Newborn Screening: Talking to Parents.

Hello, I'm David Kronn. I'm a medical geneticist at Westchester Medical Center in New York. And we have a newborn screening referral center at Westchester Medical Center to cover the lower Hudson valley. I've been involved in newborn screening for over 25 years. And this talk is about talking to parents when they receive an abnormal newborn screening result and some of the background involved in those decision making trees. So we always start thinking about what is the rationale for newborn screening? And this is from the New York state guide for newborn screening. The goal of newborn screening is early detection of children at increased risk for selected metabolic or genetic diseases so that medical treatment can be promptly initiated to avert metabolic crises and prevent irreversible neurological and developmental sequelae. Now, this has always been the idea behind newborn screening and it started... of course, newborn screening started in the early 60s with PKU... and that's been the major success in newborn screening and these patients are doing so much better than they did before we had screening.

Not all diseases can we actually prevent irreversible damage, but if we find out about a disease early, then we can do a lot about it. And that's really the critical component about early detection of these diseases. Now there is... newborn screening has expanded over the... over many years, in particular in the early 2000s, with the introduction of tandem mass spectrometry. And now most screening programs screen for over 50 diseases at this point in each state. So, this is sort of an outline of the core diseases, these are the primary diseases that are screened for. There are secondary diseases which are screened for with the same metabolites.

So, there may be one or more disease that is picked up with one particular metabolite or one particular test. So, in terms of the metabolic disorders, we have the organic acidemias like methylmalonic acidemia. We have the fatty acid oxidation disorders, in particular MCAD deficiency,medium-chain acyl-CoA dehydrogenase deficiency. We have the aminoacidopathies like PKU. We also have some of the urea cycle disorders and of course, tyrosinemia type I. We have the endocrine disorders, hypothyroidism, general renal hyperplasia. We also have the hematological disorders, particular sickle cell disease and thalassemia. And then there's a growing group of other diseases. And some of these are being added more recently and we'll talk about that in another talk. But in particular, we have Pompe disease, we have spinal muscular atrophy. And it's also important to recognize that there are two diseases which are not part of the actual newborn screening test, which are done in the hospital, and that's particular critical, congenital heart disease and hearing loss.

So in terms of newborn screening, a patient sample is collected ideally between 24 and 48 hours of age, and we've sent to the screening lab. It's actually interesting that about 10% of newborn screenings cards or samples in New York are repeated. But we only deal at the metabolic center with actionable results. So in a way, this is how we think about it. So there are a series of values that may be slightly elevated, which aren't critical, but require repeating. So if a sample is mildly elevated, then a repeat specimen will be requested. If it's negative, then the case is complete. Of course, if it's negative in the initial phase, then of course the sample is negative. If the repeat specimen is positive then, because you've had two mildly elevated cases, then a patient will be referred to a specialty center.

If the level on the initial newborn screen is actually high, then that's considered actionable and the patient will be immediately referred to a specialty referral center. So if you have a very high level of C3, potentially a patient with methylmalonic acidemia, then that patient would be referred immediately for evaluation. They may already be quite sick and they may actually already be in the hospital.

When we're thinking about the newborn screening, we want to think about what a result means. And this is a little bit tricky because each disorder has a different sensitivity and specificity. And so we're always concerned about. Indeed, what is the positive predictive value? So the sensitivity is the likelihood that an infant has a disease, will have a positive test result. So we want to make sure that we don't miss any cases. But in order to have a high sensitivity, then the specificity can decrease.

And in that case, the infant does not have the disease and will have a negative test results. So that can lead with a very high sensitivity, then the specificity can go down and as a result, the positive predictive value can actually also go down. So you want to know if you have a high level of C3, what's the likelihood that this patient actually will have the disease? And with C3, it's actually somewhat low, but with other diseases it's actually much higher. So it varies with our experience and also it varies with the condition of the child. So sometimes if the child has an illness that can mimic a metabolic disorder in the initial phase. So it's important to know that. And of course, in the NICU, there's a very high level of positive values because the child is metabolically, in a way, unstable because they're quite sick.

So that all goes into the consideration when we actually see the patient or talk to the doctor who has seen the patient about what's going on. Now, in terms of the accuracy of the results, this is another way of thinking about it. So think of it as a bimodal distribution. These are all the patients who are normal with a particular metabolite. And these are the patients who have the disease. And you'll see there's a crossover where there are patients who have the disease and yet they fall within the normal range... what we would consider the normal range. But, so the issue here is where do you set a cutoff value for a patient sample? So if it's too low, then you end up having a lot of false positives. If it's too high, over here, then you may have a lot of false negatives.

So you'll miss some patients who actually have the disease. So, this is how we think about it. And ideally with if we had a very good test, this bimodal, this would be over here and this would be over here. So there'll be huge separation or very good separation between normal and diseased. So this is where we come in with the experience and what's the likelihood of that patient actually having the disease. And that's why it's important that we have a dialogue with the metabolic center or the newborn screening referral center, and that's why we report all the cases to newborn screening, so they can actually analyze the data and think about how they can make the cutoffs better or use other markers for patients with particular diseases.

So often what's happening is you have an initial test and then if it's positive, you may have a secondary test, like a molecular test to try and confirm the diagnosis. So that's an important part of the screening process. And of course, if the patient is referred, then we would do a diagnostic workup. Looking at some of the diseases, this is from some of the data from New York state. So it varies so if you have an actionable result, which is very elevated, then you're more likely to have a positive case.

So in PKU, if the level is actually consistent with a PKU patient, it's most likely that the patient actually has the disease. With Krabbe disease, which we had had a number of issues with, and a lot of patients actually were false negatives. And so there were quite a small number of actually screened cases that were positive. So it can be quite troublesome. And with congenital adrenal hyperplasia that became an issue because the levels are a little bit higher in the NICU population. So there's a lot of positives in the NICU population which then turned out to be negative on follow up.

So in terms of timing of newborn screening, there is a process called timeliness, in that if we're a critical condition, we want to have the results of screening by at least five days of age. So, if in the whole newborn screening process... if we had a patient with a severe methylmalonic acidemia, we would hope that this patient will be referred to a metabolic center by about four or five days of age so that the patient can be brought in and started on management as soon as possible. So with a critical result, that's why the whole process is very timeliness orientated. So now the screening occurs at around 24 to 48

hours of age. The sample is sent immediately the following evening to the metabolic, to the newborn screening referral center where it's analyzed.

And usually the result is available within 24 hours. So the process is shortened so if we have a positive patient, that patient is picked up as soon as possible. So, when a patient is referred with a positive result, the initial call will be to the pediatrician, but also if it's critical result, then we will also receive a referral. And there is a good resource of information on how to manage patients called the ACT Sheets. And this is on the American College of Medical Genetics site. And here is the link. And here tells you what to do for a PKU patient. So a patient with an elevated phenylalanine, potential PKU., this is how this patient would be evaluated. So remember that this is a newborn screen, it's not a diagnosis. So a patient has an elevated metabolite and that is a potential indication of a disorder. We then need to do a diagnostic testing for the patient.

So if it's a critical condition like methylmalonic acidemia, where the patient can be quite sick, then in some cases we need to bring the patient actually into the emergency room because the patient can be sick. So with each disorder there is sort of a tree about how we manage these patients. And a lot of this information is on the ACT Sheet. And that's a good resource to use when you are presented with a potential referral. There are over 50 diseases so it's hard to remember offhand what to do for every patient. And so we will coordinate with the pediatrician to help with patient management. If it's an actionable result, obviously we work quickly and we try to get the patient in as soon as possible.

So at our center, we have established a sort of a rapport or way we manage these patients. So if a patient is referred to us, we will contact the pediatrician first, because they may be the initial contact for the patient. Often we don't have a pediatrician of record, especially if in the NICU that may occur. So we often will call the family. Now, our goal is that we try to see every patient within 24 hours of referral. Obviously if it's a potentially sick patient, we may actually want to bring the patients really into the hospital or partner with the pediatrician, if the patient is far away, to have the pediatrician check the child to make sure the child is doing fine. So we tried not to be too alarming with the family and tell them that there's an abnormal result and we need to bring you in to do the evaluation.

So if we can call the patient and bring them in as soon as possible. So, ideally we call the patient in the morning and the patient will come in in the afternoon or that evening to come in the following morning. So we try not to leave a gap between calling the family and bringing them in to be seen.

This is a slide we put together to talk about tips for talking to parents about newborn screening results. If the results in newborn screening are elevated, physicians need to see the baby and the test needs to be repeated. And so usually we try to get the patients in within 24 hours. Remembering that the screen is not a diagnosis, the physician needs to see the baby as soon as possible. We try not to discuss the specific disorder over the phone. It's better to explain this in person.

And of course, this is a very vulnerable time for parents. They can be overwhelmed, and confused, and sleep deprived. So you have to take that into account when you're talking to parents. We try not to give them too much information at once, as they can get overwhelmed. And so we talk about the diseases in general terms. And if the child is doing well and I think it's less likely then we try to reassure them. But of course we tell them that it's very important that we do the testing to make sure that we rule out the disease or if we have to rule it in. Okay, so here we have a experience of a family.

So my advice would be to just be honest and really do the research on what the disease is. And figure out where your referrals need to go and what specialists that you need to be seen. And just learn as much as possible. Know that there are treatments out there and the faster that you can get a treatment, the better outcome that it will be.

So the newborn screening is a really important process and it's the largest public health program in the country. Over 4 million infants are screened every year. And the results of newborn screening really change lives. So, remember also that preliminary test results are not diagnoses. And so when we do that... when we call the family, we tell them this is not a diagnosis, this is an abnormal result and we need to do further testing. So it sort of eliminates them saying, "Well, what's the diagnosis?" And we contact the families early and we work with the pediatricians. And actually during COVID, we ended up having to partner more with pediatricians and have them evaluate the child, especially when we started working remotely. And so the local pediatrician can be invaluable in helping us see the child.

And we also can see the child through a Zoom visit. So that's actually something else that we've done during COVID. So we can actually see the child early on if necessary. So we can actually do that in an emergent basis as well. So that's been something that we've sort of become more comfortable doing at this time. Don't forget that there are management sheets available so that if you want to look... you want to learn more about the disease quickly. The ACT Sheets are a very valuable resource in helping you to sort of look and see what needs to be done for the family immediately. Thank you.