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Feasibility of Targeted Next-Generation DNA Sequencing for Expanding Population Newborn Screening

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Guest: Dr. Glenn Bennett from Genepath and the School of Population Health at the University of New South Wales, Sydney, Australia.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Since its inception in the 1960s, newborn screening has identified inherited conditions in countless newborns, facilitating early intervention and improved quality of life for affected children and their families. Some form of newborn screening is now the standard of care in developed countries, and high rates of compliance reflect a widespread understanding of the population health benefits newborn screening provides. Initially, newborn screening evaluated only a small number of conditions, but the development of multiplex mass spectrometry assays has allowed the list of tested conditions to expand dramatically.

However, there are still some inherited conditions that would benefit from early detection and intervention that cannot be assessed by currently available newborn screening assays. Adoption of next-generation DNA sequencing has the potential to further increase the number of disease states included in newborn screening panels. But this comes with ethical, financial, and practical considerations that must be resolved.

A new article appearing in the August 2023 issue of *Clinical Chemistry* tackles these considerations and demonstrates the feasibility of performing targeted next-generation DNA sequencing to expand newborn screening. In this podcast, we're excited to talk with the article's senior author. Dr. Glenn Bennett is a founder and the Chief Medical Officer for Genepath. He is also an adjunct fellow at the School of Population Health at the University of New South Wales, Sydney, Australia. He's an emergency physician, a molecular geneticist, and is passionate about population health. Dr. Bennett, let's start with the basics. What is genomic newborn screening, and how is Genepath's genomic newborn screening test different?

Glenn Bennett: Well, newborn screening itself is a public health intervention that looks for treatable genetic conditions in newborns so that you can start treatment which is potentially life-saving. And genomic newborn screening is using a genomic assay in order to identify these conditions. The reason our test is different is because we use a technique called targeted gene sequencing. And what that means is we do comprehensive analysis of specific preselected genes that cause treatable genetic conditions. So it's not a whole genome test, which sequences over 20,000 genes, a person's entire genome.

Bob Barrett: How did Genepath develop this test and what research has been done to date?

Glenn Bennett: Well, we've developed this test over a period of about seven years. We published a method-based validation in 2017 and that showed that the assay had high analytical sensitivity and specificity. Both were greater than 99%. We subsequently had the test accredited to ISO 15189 standard, which is the standard for medical grade genetic testing. Following that, we did technical validations for cystic fibrosis and spinal muscular atrophy to show that this next-gen technology could detect those as part of a newborn screening test. And the reason for spinal muscular atrophy is because there are bioinformatic challenges for next-gen sequencing tests in testing for this condition. So after seven years of validating the assay, we did this feasibility study, which is what we published on just recently.

Bob Barrett: Well, let's talk about this current study. What did you find there and were there any results that were surprising?

Glenn Bennett: Well, what we did for this study is that we first of all constructed a gene panel of 164 genes which would be useful for newborn screening. And then we developed a laboratory workflow including automation and bioinformatics and reporting software, which we developed ourselves. And then we used that platform on 2,552 newborns. And what we found was the test had excellent analytical sensitivity and specificity, yet again, both greater than 99%. 1.3% of all of the newborns screened positive for one of the conditions, and the sample failure rate was zero, and the turnaround time was 7 to 10 days. So this demonstrated this technology could feasibly be incorporated into newborn screening programs.

One of the things that really surprised us was that the problem due to variance of uncertain significance was a lot less than what we expected. So in the literature, there was a lot of concern about variance of uncertain significance in newborn screening and whether or not that might lead to uncertainty in the testing process. And what we found was that less than 1% of all of the newborns had variants of uncertain significance in a potentially disease-causing

configuration. So that was a lot less than what we previously thought and showed us that this technology doesn't necessarily, well, it's not necessarily as confusing or causing as much uncertainty as what people had thought.

Bob Barrett: Well, what's coming up? Is there any future research planned?

Glenn Bennett: Yes, actually, we're right in the middle of something at the moment. So we have a $3 million grant to use this platform to test 10,000 newborns here in Australia. In Sydney, Australia. And what we're going to do is we're going to do health economic analysis, and parental acceptability, and more metrics of how accurate the platform is. And our aim is to demonstrate that this platform can be used for population newborn screening programs here in Australia.

Bob Barrett: Well, finally, Dr. Bennett, overall, what implications does this all have for newborn screening?

Glenn Bennett: This has massive implications for newborn screening because what our paper showed is that this platform can increase the impact of newborn screening tenfold. And so this is going to revolutionize newborn screening programs throughout the world.

Bob Barrett: That was Dr. Glenn Bennett from Genepath and the University of New South Wales. He and his colleagues published a study demonstrating the feasibility of newborn screening by targeted next-generation DNA sequencing in the August 2023 issue of *Clinical Chemistry*. He's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.