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

Owing to technological advances made just over the last decade there has been a paradigm shift in the way that newborns are diagnosed for inherited metabolic diseases. The introduction of Tandem Mass Spectrometry, which is sensitive enough to measure many metabolic biomarkers simultaneously in small blood spot samples, has caused a shift in the speed and number of conditions that can be found.

In the February 2012 issue of '*Clinical Chemistry*' Dr. Michael Bennett, 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 interviewed five leading thinkers in the field in order to provide their insights into newborn screening as it relates to metabolic disease.

Dr. Bennett is our guest in this podcast. Doctor, can you describe the present status of newborn screening for metabolic diseases?

Dr. Michael Bennett: Yes. Up till about a decade ago the states in the United States and countries who had newborn screening programs screened for relatively few metabolic diseases, just a small handful in each state.

This is mostly driven by technology whereby they could do one test per condition. Advances in Tandem Mass Spectrometer which allow us now to measure multiple amino acids and acylcarnitine species at the same time have revolutionized the way in which we approach newborn screening for metabolic diseases such that now we can eventually simultaneously screen for up to 30 or 40 different conditions on the same blood spot at the same time.

Nowadays, in all of the states within the United States and in countries where there are screening programs this technology is being used.

Bob Barrett: Now what are the advantages of diagnosis of metabolic disease in newborns?

Dr. Michael Bennett: When I first started in this business, we'd actually diagnose metabolic diseases in children who presented clinically ill to hospitals and often they had very, very severe catabolic episodes including profound hypoglycemia, metabolic acidosis, and hyperammonemia. Many of these children actually would die with those presentations and the survivors would actually have profound neurological deficits

as a result of the insult.

So the whole concept of getting those diagnoses in the newborn period is to try to establish a diagnosis before the child has one of these catabolic and often life-threatening events.

Bob Barrett: Are global newborn screening programs uniform?

Dr. Michael Bennett: This is actually a good and a sort of compelling question for today. In 2006 the American College of Medical Genetics generated a list of conditions that they recommended should be screened for in the newborn period. And amazingly across the United States every single state essentially as it did to those particular conditions, which is quite surprising, because each state mandates its own rules for newborn screening.

In today's environment, in fact, across the United States everyone sort of includes the conditions that are recommended by the American College of Medical Genetics in their programs.

Now other countries who have newborn screening programs have different programs, such that in the Netherlands for instance they only screen for 13 different conditions at the moment compared to the 30 or 40 in the US. In my own United Kingdom they are only adding in one more condition to their screening program at this point in time as they evaluate the advantage of identifying other conditions. So the programs are not globally uniform, but across the United States they are.

In fact as a result of involvement of the CDC, the American College of Medical Genetics, and various regions involved in newborn screening and in particular Dr. Piero Rinaldo's Region 4 there has been a move towards much improved quality control of the whole process such that a baby screened for metabolic disease in one state will get exactly the same outcome as a baby screened for a metabolic disease in another state.

Bob Barrett: Well, let's talk about those clinical outcomes. For children with metabolic disease are the outcomes better as a result of the screening?

Dr. Michael Bennett: Intuitively, when the program started we all assumed that, yes, we would do much better, because we are going to catch these children before they get those very bad catabolic events, but of course the proof of the pudding is in the outcomes, the longer-term outcomes studies. And I think the most significant study that's been published today just came out of the Australian screening program with Dr.

Bridget Wilcken who presented data very recently in the Lancet regarding outcomes for a condition called Medium-chain Acyl CoA dehydrogenase deficiency in Australia.

Prior to the screening program the majority of children had those catabolic events and many of them died. Within a few years of screening the outcomes were such that every single one of those children actually is quite normal.

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So yes, intuitively we feel the outcomes are going to be better. For some of the other conditions which maybe a little rarer, we don't have enough data yet, but again we still feel that we're doing better by getting these diagnoses in the newborn period.

Bob Barrett: Have there been any unanticipated outcomes as a result of the present screening programs?

Dr. Michael Bennett: Yes. One of the first things that was spotted, all of a sudden we were actually diagnosing more of these metabolic conditions in the newborn period than we had been doing previously from symptomatic presentation. It sort of leaves questions as, did we miss those cases before, did they die or are some of the conditions less severe than others?

To that aim there are a couple of conditions who we found to have a much higher prevalence than ever anticipated for which now we are starting to question, is this a real disease? So there is a condition called Short-chain Acyl CoA dehydrogenase deficiency, which many people now believe to be benign. And in fact the Australian program had dropped that from their screening repertoire. That's not true yet in the US as the American College of Medical Genetics hasn't made a decision as to where we should go with this particular condition.

Also, in the Dutch program they actually identified what they thought were more cases of a particular genetic disease, the biochemical metabolic disease. And then in looking back at those cases, they realized that there was actually a baby product which gave it sort of an abnormal profile, which the Dutch population were using. So it's sort of taught them to reevaluate that program. So there certainly have been a number of unanticipated outcomes from screening.

Bob Barrett: Well, right now not all metabolic diseases are being identified by newborn screening programs. Are there opportunities to add more conditions?

Dr. Michael Bennett: Yes, my guess is, at the moment we can probably screen or

we are screening for about 10% of the total metabolic conditions that are out there. Methods using the same Tandem Mass Spectrometry technology, methods are being developed to identify many other of the metabolic diseases that we have out there.

So the tools are available and slowly the methods are becoming published that we can eventually adapt to newborn screening programs.

In particular, at the moment there is a group of conditions known as the Lysosomal Storage Diseases, which again until a few years ago we thought these would be very untreatable conditions, and within the last decade a number of treatment options have become available, and it's very clear that treatment in the newborn period is going to be much more successful than treatment by the time a patient is presented with all the clinical signs and symptoms of the lysosomal diseases.

And to this effect, a number of states are already starting to include those conditions in their program. The New York State Screening Program for instance with Dr. Pas introduced a disease called Krabbe disease, a short while ago, and I noticed that a number of other states are now starting to follow suit by introducing lysosomal diseases into that program.

So I think the technology is most definitely there to continue to add diseases as we get good biomarkers for them.

Bob Barrett: Well, how will the addition of these conditions impact newborn screening programs?

Dr. Michael Bennett: At the moment the technology requires that a single blood spot be used for as many possible tests as possible. So the present program utilizes one test to diagnose those 30 to 40 conditions that the states are screening for.

If additional conditions can be identified using that same test, then the actual addition of additional technology, the instrumentation is probably not going to be required. It's just a matter of handling the data.

But at the moment many of those other methodologies that are being developed require additional platforms. So that certainly could impact newborn screening programs by the need to just add more platforms, more programs, and it would certainly have a personnel effect.

But from a prospect of getting early diagnosis with some of these diseases, I think the actual output for the children is

going to be much, much better.

Bob Barrett: Well, finally, Dr. Bennett, will the current expansion of next-generation sequencing tools change the way in which we approach newborn screening for metabolic diseases?

Dr. Michael Bennett: So at the moment consensus from the experts is that for the time being or maybe over the next decade, the whole process of newborn screening is going to be driven by further advances in mass spectrometry technology, primarily because from a cost-effectiveness this is still the most inexpensive approach to take.

I don’t think there is any doubt that ultimately when the next-generation sequencing becomes cost-effective it's a tool that could be used to cover many of the metabolic diseases that we have, but I think that's not going to be within the next decade or so.

Bob Barrett: 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. He has been our guest in this podcast from ‘*Clinical Chemistry*’.

I'm Bob Barrett. Thanks for listening!

Total Duration: 10 Minutes