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Newborn Screening by Sequence and the Road Ahead

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Guest:
Dr. Neal Sondheimer is an Assistant Professor of Pediatrics at the University of Pennsylvania, and a Clinical Geneticist at the Children's Hospital of Philadelphia.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. The collection and transport of dried blood spots has facilitated population screening of newborns worldwide. In the July 2013 issue of *Clinical Chemistry,* researchers from the Wadsworth Center at the New York State Department of Health in Albany described a convenient technique to extract DNA from these dried blood spots to further expand screening to nucleic acid testing.

Accompanying that paper was an editorial by Neal Sondheimer, an Assistant Professor of Pediatrics at the University of Pennsylvania, and a Clinical Geneticist at the Children's Hospital of Philadelphia. He is our guest in this podcast.

Dr. Sondheimer, can you tell us a bit about newborn screening and why it was developed?

Neal Sondheimer: The purpose of newborn screening is actually to identify patients, newborns, with treatable disorders before they ever become sick. It's a program that's actually at an interesting landmark, because 50 years ago this year the first voluntary screening programs were started.

And the program has really been fantastic. It protects more than a thousand infants every year from the consequences of their inherited diseases, and as a public health measure only things like car seats or vaccinations are really in its rank. The program saves lives and has enormous economic benefits for the U.S. and the states by preventing people from becoming disabled and associated costs with disability.

Bob Barrett: And these programs are still effective 60 years later?

Neal Sondheimer: They are. The disorders that they are designed to look for cannot be detected by looking at a baby right after they are born. They are increasingly effective because new measures are introduced sort of as time goes along and new technologies are introduced to improve the ability to discriminate infants who do and don't have disease, and to

give us better and better predictive information about who needs to be treated immediately, who can be seen sometime later, and who is healthy and doesn't need further evaluation.

Bob Barrett: Well, what about the nuts and bolts of all this? Who runs these programs, and how are samples taken from infants, what are the costs, that type of thing?

Neal Sondheimer: The programs are actually run by the states, so each state has its own set of laws for how the programs will be run, and all of the samples are taken from infants shortly after birth, usually between one and two days of life.

The details of the program are different, but all of them are based on a heel prick blood sample, which is easier to get from an infant, and some parents have had the experience of actually seeing this done to their newborns, which isn't terribly pleasant, but doesn't hurt the babies very much. Only small drops of blood are taken from the infants.

And the costs of the program are really quite reasonable, considering the number of disorders screened. In my state, Pennsylvania, there are typically no costs to families for screening, and the actual cost to perform the screening is about $50 per newborn.

Bob Barrett: Right now I am just raising my hand, because I watched them do it to my daughter too, and I was cringing when it happened, so yeah.

Neal Sondheimer: It actually probably bothers the infant more to have their heels squeezed than to have their heel poked.

Bob Barrett: Now, what types of disorders are screened for and what methods are used?

Neal Sondheimer: Traditionally, the screening disorders are inherited defects in the processing of nutrients, so protein, carbohydrates, and fats that we get from our diet. The first screening disorder was something called phenylketonuria, which interferes with the metabolism of one of the building blocks of protein, the amino acid phenylalanine.

Over time the word screening has increased and includes problems with red blood cells, problems with the immune system, endocrine defects, and now even hearing in most states are screened for.

The methods have changed, the technology has improved. The first test for phenylketonuria actually used the growth of a specific bacteria in the presence of the infant's blood. But modern testing now relies mostly on the use of something

called tandem mass spectrometry, which is a technique for sensitively weighing and identifying compounds within an infant's blood.

Bob Barrett: You mentioned that the testing differs from state to state, but is the scope pretty much the same in each state?

Neal Sondheimer: The scope has sort of become quite similar in all of the states. There were some consensus studies done at a federal level about 10 years ago, and also through the March of Dimes and through the Genetic Society, the professional society for geneticists, which sort of agreed on a consensus list of disorders that should be screened by everyone.

However, as time has moved along and technology has increased, more and more tests are being added on into each individual state, so not every state looks the same.

Bob Barrett: Well, let's talk about the testing for DNA sequences. The paper from the New York State Health Laboratory that accompanied your editorial describes a technique to do that, but testing from blood spots seems difficult. Is there really enough there to test, and can we really sequence the whole genome from just a drop or two of blood?

Neal Sondheimer: Well, DNA is surprisingly robust and quite easy to work with. You have to remember that DNA has been taken from a variety of really unusual sources, like skeletal remains, and used to perform fairly complete genomic sequencing, so sequencing of all the DNA. And there's a lot of DNA present even in tiny drops of blood that are taken from infants.

We actually currently routinely use DNA for diagnosis of several disorders. In Pennsylvania, for example, there is a screening for a disorder called Glucose-6-phosphate dehydrogenase deficiency, and that's a primary DNA based test. So we are already performing that type of testing.

And almost all the states use a variety of what are called secondary genetic tests. In a secondary test you suspect a disorder because a test shows that there are suspicious chemicals in the blood. And then you look for mutations that may be causing the disorder you suspect. And it turns out to be true that if you can sequence any particular gene by looking at DNA from a blood spot, you can probably, at least theoretically, sequence all the genes from that blood spot, because it means that basically all the DNA that's in an infant's cells is probably there.

Bob Barrett: Well, what if parents don't want the state to have genetic information about their infants, are there laws in place to give parents the right to refuse this testing?

Neal Sondheimer: The laws are actually very interesting. The rules vary a little bit from state to state, but it's very difficult to refuse this testing.

In Pennsylvania, where I work, parents can decline, but in order to do that they have to sign a written statement of their objection, and this is pretty much the most liberal standard available for refusal.

In other states parents have to state a specific religious objection to testing. In other words, the burden is actually on the parents to show that their particular religion would object to testing, not simply that they personally object, and this has been tried out in courts. The State of Nebraska was sued over their newborn screening law by parents who wanted to use their religious beliefs to refuse testing, and the courts actually decided in favor of the state, to enforce testing.

The issues of genetic privacy have come to the forefront as genetic testing has increased generally in medicine. In several states the use of DNA on those blood cards has led to some legal struggles.

There was an interesting example actually in Texas, where the State Department of Health cooperated with federal authorities to use DNA from newborn screening cards to create a database of DNA, that they actually wanted to use for forensic and legal purposes. And the parents sued in Texas, and the state was forced to destroy all of their leftover newborn screening cards, and as result of these cases several states have actually passed new legislation to prevent the sequencing of DNA from blood cards for research purposes.

Bob Barrett: Why would we want to sequence an infant's entire genome?

Neal Sondheimer: The reason we would want to do that is that not every disorder that we might want to treat or might be worth diagnosing in an infant can be detected on our current screen, which is mostly based on certain chemicals that are present, or enzyme defects that we can detect within blood.

So a great example of this might be a defect in the protein that allows sugar to enter into the brain. We have a pretty good treatment for this defect. We know how to prevent kids from having seizures and having a bad neurologic outcome, but we have to know that patients were going to be affected by this disease in order to treat it. It would be much better to start treatment for this disorder before children ever got sick.

So if we identify the patient with this disorder or disorders like it, we could reduce or prevent the symptoms of disease, or help families prevent the disease from happening again in other pregnancies. But this disorder is not detectable in the current newborn screen. However, if we did genetic testing, it would be.

Bob Barrett: Well, you can see some objections to this coming, about it being dangerous or stigmatizing. People could be concerned about the government or insurance companies having this information.

Neal Sondheimer: And this is an important and extremely valid concern. People have a good reason not to like the idea of the government knowing their entire genetic makeup, or insurance companies. It has real implications for privacy and for genetic determinism, which is the idea that people's genes control their future, that there are things they can and cannot do because of their genotype.

It's easy to sort of make fun of popular culture or movies like *Gattaca,* but genetic dystopias have been imagined before and there's a good reason we don't want to volunteer an infant's genetic information for no purpose. We don't want anybody making decisions about our health, our finance, insurance, employment, or schooling using information that you can't change.

At a federal level, the Genetic Information Nondiscrimination Act was passed for almost exactly this reason, and it protects the privacy of genetic information for being used inappropriately.

It seems almost certain that newborn screening agencies are going to want to do genome level sequencing in the future. The cost of doing the testing and analyzing the data are going to continue to go down, and the value of the information as we do more and more testing on the relationship between DNA and the disease is going to rise.

The National Institutes of Health is actually looking at this question, and is funding several centers to look at how and when genetic data from newborns should be used to prevent disease and improve health. But we are going to have to have safeguards put in place for the use and disposal of this information and they are going to have to be very convincing to the public.

Bob Barrett: What can be done with information that suggests that an infant might become sick with something but that something won't affect them until much later in life?

Neal Sondheimer: Well, that's a classic and very important question that we have to consider all the time, even in our normal care of patients for whom we do a lot of DNA testing. What we do with the information is important, especially for things that we don't really want to know.

Typically we think of this from a disease perspective, and the classic parlor game we sort of play is with Huntington's disease, and this is an autosomal dominant disorder; it's neurodegenerative; it usually starts in adulthood; and it's currently incurable.

Our default position could be that if someone is being screened for a specific set of problems and we find out genetic information for another problem entirely, that we would want to censor that data. We wouldn't want to give people answers to questions that they didn't ask.

However, we wouldn't do that if it was a disorder we could treat. For example, if we were testing a child for a movement disorder and we found out that the child had a genetic predisposition to having high cholesterol or heart disease, we would want to communicate that information.

The problem is that censoring information is a tricky position. It's actually something called paternalistic position. We should be very careful anytime we say that we can look at information as physicians, but that family shouldn't get to know the results of a test.

The other problem is that we are making a prediction that a disorder we have detected, which may be untreatable today will always be untreatable. This isn't a safe assumption with an infant who is going to live for many, many decades. We all hope and believe that scientific progress will expand the number of treatable diseases over the life of this newborn who we are testing, and we don't really have a sense of what medicine is going to look like in 60 years. This makes it possible that full disclosure may be best, but it's a complex issue and it will require more thought before genome level testing is used routinely in healthy infants.

Bob Barrett: Well, as long as we are talking about making predictions, it looks like whole genome sequencing is in the future for newborn screening programs. When do you think that's going to happen?

Neal Sondheimer: I think most of us believe that it's inevitable. The benefits of the technology are simply too great to ignore and the costs are going to decline too rapidly, and again, there is going to be a real financial benefit for the healthcare system of diagnosing disorders before they cause symptoms, but it's going to take probably many years. I would say it's probably

going to take 15-20 years before we reach a state where the physicians taking care of patients, and the public, is willing to accept the idea of whole genome or whole exome sequencing within the context of the newborn screen.

Bob Barrett: Dr. Neal Sondheimer is an Assistant Professor of Pediatrics at the University of Pennsylvania, and a Clinical Geneticist at the Children's Hospital of Philadelphia. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!