Newborn Screening: Hemoglobinopathies and Newer Disorders on the RUSP

I'm David Kronn. I'm a medical geneticist at Westchester medical center in New York. We have a newborn screening referral center, which covers the lower Hudson valley of New York. I've been involved in newborn screening for over 25 years. We're going to talk about newborn screening for hemoglobinopathies and some of the newer disorders on the RUSP, the recommended universal screening panel.

So just to start the talk, let's talk about the criteria for newborn screening disorder. In general, the disorder produces irreversible damage before onset of signs and symptoms. So, ideally the patient is clinically stable and well when we actually screen for the disorder. This is not always the case. The patient actually may also be sick for some of the severe organic acidemias and urea cycle disorders. But in general, we hope to find the patient before they really get sick. The treatment is effective if begun early. So, ideally in the presymptomatic phase of the disorder. So if we can diagnose a patient with a lysosomal storage disorder, identify the patient, begin therapy, hopefully the patient will not progress. The matter history of the disorder should be known. So we should know how the patients are, if they're untreated, and also how they respond to treatment. So, some of the new diseases are on the RUSP because of new treatments that have been developed.

So here is another look at the RUSP and I'm just highlighting the diseases that we will talk about today, hemoglobinopathies, and some of the new disorders on the newborn screening particularly Pompe disease and spinal muscular atrophy. Also, recently MPS 1, or Hurler syndrome was added and X-linked Adrenoleukodystrophy was also added in the last 10 years. So the hemoglobinopathies had actually been on newborn screening for quite some time. The rationale early on was based on the benefit of understanding, identifying patients, and putting them on penicillin prophylaxis and this prevented life threatening pneumococcal infections in infants. But also now we have newer therapies for the disorder, and if we can identify patients early on, we hopefully will prevent these patients from having crises and that's leading to better morbidity and mortality for these patients. So following the advantages of newborn screening for sickle cell disease life expectancy has increased from a median of 14.3 years to 42 - 53 years in males and between 46 - 58 years in females. And actually the new treatments and perhaps hydroxyl urea has actually improved that, will improve that hopefully.

The annual prevalence of sickle cell disease is approximately one in 1,941 live births in the United States. And since 2006, all states and territories, except for Utah, have been screening for the disorder. And testing is done on the dry blood spots with isoelectric focusing and HPLC. Most newborn screening programs have a two-tiered approach. The initial screen is followed by a complimentary method, frequently molecular analysis.

So moving on to another new disease, we have Pompe disease. And this is a rare lysosomal storage disorder with an estimated instance of about one in 40,000 overall. There are some ethnic groups which have higher instances, particularly the Dutch where they have quite a number of patients. This is a spectrum disorder and we have patients who have early-onset, also called the infantile onset Pompe disease. And then, anybody who presents after a year of age is generally considered late-onset Pompe disease. The infantile patients are characterized by cardiac involvement and they may have cardiomyopathy at initial presentation, whereas the later-onset are more predominantly into muscle

weakness and respiratory involvement. And so that's how we characterize the patients. At this time approximately 28 states are screening for Pompe disease on their newborn screening panels. This is the map of where Pompe disease is screened for as opposed to the map of sickle cell disease, where you see that nearly every state in the country screens for it.

The rationale for screening for Pompe disease is very interesting in that before we had enzyme replacement therapy, patients did not do well. And the median survival was between one and two years of age. Whereas with the advent of therapy, these patients have done much better and even better once we detect them early. So patients who are diagnosed through newborn screening now, generally their survival is really very, very good and most survive on the vent and are ventilator free. And that's been our experience.

Patients who are diagnosed clinically don't do as well, because usually if a patient presents clinically, they have either some muscle weakness, maybe they have quite severe degeneration. And so by the time they're diagnosed, they may already be quite sick. And we do know from the screening programs from Taiwan, where they did a pilot program screening patients, half were screened by newborn screening and half were picked up clinically. If a patient was not picked up before six months of age, then the prognosis was quite poor. So it became quite clear from this early pilot that the benefit of newborn screening was really very important because these patients are doing very well.

So in 2013, we started thinking about newborn screening in New York state. And it was actually introduced in 2014. This is a busy slide, which talks about how we make the diagnosis of a patient with Pompe disease. But what happens in reality is the patients are screened by doing the enzyme assay first. If the enzyme, the GAA is low, then a second tier test, which is a molecular analysis is sent and done actually at the newborn screening lab. And if you have two pathological mutations in trans, then you likely have a patient with a disorder. Obviously you can't prove that until you actually do the referral and see the family. But if you have a very low level of GAA and you have mutations, which are suggestive of the disorder, you may be already on your way to making a diagnosis. So this is a critical disorder in that if you have a potential infantile-onset disease patient, you need to see the patient as quickly as possible because they may already have significant cardiomyopathy.

So we tend to see patients as quickly as possible. And when patients are referred, they will have an echocardiogram at the time they're seen. So this is important because once a patient is referred, we're not sure based on the initial data from the screen, from the state, if the patient has infantile-onset or likely late-onset disease. So we do a cardiac echo for every patient. And that's important for deciding how we manage the patient. If a patient has significant cardiomyopathy, then we will then plan to admit the patient so that the central line can be placed to begin ERT and also we will want to know the CRIM status of the patient. So that becomes a little bit complicated, but it's important to do that evaluation. Here is the, talking about the experience of a family member, a mother with a patient who has diagnosed with spinal muscular atrophy.

This 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 type ones it could be a life and death.

This is another disorder that was added to the RUSP quite recently in 2016. And this is a spinal atrophy disorder also known as Verde Kaufman. It is characterized by muscle weakness, atrophy, muscle atrophy, and results from progressive loss of anterior horn cells in the spinal cord and brain stem nuclei. So the onset is prior to birth to adulthood. It's a spectrum disorder as well, depending on the number of SMN2 molecules, it's quite complicated, but what's important is that there have been tremendous advances in their treatment. There were two drugs called Nusinersen and Risdiplam, which improve the number of SMN2 molecules that are expressed.

And also there's a gene therapy here for the drug, for the disease. And that's very effective. It's very expensive, over a million dollars a dose I believe. The severity of SMA is quite complicated, but obviously the number of SMN2 molecules that are present, it makes a difference, number of copies makes a difference in the expression of the disease. And the most severe patients have one or none. These are the most severe patients. And then as you have more, you have patients who present with the later-onset forms of the disease. So it's a spectrum disorder, but in general, the more severe patients are more common.

Screening for SMA is now done in 27 states. The implementation is complicated because it requires molecular analysis in the lab. And also it requires availability of the drug for the disorder. So how newborn testing can change lives of people with conditions? Hemoglobinopathies: life expectancy is improved with early teens to mid, late adulthood, many patients. And this is actually improving with new therapies. There will also be recent advances in gene therapy that may also make a lot of improvements. Infantile-onset Pompe disease: ERT is effective in extending life significantly. And there is a next generation therapy that has become available. And so we're hoping for improvements with that, but it is clear that early diagnosis of patients with IOPD is making a huge difference to these patient's lives. So it's very, very important. The SMA: it's a little bit early to know long-term, but these patients now are doing much better. They're walking, where they would not have been walking before and things, these patients are doing quite well. The need for ongoing therapy and repeat therapy for gene therapy is unclear at this time, but the outlook looks pretty good.

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 in the NICU that may occur. So we often will call the family.

Now, our goal is we try to see every patient with L referrals within 24 hours of referral. Obviously if it's potentially a sick patient, we may actually want to bring the patients immediately 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 try 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 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 in them in to be seen.

That's really important. And we try, when we call, we try to not go into the actual disease. And so I have my staff call and we say the doctor needs to see you. I try not to speak to the family directly until we

actually see them in-person. If the patient is already sick, then obviously we have to act more quickly. And that's sort of part of what we do. So just finishing up, clinical pearls, hemoglobinopathies are not on all newborn screen panels. We need to remember that these Pompe disease and SMA are on the panels because we have new treatments. So there are other diseases in the wings that may likely be on newborn screening in the future. Once therapy becomes available in particular, we can think about like Duchenne muscular dystrophy.

And obviously for these disorders, early diagnosis is critical and early treatment, when available, it should be given. It's important to remember how to talk to patients about these disorders. We try not to tell them what the disorder is when we call them with the result. We like to talk to the families in-person so that we can review what the results share. And remembering also that there are act sheets available for pediatricians and anybody who needs information on how to manage these patients and what to talk to with the families early on. Thank you very much.