I versus when we were starting with Pompe is that there is at least one publication that is here, that helps us predict where these babies are going to fall in terms of what their phenotype is going to look like. This is an article by Sandra Kingma and her group based out of the Netherlands that came out in 2013. Because it was obvious that we were heading towards doing newborn screening for MPS I, they worked to develop an algorithm.

Next slide. This is what it looks like. You've got babies that have ... Basically based on the enzyme activity, you can get a sense of, if they have very low enzyme activity that's looking more like a Hurler phenotype, you can also include information, like the mutation analysis. Is the baby homozygous for a known mutation for example? That would move him more towards a severe phenotype. Again, Hurler and severe, it's the same thing.

Or maybe the baby has greater enzyme activity, doesn't have mutations that will move him more towards an attenuated MPS I. They did identify in their studies some clinical characteristics that can possibly help distinguish that. That includes whether the baby has an inguinal hernia, or an upper airway obstruction that can possibly help move you one way or another.

This is stuff obviously that we're not going to have to figure out at Newborn Screening Programs. The specialists will be asked to determine this, but I think it's going to be really helpful for the specialist if there are some guidelines already out there to help them figure that out. I can at least speak for the New York group of providers, that they will be happy about this, or happy that this exists anyway.

Next slide. We were also given the advice to work with a specialist to clearly define the disorder and the variants, and their subsequent classifications so that everybody is calling the outcome the same thing. Everybody is calling severe MPS I the same thing, for example. Just to note that we do know that NewSTEPs is working to create case definitions for MPS I, so that's in progress but not ready just yet.

As best you can, try to work with the specialists in your state to ensure that there are available resources and support for families. If you can, planning for long term follow-up is helpful. We were given the advice that you should do

broad parent and pediatrician education, and that ideally that should be done at least a couple of months in advance of when you start the screening.

Next slide. That brings us to our last section which is just about education. Next slide. Again, thinking about the stakeholders involved in screening for MPS I, our specialists are a really good resource for helping us put together educational materials, getting advice from them, having them help review materials we have put together. Just a plug, I am a genetic counselor myself, full disclosure but genetic counselors have to be really good at putting together educational materials. That's something that we literally do as part of our training.

If you have genetic counselors in your state, and I'm sure I guarantee all of you do, they're a good source to help be able to put resources together. If you have genetic counselor in training programs in your state, they might have eager students who would be willing to help put educational materials together for you. Also, other audiences just to consider in terms of putting together educational materials are your pediatricians in the state. What are they going to need to know when they have a baby who is a patient of theirs test positive for MPS I?

There is not currently an ACMG fact sheet available. I know that a lot of states use that. There's not currently one for MPS I. Hopefully one will be coming. You may need to consider putting something together if you have relied on the ACMG fact sheets in the past, or ACT sheets I should say. Hospitals, again, I think will appreciate knowing that MPS I screening is coming. Sometimes they need to make configurations with their laboratory, like information systems as well.

Some basic level of communication and education with them, I think will be very appreciated and go a long way to make this as smooth a process. Then with the public and parents, it's hard to do of course a mass education effort with that wide audience, but certainly making patient friendly, family friendly fact sheets and brochures is really important.

Next slide. Just some thoughts about different ways that you can get your education efforts out there, doing brochures and fact sheets on your website is a good way to get information out there.

Next slide. Just some last considerations when it comes to education and is just thinking about the timeline of education efforts when it comes to rolling out screening for MPS I. Thinking about this, there's some different approaches you could take. You could do a big education blitz just prior to the start of your rollout. Some states have chosen a more just in time education to pediatricians, so maybe not notifying all pediatricians ahead of time for fear that that might just get lost in all of the noise that all of the other communications that they get all the time, but perhaps giving them education on a case by case basis as they get referrals for babies that have screened positive for MPS I.

I'm not saying that one of these is the right approach or not. I would actually just urge you to consider what has worked or not worked in your state in the past, or have you set a precedent in the past with your providers in your state about how you handled that? That's going to be very dependent from state to state, I think. These are just some food for thought.

Next slide. Lastly these are just some education resources that are out there and available right now if you just want to have a place to look to get started. Baby's First Test has a page about MPS I. Genetics home reference is always a good resource. There is also the National MPS Society who has a lot of good information about MPS I. Like I said, the ACMG actually they're not yet available for MPS I but hopefully will be before too long.

Next slide. Last is just QA and closing. Next slide. I'm going to turn that over to Patrick in a minute, but I just [inaudible 00:52:50] wanted to say a thanks to the colleagues who I spoke to at the five programs screening for MPS I. In Illinois that was Claudia, Rong and Khaja. In Kentucky, Darrin, Pennsylvania it was Kelly and PJ, in Missouri Patrick, Jami and Tracy, and in Ohio, Rosemary. Thank you to all. All of these folks were so kind and helpful to allow me to pester them with these questions.

Next slide. These are some references that you might find helpful. Next slide. This is my contact information, as well as my colleague's Beth Vogel. She's a genetic counselor here in New York who many of you know. If you have any questions, you can reach out to either of us here at the New York lab.

Patrick Hopkins: Thank you, Sarah, very much for excellent presentation. We will now begin taking questions. Press *7 to unmute yourself and ask a question over the phone, or type into the chat box and we'll read it off. Please call with your questions or enter them.

Laura Russell: We do have one question in the chat box. You mentioned gaging whether the sample results are inconclusive based on other enzyme values. How low should the other enzymes be to say that the results are invalid?

Sarah Bradley: I'm sitting with Joe Orsini from the New York lab and I'm going to let him answer that because he does a lot of that with our pilot results.

Joe: This is Joe. We do not have what I would call a way of doing it for MPS I that I would recommend just yet, but I will have some ideas on the talk coming up Wednesday if you would listen on that. I can tell you, we do set up a borderline range from what we're doing with Pompe and Krabbe right now, where we're in the range of enzyme activities that we really have not seen. It's a conservative range that we have not seen. Many cases are real cases and we see other enzymes, if they're all low ... What we end up doing is running a sixplex or anytime we see a low GAA, [inaudible 00:55:27]. If all the remaining enzymes are low, then we adjust up based on the results of that test.

If all the enzymes are low, and for us we use a 20% of mean category, if we see several enzymes below 20%, including MPS I, then we request a repeat of those. Where it gets a little tricky is when you have low results or moderate results, which I think this question goes to, honestly that's where we're looking for with [inaudible 00:56:00] in the database to help decipher some of those.

Laura Russell: Thank you, Joe. If you would like to ask a question over the phone, press *7 to unmute yourself. We do have a few more questions in the chat box. If 2nd tier tests are negative for MPS I, does this mean that MPS I is ruled out?

Sarah Bradley: In New York what has been our approach with Pompe and what will, I think, likely is going to be our approach for MPS I, is if we have a baby with low enzyme activity who has 2nd tier molecular testing but no mutation is detected or only pseudodeficiency alleles, we don't refer those babies out. The mailers are sent out. If no mutation is detected, we state that. It's a screen negative result. If pseudodeficiency alleles are detected, we report that they were detected but that we don't expect that the baby will have disease and say that no further testing is required.

Laura Russell: Great, thank you. We have another question in the chat box. This person just wants to clarify that Mayo has 2nd tier testing for MPS dermatan and heparin sulfate on dried blood spots.

Sarah Bradley: That's a great question. I didn't ... Oh, you're saying that they do? Sorry. Is that a question or a comment?

Laura Russell: It's just that the person wanted to clarify that Mayo has the 2nd tier testing for dermatan and heparin sulfate on dried blood spots.

Sarah Bradley: They do have a 2nd tier test available. They're doing this testing for Kentucky. I know that they are working to develop a 2nd tier test of the dermatan and heparin sulfate. It didn't sound to me like that was live 100% yet. In terms of the actual confirmatory testing, they've not contracted with Mayo for testing. I know they do the urine GAG. I don't know if they accept other sample types for that or not. I didn't think to ask that question. That's a good question. You might want to ask Mayo directly.

Donna: Can you hear me?

Sarah Bradley: Yes.

Donna: Hi. This is Donna. I'm a genetic counselor at Mayo clinic. I was a clinical counselor in Missouri. Yes, we've had orderable dried blood spots for 2nd tier MPS testing. It has been live and orderable since November.

Sarah Bradley: Oh, good.

Donna: It is available to be contracted through Newborn Screening Programs. Before it's reported out, we can accept them. We're also getting samples as part of the confirmatory testing process from ordering clinicians who have been referred abnormal newborn screening for MPS I.

Sarah Bradley: [crosstalk 00:59:28]

Donna: To our knowledge, if it's normal, it's most likely either due to a pseudodeficiency or false positive. There's not been any reports of a missed case with a normal 2nd tier test. Usually the blood and the urine correlated. As far as I know they have so far. It's a nice option because I know getting urine on a baby is not always easy.

Sarah Bradley: Yes, thank you for that information, Donna. That's really helpful.

Donna: I just wanted to make sure everybody who's listening is aware.

Sarah Bradley: Thank you.

Laura Russell: Great, thanks. I know it's the top of the hour. We are going to go ahead and wrap up. Patrick?

Patrick: Okay. The next webinar in this series on clinical aspects will be held Monday, May 22nd at 1:00 PM Eastern Time. The third webinar in this series on available screening methods will be held on Wednesday, May 24th, at 1:00 PM Eastern Time. Webinar access information will be sent out via the listserv, and will be posted on the APHL Newborn Screening training page at aphl.org.

You'll receive a link to this page in the post-webinar follow-up email. P.A.C.E. credits will also be awarded for attending this webinar. To receive P.A.C.E. credits, participants must complete the post-survey evaluation which will appear in the post-webinar popup window and followup email. If anyone has any questions, they can contact Laura Russel at APHL. Thank you all for calling in today.