Newborn Screening: From RUSP to Reality

Hello, I'm Jerry Vockley and I'm the Chief of Genetic and Genomic Medicine at the University of Pittsburgh and the UPMC Children's Hospital of Pittsburgh. And I'm going to be talking to you in this session about newborn screening, from RUSP to reality. And we'll define RUSP in a second so you know what that silly acronym is. Let's start with some statistics. And for many people, these are a bit of a surprise. And that's because what is often viewed as rare disease, genetic birth defects, are not so rare. In reality, 3% of infants are born with a genetic problem that brings them to medical attention.

Some of these are the autosomal recessive dominant disorders that you might be familiar with. Some of them are chromosomal problems, and some of them are multi-gene conditions like cleft lip and palate, or congenital heart disease. Of babies that are born, and this is in the United States, about 0.5% have an inborn error of metabolism. And these are the traditional, or at least the early target of newborn screening, because this is often diseases that we can do something about. The consequences of these genetic disorders are quite devastating, they account for 40% of childhood mortality, 50% of childhood hospital admissions, and a quarter of adult hospital admissions. Those last two are sort of depending on how you define them. So we count a child with down syndrome coming in with a respiratory infection as a genetic disease. So we cheat a little bit on that one.

Let's start off with talking about newborn screening, finding its role in medicine. Newborn screening is really a public health initiative. It's aimed at preventing mortality, morbidity, and disabilities, but it's not a diagnostic test. So it has to be followed up by diagnostic testing that then confirms or eliminates the diagnosis suggested by the screen. Most of the disorders that we'll be talking about are screened for on blood spots, that is the baby gets a heel prick, you put it on filter paper and from that piece of the blood on a piece of filter paper you can measure lots of metabolites, you can measure some enzymes and you can get enough DNA to do molecular testing.

However, there are other types of screening that we call point of care, that is things that have to be done by someone at the bedside of the baby to determine the outcome and the screening. And the two that are currently in place are hearing testing, which is done by a very simplified brain stem auditory evoke response instrument, and then pulse oximetry, which identifies critical congenital cyanotic heart disease, basically anything that can reduce oxygen in the blood.

I'll review PKU as the test case for newborn screening. And it's out of experience with PKU that everything else evolved. PKU is phenylketonuria, and it's a caused by a deficiency of the enzyme phenylalanine hydroxylase. And in the early 1900s, it was defined as a cause of mental disability. It was also recognized by identifying subsequent children of families who had a first child with PKU, that if you treated it, you could prevent those symptoms, the intellectual disability. The treatment in the case of PKU is dietary and had to be started right at birth, and that was the impetus for newborn screening. Bob Guthrie, back in 1958, developed something called the bacterial inhibition assay. By today's standards, it's relatively crude, but it was effective enough that it could be used to screen babies in a way that was never done before, that is in large numbers, right at birth, with a result quickly enough to be able to get the result back to the family in time for treatment.

And then in the early '60s, first in New York in a pilot, and then a statewide screen in Massachusetts, screening was tested and eventually became a standard of care across the United States. As PKU was starting to become standard, other disorders started to become candidates for newborn screening. And health organizations realized that they really had to deal with this in advance to try to be sure that newborn screening was done correctly. The World Health Organization in the mid sixties convened a conference that eventually spun out criteria that were published in 1968. Over the next really two to

three decades, disorders were added to the newborn screening panels across the United States, one at a time and very slowly so that by the turn of the century, most states were really only screening for about a half a dozen diseases.

And then there was a new development called mass spectrometry where investigators around the country and around the world figured out how to do metabolite analysis on blood spots from babies that they're taken in the newborn period. And this test was capable of identifying dozens of disorders at once. And so it really opened up not only the scope of newborn screening, but a Pandora's box of issues related to how they were going to be added to the newborn screening, who was going to kind of monitor that and when new diseases would be added. HRSA, in the United States, Health Research Service Administration, put together a committee called the advisory committee on inheritable disorders in newborns and children, whose job it was to look at newborn screening. At the same time, The American College of Medical Genetics had been commissioned by the American Academy of Pediatrics to look at the diseases that could be identified, potentially, through newborn screening, and to make some recommendations about what should be on the standard panel.

So this advisory committee looked at those recommendations and put together what's called the Recommended Uniform Screening Panel, or the RUSP. And the RUSP follows criteria that look very much like the World Health Organization criteria, but were developed by the American College of Medical Genetics. And they're just a little bit different as a result of the technology, the RUSP criteria includes specific and sensitive tests available to detect the disease.

The health outcomes of the condition are well understood. Notice, that doesn't say you have to be able to treat it because there are some conditions that you might be able to find that don't necessarily have treatment, but you might still have benefit from identifying them in the newborn period. Ideally, effective treatment is available, but it's actually not essential in the context of the secondary disorders on the RUSP, and we'll see those in a second. Then finally, identification of the condition can affect future reproductive decisions of that family. So regardless of whether the condition is treatable, there's some wiggle room in there about putting disorders on that panel.

So if you look now at the core RUSP, and it has been added to over the course of time since it's establishment, what you see are a large of metabolic disorders. These are all identified by tandem mass spectrometry. There are a couple of endocrine disorders, which are mostly identified immunologically, and then hematologic disorders typically identified by hemoglobin electrophoresis, and then a variety of other things that are identified through different technologies. For example, I mentioned congenital heart disease by pulse-ox, cystic fibrosis usually screened for by alpha-1 antitrypsin gene in the blood, and then some lysosomal storage diseases that are starting to hit the RUSP, Pompe disease, MPS type one, the most recent one added is spinal muscular atrophy.

Now I mentioned secondary disorders a bit ago and what these are, are conditions that you identify because you do a test for a primary disorder, and this one comes along for the ride. So for example, methylmalonic acidemia with homocystinuria, the first one there, those are caused by defects in vitamin B12 metabolism, and so they're considered secondary methylmalonic acidemia. The primary methylmalonic acidemia or methylmalonyl CoA mutase deficiency is the primary disorder, but you'll find some of the cobalamin deficiencies, the vitamin B12 deficiencies, with mass spec and so they're called secondary disorders. It doesn't mean that it's not useful to find these, it just means you don't have to have any additional effort based on what you're already doing to get those disorders.

Probably one of the most important things to remember about newborn screening is it is a State by State affair. That is, the RUSP is a federal recommendation through the HRSA committee, but it is not mandated. And each State then decides which of those disorders are going to be implemented. As it turns out, essentially every State now in the country meets all of the metabolic conditions on the RUSP,

and then some of those other miscellaneous conditions have yet to be added in some States, although you see a couple of States here, including mine, Pennsylvania getting a C average. In fact, Pennsylvania does all of the RUSP, but actually exceeds it. It just doesn't report them all out the way that gets recognized when the counting is done by the National Organization of Rare Diseases that puts this map together.

But keep in mind that when you're seeing a child, excuse me, who has what might be a metabolic disease, you can't just assume they've been tested for metabolic disease based on the RUSP because, number one, it doesn't identify all metabolic diseases, but number two, they may have been tested in a State at a time when the disorder that child could have wasn't on their State's screen. So you still always have to be alert to these disorders.

And that brings me to what I've been calling the politics of newborn screening. And I've already mentioned that each State decides what to put on the RUSP for its own conditions, and that's really one of those things that is often not pretty to see. It involves the legislature sometimes, there are usually advisory committees, but States aren't necessarily required to follow what the advisory committee says, and so it's a bit of a hodgepodge as to how things are added and when. And so you have to keep that in mind when new disorders are added. And unfortunately, one of the realities is that State legislatures, if they are involved, oftentimes will mandate throwing something on the RUSP, but then not include any funding for it. Why do you need funding? Well, you need testing instruments, to train people to know how to use those instruments and how to interpret the data, then all of the other personnel involved with newborn screening, the follow up individuals in the State Health Department and the administration all have to understand those disorders. So there's really a lot of training involved when you add a new disorder to the RUSP.

And the reality of it is getting something on the RUSP is really most often a team effort. It involves clinicians, very prominently, patient advocacy groups, laboratories that know how to do the testing, pharmaceutical companies sometimes get involved because they provide the therapies for this disorders, and so it's a team sport.

And let's talk a little bit about the ethical issues. It's not cut and dry that newborn screening ought to be happening. We have, as a society, decided that the burden of false positives and negatives are outweighed by the benefits of the screening. But keep in mind that newborn screening, by definition, is an invasion of privacy. Those babies aren't asking to be tested, and in most cases, families are given the opportunity to opt out, but they don't have to agree per se, to do the testing. We always worry about any disease about potential stigmatization in an individual with that disease, and so, again, the individual involved here, the baby, doesn't get to decide about that. Most laws consider newborn screening compulsory and may or may not involve informed consent. And so that's another nuance in looking at the ethical side of things. It most certainly violates the right not to know and it violates confidentiality because when the screening lab gets an abnormal, it gives it to the State program who calls the newborn screening center or the patient's primary care physician.

So all of these things are included in the legislation that empower newborn screening to happen, and we've accepted them as a society. It turns out that almost everybody in the United States gets screened. There's usually a percentage or two of people who opt out on the basis of religious or ethical, moral concerns, but the vast majority of patients do.

So what happens when you get a call about a newborn screening if you're a PCP? Well, there is help out there, The American College of Medical Genetics and Genomics puts together what are called ACT sheets. And these are information sources that talk about what newborn screening is, what things are found when you do analysis in a newborn screening and their clinical significance. They link typically to informational resources, and they include a diagnostic algorithm and sometimes a first response

algorithm, this will help you understand what the disease is. And the first response is always to the screening center, the center that's going to follow up for that child, the specialist.

The last 10 years have really been remarkable in newborn screening with an expansion from, as I mentioned, about a half a dozen disorders up to close to 50. But the next generation newborn screening is going to be even more remarkable because we're going to be looking at things that aren't just identifiable by blood spots, not just metabolic diseases, but anything that can be run by a molecular test, so other genetic disorder. We'll also be looking at things that are non-genetic, infectious disease is a classic example of something that can be identified in a baby presymptomatically and may be helpful to do so. And we'll be using more and more point of care technology and relying less and less on metabolite analysis, so different technology than we have before. I throw out there non newborn, and that's kind of a non sequitur because if it's newborn screening, there has to be newborn. But it's just there to remind me to tell you that the same thing that we do in newborns, we can do at any age. And especially as we get to the molecular era, you may see that happening with time.

What's the effect of newborn screening been on infant mortality in the United States? If you look at the Department of Health statistics, 1935 to 2020, what you can see is that infant mortality dropped quite dramatically all the way through, even up to about 1980, '85. At that point, we had the implementation of expanded newborn screening. And you can see that continued slope there is not too much different than the decades before it, but might well have been a lot more shallow had we not been doing that newborn screening. And evidence of that is what you see after 2000 where most of the disorders have now been identified or the new screening technologies had been implemented and we're now pretty flat. And in 2020, you can see that birth defects, genetic disorders, still account for 20% of infant mortality with probably some of the individuals in those next three categories also being genetic diseases.

How will we get beyond that? Well, really, what it's going to be is looking at a whole genome or whole exome sequencing, looking at all of the genes all at once. There have been a number of studies, and I'm not going to read through this slide for you, but looking at the use of whole exome or whole genome sequencing for newborn screening, it's not quite ready for prime time yet, but it's not far off. And I suspect in the next decade, we're really going to see more and more implementation of a broader based molecular screening in the newborn period.

So, in summary, we talked about the RUSP being a recommendation and not a mandate and that's really important to remember. It takes many years for a condition to be added to the RUSP, typically, and then even beyond that, it takes years sometimes for States to adopt the recommendations for the newborn screening panel, and it is the State that controls newborn screening. Newborn screening is designed for diseases that are difficult to detect early, but that early detection can guide treatment and attenuate disease progression. There are indeed financial issues, there are political considerations, but newer methods are inevitably going to come to the RUSP and you'll see that technology is always really constantly being fine tuned to optimize outcomes. And if you have the opportunity, it's always best to be part of the solution rather than the problem. Get involved with your State's newborn screening program, and you can help drive the future of newborn screening in your State. So thanks for listening, and I hope you've gotten some useful information out of this presentation.