Newborn Screening: Metabolic Conditions

Hi, I'm Jerry Vockley, and I am the Chief of Genetic and Genomic Medicine here in Pittsburgh at the children's hospital, and Director of the Center for Rare Disease Therapy. And I'm going to be talking to you about newborn screening today, with a focus on metabolic conditions and how they affect families, and how we need to speak with families about the results of the newborn screen. So here's my agenda, I'm not going to read this to you to save a little bit of time, but you see our learning objectives at the bottom to develop a framework to explain positively newborn screening results for rare conditions that are on the newborn screening panel that is called the RUSP or the Recommended Uniform Screening Panel.

So newborn screening, it's important to realize, is not diagnostic testing. It's a public health initiative. It's aimed at preventing mortality, morbidity, and disabilities. Screening for metabolic diseases, as well as most of the endocrine disorders, and some of the immunologic disorders that are on the screen is from blood spots, but there are also other types of screening. And these include things like hearing with brainstem auditory evoke response, or pulse oximetry for congenital acyanotic heart disease.

We'll start by hearing from a parent who learned about a newborn screening result for Pompe disease, as well as a parent who will be talking to us about her experience with screening with spinal muscular atrophy, and telling us a little bit about why she feels newborn screening is so important.

> *It's terrifying because most people have never heard of Pompe disease, not even the physicians a lot of times. And so you have a brand new disease with outdated information on Google, and you just learn that this disease is... could be fatal for your baby. So really just having support and looking for parents who have been through the same thing as you, and making sure that your child is going to get through this.*
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> *Because, newborn screening was not given to my son. He went from what, all the data and historically now shows he would be probably not symptomatic at all if he had been treated right away, because for the first six months of his life, he had no symptoms. And what data shows for all of these treatments is in the children who are dosed with any of these drugs, pre-symptomatically, they typically are not developing symptoms ever. So in that six month window, if he had gotten any treatment, he would've never developed symptoms. Instead, he's now in a wheelchair struggling to attain basic motor skills that he had at one point. He had all his motor neurons, time is motor neurons in this disease and when you have newborn screening, you're in a situation where you catch it before you get symptoms or if you're one of the worst types, it could be a life and death.*

Talking to parents is fraught with difficulty during a period that's very emotional. You've just called a family. Or you're just speaking with a family in the hospital, in the newborn nursery, telling them that their childhood looks perfectly well, has a potentially life threatening disease. And that's really hard. Parents sometimes don't hear what you're saying and sometimes they don't hear it properly and you can see that families have varied responses to it. It can be scary. The first thing they do is run out and look things up. And so your job is to really try to be simple enough for them to understand what you're saying, comprehensive enough for them to recognize that it's important but not so overwhelming.

Newborn screening started back with Phenylketonuria, PKU, and it was identified that it was a cause of intellectual disability back in the 1930s, and then not too long after that, it was recognized that those symptoms could be prevented if only you treat a child soon enough.

And it turns out that needs to be done at birth and that requires newborn screening. So Robert Guthrie in 1958 developed an assay that could be applied to newborn screening and a couple of tests, cases in

New York and Massachusetts, it started to become proved for general use across the United States. So that really by the late 60s, or early 70s, everybody was screening for it. But there are many disorders that like PKU have intervention early and improve the outcome of the disease and this has really been increasing over especially the last decade with the implementation of mass spectrometry for newborn screening. And so this led the HRSA to put together what's called a Recommended Uniform Screening Panel, a committee of individuals interested in newborn screening and including their parent advocates meet on a regular basis to identify disorders that could benefit from newborn screening, the technology is available. It looks like outcomes are improved as a result of that screening.

So this is the current uniform screening panel, and it includes a whole bunch of metabolic disorders, but all of those disorders are identified by that one test that I mentioned, the Tandem mass spectrometry. The endocrine disorders, and the immuno deficiencies can be identified by blood tests, but they're different blood tests. They're either immunologic in the case of the endocrine disorders and molecular in the case of the immuno deficiencies. The hemoglobin disorders are identified by hemoglobin electrophoresis. And then there's a whole list of other disorders that are identified either by direct enzyme analysis or mutation detecting, the detection or this point of care testing, such as hearing loss or pulse oximetry for congenital heart disease. This just shows the list of metabolic disorders and it's quite broad.

They are complicated disorders to take care of. For those of you who dreaded your biochemistry in medical school or undergrad and this really is the bread and butter of those metabolic disorders. And it is very helpful for those of us who take care of these disorders to understand those metabolic pathways, but you don't necessarily need to be able to talk to families about those disorders.

Here I just have for example, the disorders of fatty acid oxidation, that are part of that primary screen. And the most important thing to keep in mind about newborn screening is that it really does change the outcome for these babies in whom we develop it. In the case of PKU, it prevents the devastating neurologic symptoms that leave patients with essentially no intellectual development in a horrible movement disorder if they're not treated from birth.

Treatment is lifelong. And so there are tremendous impacts on both the patient and the family and it requires a knowledgeable team to optimize the outcome. Many times you'll see, as in the graphic here on this slide, that they're the subject of pretty significant practice guidelines. The American College of Medical Genetics put one out on the treatment of Phenylalanine hydroxylase deficiency or PKU in 2014 and is updating that now but the end result is that you have individuals who otherwise would've been devastated neurologically, living perfectly normal lives.

If you look at something like the fatty acid oxidation disorders that I mentioned, these are disorders that prior to newborn screening were identified largely by sudden death. A patient would drop over because they had either low blood sugar or heart disease. They can develop cardiomyopathy and arrhythmias and if you look at two of the disorders in this family, VLCAD deficiency, Very-long-chain acyl-CoA dehydrogenase and Long-chain 3-hydroxyacyl-CoA dehydrogenase or LCHAD deficiency.

What you can see is that the common manifestations of these disorders, which are cardiomyopathy, hypoglycemia and hypotonia, and I didn't even include cardiomyopathy or rhabdomyolysis here are all reduced by identifying these patients through newborn screening. While patients can still die of these diseases, sudden death with the disease being an unexpected issue is essentially been eliminated by newborn screening and their outcomes are much improved.

If you're taking phone calls regarding newborn screening, especially if you're not a specialist in these disorders, the American College of Medical Genetics does have online resources for getting quick information on them. They're called the ACT sheets. They've been put together by experts involved in diagnosing and treating these disorders. If you are a PCP and your State Screening Program is calling you

to talk to the family. You may need to be on the front line returning these results or at least telling the family that a little bit about them so that they know that they really need to get to see the specialists. So these are valuable, they can be found on the ACMG website and they have an iPhone and an Android app that you can download.

We spent the last couple of minutes talking about some of the things that I've learned over the years about talking to parents about newborn screenings. So if you're a PCP involved in making that phone call, keep in mind, the first contact is likely to be by phone. So this is a hard way to have to interact with families, especially if they're not your primary a patient, if it's a weekend or it's overnight, and you're covering for a colleague, that's a tough phone call to make. So have your info available on the disease. Check out those ACT sheets, just do a quick look so that at least you know what the disease is and who your referral lines should be. Your newborn screening program at the State level should be able to tell you that, they should tell you that when they make the phone call.

I recommend keeping details to a minimum. Families are going to ask you all kinds of questions. I suggest that you simply say, "Look, this is not my area of specialty, but I'm going to refer you to a specialist. Who's going to help you understand these diseases." Please keep in mind that this a preliminary test, the test may not even be correct. So let's keep things calm until we get that final result back. If you've done your homework up on that second bullet you'll know whether or not this condition has a treatment as most of them on the newborn screening panel do and so that's also can be very reassuring to families saying that, "Yes, if we find something here, we will have some treatment for you."

For folks like me who then see these patients in referral. Some of the things that I've learned to do over the years is really just to try not to make that first meeting overwhelming. We don't want to add to the problem. We don't want to give them so much information that they can't deal with it. I usually tell my trainees that the family remember 10% of what you tell them. So tell them what you need early. Keep it simple and direct and then plan on coming back and filling in details later. I always remind families that information on the web may be outdated. So don't go out there and ask Dr. Google. If you're dying to know something, go ahead and ask me, I'll tell you, I'm not trying to avoid things. I'm just trying to make it simple now.

The response to newborn screening really is a team approach. It involves if it's a metabolic disorder, they're usually a geneticist, but if it's a spinal muscular atrophy, it will be a neurologist. If it's an endocrine disorder, it will be an endocrinologist. If it's a hearing disorder, it'll go to one, an audiologist. So you've got to get it to the right care provider. And then all of these disorders are genetic. So we have a genetic counselor as part of our team. And if it's a metabolic disorder, we do have a metabolic dietician participate right from the very start.

Some of these diseases can wait a few days or a few weeks while you get the final answer if that's an issue, but some of them need urgent treatment. And then we may tell the family we're going to start treatment right now, while we sort out the disease. I will tell you that the Tandem Mass Spec results are usually pretty reliable. If the newborn screening program says this is a positive, it probably is. And so when I see those families, I'm leaning towards saying, "I think this is probably real." And almost inevitably families will say, "How can I have a genetic disease? No one in my family has ever had anything like this." And of course, that's the reality of autosomal recessive disorders, parents are carriers, but their children are at risk to have the disease and nobody else in the family ever has.

So it takes a little bit of a reminding to, for them to understand that. And so in summary, I can offer some clinical pearls to try to get you through that first contact with the newborn screening program and the families remember that metabolic disorders are a major part of the newborn screen, but there'll be others. And you'll have to look those up. If you don't know what they are, newborn screening definitely

changes the lives of babies of people with metabolic disorders and that's why we do it. And we just have to keep emphasizing that to the families as they go through the real trauma of learning about this. And they're apparently, well baby. Past experience says unequivocally there's room for improvement in communication with families.

So do your best, listen to your families, hear what they're telling you, because that's what they've heard. They didn't hear necessarily what you said. And so just keep feeding it back to them and until they get it right, when you're talking with parents, do your homework, be empathetic and recognize that best practices are put out by newborn screening centers to deal with these patients. And that they will be your partner in doing that. So with that, I'll say, thank you for listening to this. And I hope you found it useful.