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From the Perspective of the Child: Ethical Considerations for the Implementation of Genomic Sequencing into Neonatal and Pediatric Care

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Guest: Dr. Jill Maron from the Women & Infants Hospital of Rhode Island and the Warren Alpert Medical School of Brown University in Providence, Rhode Island.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Genomic sequencing technologies have the potential to revolutionize the care of children with a genetic disorder by quickly and efficiently identifying the underlying condition and facilitating initiation of appropriate care. As the cost of testing decreases, genomic sequencing is becoming increasingly available but technological advances may be outpacing our ability to resolve important ethical considerations. For instance, more widespread testing will invariably lead to more frequent detection of variants of unknown significance. What guidance do we provide to patients and their families regarding these poorly characterized variants? What about the identification of variants that are not actionable in the neonatal period but predict risk of developing disease later in life? Is it appropriate for parents to provide consent for their minor children when testing may impact care well into adulthood? How about the discovery of non-paternity or other unexpected familial relationships? Lastly, how do we preserve access to one's own genomic sequencing data while simultaneously ensuring data do not fall into the wrong hands?

A new opinion article, appearing in the January 2025 Genomics Special Issue of *Clinical Chemistry*, raises these ethical questions, highlighting the need for guardrails that ensure neonatal genomic sequencing is performed in the best interests of the child. In this podcast, we welcome the article's lead author. Dr. Jill Maron is the Pediatrician-in-Chief at the Women & Infants Hospital of Rhode Island in Providence, RI, USA and the William and Mary A. Oh/Anna Elsa Zopfi Professor in Pediatrics for Perinatal Research at the Warren Alpert Medical School of Brown University. She has spent her research career working towards the integration of the latest technological advances into neonatal care to non-invasively care for diagnose and monitor the newborn.

Dr. Maron, let's start off with this. How do you see genomic sequencing integrating into neonatology and pediatrics over the next decade?

Jill Maron: I think we're going to see a rapid integration of these technologies, specifically into neonatology and extending into the older age child over the next decade. What we're learning from some of the very large genetic trials that have been conducted is that these tests are very powerful and very accurate, and very timely at getting us the diagnosis, particularly in babies and children who we believe have a genetic syndrome but we can't figure it out on any other platform. So I think we're really going to see the landscape change on how we utilize these technologies, what we can learn from these technologies, and we'll see this cost coming down of these technologies, so this should be one of the more common tools, I think, in the next decade that we're going to see, particularly in those children who we believe have a genetic disorder.

Bob Barrett: What is the difference between phenotypically driven and population-based sequencing?

Jill Maron: Sure, it's a great question. You know, when we say phenotypically driven, it was what I was just referring to. It's a child who you suspect has a genetic disorder. They have an anomaly. You're seeing developmental delays, we're worried about a metabolic condition, these are children who present with some sort of symptom of a genetic syndrome and those are a phenotypically driven testing modality when we use it that way. This is a wonderful tool because we know right now, if we do whole genomic sequencing, it's the most accurate and the broadest ability we have to diagnose that child, and most studies are showing now about a 50% diagnostic rate in the setting of using genomic syndrome with babies, neonates and infants, and children who we suspect of a genetic disorder.

When we talk about population-based genetic sequencing, that's sort of a fishing expedition. That's you look perfectly fine but there may be something in your DNA that leads us to believe that later in life or maybe even in your own childhood, you were going to present with the genetic disorder, and that's a very different concept. That's looking broadly across every person, attempting to look across all ethnicities and racial groups to understand how our DNA could inform us about a pending condition even though we have no current symptoms. We know the diagnostic rate there is much, much, much, much lower. Some of the most recent studies looking at this at a population-based level are seeing less than 1%, or hovering between 1% to 2% diagnostic rate compared to that 50% when we suspect that there's something wrong because you have a symptom of a genetic disorder.

Bob Barrett: Doctor, are there concerns with a broad-based approach to sequencing children?

Jill Maron: There are many concerns associated with that broad-based approach. The first is really ethical considerations. You know, our DNA holds our entire code. It can hold a lot of secrets. It can diagnose adult-onset diseases. It can identify perhaps you know, non-paternity. It can identify that you are not who you thought you were. All of these issues are really, have to be taken very, very seriously when we approached it to a child who we are doing sequencing to without consent, their parents are serving as their surrogates, and this is not something that they choose. So once you do something as broad as genomic sequencing, you undoubtedly will uncover something in someone's DNA and you have to be very careful about how you relay that information back to the child. For example, if a child is found to have an adult-onset disease, such as Huntington's disease, when would you ever tell the child? How could you not tell the child or at least not have the ability for the child to learn that, should he or she choose to when they become either an age of assent or an age of consent. So these are really big questions that the field has to consider and quite frankly, we haven't figured out the answers to them.

The other real issue with genomic sequencing is how do we protect the data. Currently, all platforms that I know of, even commercial platforms that allow you outside of the research study to have genomic sequencing, upload the sequence to databases, and that's not being done in a nefarious way but it's so that we can continue to learn and understand DNA and how it works. But once you have a sequence, you really can never fully de-identify that sequence. That is your identity. So while we may wipe your name off it or anything we think could identify you or link you to that sequence, at the end of the day that is the most identifying piece about you. It is your absolute identity. So all these sequencings are being uploaded into sometimes national databases, research databases, and we really don't have protections in place to ensure that they aren't used in other ways that we know are occurring, such as when law enforcement are trying to identify a relative of someone who they believe is committed a crime. And this approach is happening across America and there have been many civil cases brought against such an approach when law enforcement does infiltrate to look at DNA. Again, law enforcement is trying to do what they believe is right and the researchers are trying to do what they believe is right. But the end of the day, we have a child whose DNA is in databases and they did not consent to it and there was no medical indication for it.

So as a profession, we have to be very cognizant of that and do our best to be sure that our children are protected, particularly in population-based genetic sequencing when we really aren't sure what the full benefit of it is and there are

privacy risks at stake. And then finally, while we have laws in place such as the GINA law that protects us right now from insurers penalizing us for have a genetic condition, there are concerns over time that if we sequence a baby at birth and find out that they're at risk for several disorders later in life, will they actually be insurable when that data is released? So, there's a lot of work we have to do in terms of, how do we ensure that child has access to their sequence at the right time, knows it was done and why it was done, and how can we help them if there is something that could be seriously found in their DNA such as an adult-onset disorder. We have to make sure we have protections in place against law enforcement so that these tests are being done for health reasons and can't be used to identify criminals, as easy as that may be and as nice as that may sound. And then finally, we have to worry about the burden of making sure that children are not discriminated against based on their DNA, particularly in the setting of population-based genetics.

Bob Barrett: You emphasize the 'child first' philosophy. Why should we, and/or why don't we, contextualize these technologies through their point of view?

Jill Maron: I think one of the challenges has been this has been this amazing technology, and as scientists and researchers of which I consider myself one, we want to use this very quickly because we've never had such a powerful tool.

And for many, we're thinking "but we will help the child" and that's an immediate feeling, that's we will help this child right now. But when it comes to something like sequencing that is a footprint that is forever there and will be downloaded and can be accessed and may be interrogated by insurers, we have to be brave enough right now to think of "Okay well we have the child now and we're going to sequence now. But what happens five years from now, 10 years from now, 15 years from now to that child once we have done that sequencing?" So for example, we may have a very sick baby in the NICU, the Neonatal Intensive Care Unit, that we believe has a genetic syndrome, we sequence that baby, we make a diagnosis but it turns out that baby is also at risk later in life for various types of cancer. We have to be brave enough and really cognizant and thoughtful enough to think "well I know I made a diagnosis now but this test is so powerful, there's more in it. How do I ensure that that child will have access to that information, counseling to that information, maybe doesn't want to know that information but was given a choice to know that information." And we have to put that child first, not just in the moment, but throughout the child's life course, and it really is our responsibility to use these technologies in that way. This is not to be used for instant gratification because it's too big a test. You know, when we did newborn screening and we still do newborn screening, that really is

one moment in time based on a metabolite the baby is producing. It truly is just at birth that we make the diagnosis.

When you move to something like sequencing, it has ramification across that child's life course, and child first has to be not just in the moment but throughout that life course. We need to be sure we have all protections in place.

Bob Barrett: Well finally, Dr. Maron, do you see a path forward where we can safely integrate these technologies into pediatric care?

Jill Maron: I do but it is going to take a lot of effort and thoughtfulness and collaboration. And I will say, Sharon Terry, who started Genetic Alliance, has been really at the forefront of trying to do just that, where rather than having sequences uploaded into databases, she puts that sequence back into the hands of the patient and the family, having them have control of it, irrespective of a medical record or database. We can all learn from that approach at Genetic Alliance and what she's been able to do. But as this technology unfolds, it's going to be really important that we don't just let the train ran away from us. It's going to be really important that we think child first, why are we doing this test? What do we hope to gain from it? Understand the magnitude of the test. Once you're sequenced, it is done, and if we're going to upload it, we need to protect it. Once it's done, the child must know it was done. It has to be recorded in his or her electronic medical record. And we need to ensure that that follows the child through his life course and that once that child, again, becomes either of assent or they have the mental capacity to consent, or of age 18 or older to know what was in their sequencing, they're provided that information and counseling is needed based on what is contained within the sequence. I think there is a path forward, but I think we have to make sure all those protections are in place. And finally, importantly, I think we have to continue to study how genomic sequencing early in life, either at birth or in early childhood, impacts what happens to the child. Do we actually make a lot more diagnoses? Do we help that child immediately? Does this lead to more gene therapy? And the only way to do that is to actually study it. Without studying it, we will inflict harm. We've got to under regulated, funded trials that have gone through peer review, gone through ethics committee, have an IRB, study the impact of genomic sequencing, and not just broad-based do this without the knowledge because then we will truly inflict harm. So if we can get all of that in place, I think there's a path forward but we have a lot of work to do.

Bob Barrett: That was Dr. Jill Maron from the Women & Infants Hospital in Providence, Rhode Island. She wrote a new opinion article on the ethics of genomic sequencing in neonatal and pediatric care in the January 2025 Special Issue of *Clinical Chemistry*

and she's been our guest in this podcast on that topic. I'm Bob Barrett, thanks for listening.