

Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

During the past decade, newborn screening for various diseases has expanded. Now, almost every one of the 4.4 million babies born in the United States is screened for up to 42 different conditions. However, not all states screen for all diseases, and not all programs confirm positive screening results.

To provide uniform services to all babies, the National Academy of Clinical Biochemistry, or NACB, recently evaluated the follow-up procedures for positive screens and provided guidelines for best laboratory practices. An executive summary of the findings appears in the September issue of the journal *Clinical Chemistry*.

Dr. Michael Bennett is a Chair on the committee and a Professor of Pathology and Laboratory Medicine at the University of Pennsylvania, and Director of the Metabolic Disease Laboratory at The Children's Hospital of Philadelphia, and he is our guest today in this podcast.

Tell us, Dr. Bennett, what are the perceived benefits of including up to 42 rare biochemical genetic diseases in a whole population screening program?

Dr. Michael Bennett: Well, up until the introduction of the Expanded Newborn Screening Program, and actually throughout most of my career, the only way in which we could establish a diagnosis of one of these biochemical genetic conditions was if a child presented symptomatically, due to metabolic decompensation. This clinical presentation was often very profound with serious hypoglycemia, metabolic acidosis, hyperammonemia, frequently led to death. In fact, many of my early studies we would perform with the pediatric pathologist in the autopsy suite or with the medical examiner.

In survivors of these conditions, there was very frequently residual and neurological damage due to that metabolic decompensation. So these are very bad diseases to have, and yet we do have some treatment options if we establish a diagnosis.

So the perceived benefits, if we could actually get a diagnosis before the children developed a metabolic decompensation, before they crashed metabolically, we would be able to much better in terms of manage them long term.

Host: So are all metabolic diseases included in this program?

Dr. Michael Bennett: No, at this point we have the capability of diagnosing up to 42 different conditions using tandem mass spectrometry, by the program, but we know up to 500 or more single gene defects that will result in a biochemical genetic disease. So we have a selected group of conditions that we can screen for, but not all of them.

That sort of presents a bit of an issue in dealing with some pediatricians, for instance, who get a normal newborn screen back from the babies, but it doesn't exclude the possibility that they might still have a metabolic disease that isn't included in the program.

Host: With that in mind, is there any evidence to indicate that these diagnostic rates in clinical outcomes have actually improved as a result of the Newborn Screening Program?

Dr. Michael Bennett: Now, that's an excellent question, because clearly in all sort of medical disciplines, we need to see the outcomes from this. Certainly, when we introduced this sort of presentation, we talked about perceived benefits, but are these real?

Outcome studies are starting to emerge now. There is an excellent study out of Australia which was presented in the Lancet in 2007, for a condition called Medium-Chain Acyl-CoA Dehydrogenase Deficiency, which is one of the more common of these genetic diseases that we now screen for.

Then before the Screening Program was introduced into Australia, this cohort study looked at 1.6 million births, identified 28 cases of this Medium-Chain Acyl-CoA Dehydrogenase Deficiency, and of those 28 cases there were 22 deaths or serious outcomes. So again, just pointing out to the severity of this condition if undiagnosed early enough.

Following the introduction of newborn screening, the cohort study presented data from 0.8 of a million births, so half as many births, in which they identified 41 cases, which was almost twice as many cases as they had from the unscreened series. Of those 41 cases, there were only two adverse events at all. Again, showing that the outcomes were much, much better if you got an early diagnosis.

I can also say that from our own experiences at Children's Hospital at Philadelphia, we now have seen greater than 20 patients with this Medium-Chain Acyl-CoA Dehydrogenase Deficiency who were detected by the Expanded Newborn Screening, and all of them are doing well. We hadn't actually had any adverse events whatsoever.

So yes, the outcome studies are starting to appear, but we don't yet have data for many of the other conditions yet.

Host: So, what promoted the NACB to develop guidelines for follow-up testing on positive newborn screens?

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Dr. Michael Bennett: The NACB recognized that with the expansion of the screening program, each state was going to identify far more positive cases than they had been doing previously for these conditions, and that there was a need for labs within the state to be able to confirm the diagnosis of the positive newborn screens.

Initially, there were only relatively few labs in the entire country who had the skills to do this, and there was a requirement for the states to actually develop labs that could do the confirmation testing. The NACB recognized a need for having some sort of guidelines, particularly for those labs that have never done this before, in order that there could be some sort of uniformity in conformation testing.

Host: So which technologies are driving the process of confirmation for a positive screen?

Dr. Michael Bennett: Without tandem mass spectrometry we wouldn't have the process at all. So essentially, the screen involves using tandem mass spectrometry. Many of the confirmation tests also require the use of tandem mass spectrometry, using more specific assays than the screening programs use.

But there are also other technologies that have been around for some time, including gas chromatography-mass spectrometry for organic acid analysis, and amino acid analysis, using some form of ion exchange chromatography.

Host: Now, some of these technologies are not completely new. Why haven't they been subjected to the degree of scrutiny provided by the NACB Guidelines Committee?

Dr. Michael Bennett: These methods, as you say, are not completely new, they have been around for many years, and indeed, many of the labs that are performing the methodologies are using slightly different approaches. In fact, an earlier NACB guideline on fetal health identified the fact that of ten very well-established labs measuring urine organic acids using gas chromatography-mass spectrometry, each one used a different process. So the NACB felt that we need to develop guidelines for basically standardizing these processes.

Host: Alright. Well, what are the sensitivities and specificities of the screening and confirmation process?

Dr. Michael Bennett: Okay. So we are dealing here generally with rare conditions, and the sensitivities and specificities of the screening and confirmation process is not totally established yet for most of the conditions. So in fact, there is a collaborative study going on, which is funded by the Health Resources and Services Administration, HRSA, and it consists of 44 U.S. states and 60 labs in 35 countries globally.

What's happening here is that this collaborative is accumulating data in order to determine exactly the specificities and sensitivities of the screening process. Now, we do know for the Medium-Chain Acyl-CoA Dehydrogenase Deficiency, which is the most common of the conditions that we are looking for, that it would appear that the sensitivity of the screening process; and essentially sensitivity requires that you have the fewest false negatives, you don't want the missed cases, is incredibly high. Indeed, many of the false positive cases for this screen have turned out subsequently to be carriers for the same disease. They are not individuals who are homozygously affected but are carriers.

In terms of specificity that's really very important for the confirmation process. You don't want to handle someone a diagnosis which is incorrect. Using a variety of metabolites, enzymatic, and molecular tests, it's possible to have a very, very high specificity for the confirmation of a positive screen.

Host: Okay, Dr. Bennett, in your opinion, what do you see is the future for newborn screening for metabolic diseases?

Dr. Michael Bennett: As tandem mass spectrometry is getting even better over the time, what we are seeing in the literature are methods that are being published to actually identify more and more of those 500 different conditions.

I think that it's not unrealistic to assume that over the next few years we are going to see other diseases added to the Expanded Newborn Screening Program. There's already some headway with a group of conditions called the Lysosomal Storage Diseases, where methods using tandem mass spectrometry are now being applied to screen entire populations.

The methodology is a little bit different. It requires the use of a separate blood spot, so it cannot be done simultaneously with the present program. So there's a degree of effort involved.

But at the end of the day, it will still be diagnosing conditions, which we now are able to treat much better than we could in the past, so I think the outcomes will be better.

I think there's no limit to the number of conditions that we can actually diagnose using tandem mass spectrometry. It's just a matter of how many blood spots can you actually get from these babies to do the various tests.

So yes, I think we will see increasing numbers of metabolic diseases that are being diagnosed in the newborn period.

Host:

Dr. Michael Bennett is a Professor of Pathology and Laboratory Medicine at the University of Pennsylvania, and Director of the Metabolic Disease Laboratory at The Children's Hospital of Philadelphia, and he has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.

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