The G Word transcript

Genomic newborn screening for rare diseases

**Naimah:** Welcome to The G Word. Today, I'm joined by Zornitza Stark, who is a clinical geneticist at the Victorian Clinical Genetic Services in Melbourne, and Dr Rich Scott, who is the Chief Medical Officer and Deputy CEO here at Genomics England. We were delighted to see the paper published by Rich and Zornitza in June in the Nature Review's Genetics Journal on genomic newborn screening for rare diseases.

And today we are going to delve a bit deeper into the review to understand and discuss the benefits and challenges of incorporating genomic sequencing into newborn screening. So first of all, could you both tell me a little bit about yourselves and why you decided to write the review? Rich, we'll come to you first on this.

**Rich:** Thanks for having us on the podcast. I am the Chief Medical Officer here at Genomics England and the Deputy CEO, and by background, I'm also a clinical geneticist. So, I've been at Genomics England the last eight years, and I guess thinking about various [00:01:00] questions to do with how we use genomics to make a real difference in clinic and move the field forward for the benefit of patients and participants in research programs. And the journey that we've been on over the last eight years has been about recognizing what the challenges are in diagnosing and even making a difference then, after diagnosis, treating people with rare conditions and recognizing how much change there has been thanks to the technology changes that have happened, the power of genomics, the big investment in research programs and in healthcare delivery. And what we've really spent time over the last few years thinking about is whether that same sort of approach can be used to address the question about newborn screening using genomics and the value potentially of using genomics in all babies to direct screening better and see if we can make more of a difference. Zornitza and I have known each other most of the time I've been at Genomics England, and we've had a lot of conversations about these sorts of questions. So that's the sort of genesis from my point of view.

**Zornitza:** My name is Zornitza Stark. I'm a clinical geneticist at the Victorian Clinical Genetic Services in Melbourne, Australia, and I also work part-time for Australian Genomics. My background is mostly in diagnostic genomics, but progressively we have also been thinking about how genomics could be applied at population screening level. As Richard said, over the years, we've talked about many things, so we've been on quite a similar journey in terms of trying to integrate genomics into our healthcare system. But over the past year, there's been some funding opportunities in Australia to try and develop new models for newborn screening. We were fortunate enough to receive a research grant, which we're a year into the research grant, and we will be leading a study to offer genomic newborn sequencing to a cohort of a thousand babies in Victoria.

**Naimah:** So, what does newborn screening currently look like worldwide?

**Rich:** So, one thing to say is just to orientate people on what newborn screening means. So screening is a word that people hear often but is worth just pausing on. What screening aims to do is look across a particular group of people. People often say a population and use some sort of test and then follow up process to identify people who would really benefit from some sort of intervention. Screening can take all sorts of different forms and is used in various adult settings. In newborns, it varies quite a lot between countries, but what's universal is that there's been some real benefit in terms of using newborn screening to look for rare conditions where there are treatments. There are a few different types of newborn screening, for example, when babies are born in most countries, they will have a physical examination to check whether they might have a heart murmur or something else were knowing about that early can help them receive the right treatment. Increasingly, countries are doing hearing checks with special hearing tests that you can now do newborn babies to pick up early children who might have a hearing difficulty and support them early.

The bit that people often jump to when they hear about newborn screening is the heel prick test where the principle here is, in the newborn period, the first few days of life, a heel prick is done and a small sample of blood is collected normally onto some blotting paper and some tests are carried out on that blood for conditions that you can pick up where there's a treatment. What tests are used and which conditions those are that are looked for varies actually quite a lot between different countries for various reasons. So, for example, here in the UK at the moment, there are nine conditions looked for that's going to increase to 10 later this year. Then, across the world, there are different numbers in different countries. So, for example, in Australia the number's 25, and in America it varies between states, but in some states it's more than 40. What's common between those conditions are that there is a test that you can start with on that blood spot that identify some children that you carry out some further testing on to say, do these children really have this condition where we are worried that they might have, and that you can be confident that you can then identify a group of children who do have that condition and where there's something really meaningful that you can do to make a difference. These are typically really quite rare conditions, so for example, the first one to be looked for was actually low thyroid in children where giving a simple thyroid medicine can help. The list has grown to, as I say, between sort of 10 or so and sort of low tens of conditions at the moment. And that's where we are today with the testing, which at the moment, while genomics testing the DNA is a small part of some of those tests, it's a small component a little bit down the line in most of that testing and it doesn't at the moment really leverage the real changes in genomic testing that have happened in the last few years.

**Naimah:** Can you tell me a bit about why there's such a difference between the different countries?

**Rich:** It's complicated. It's partly down to how hard it is to develop the evidence. Then to be clear about both the right level of evidence that the policy makers that make those decisions require, how specific to that particular country setting that evidence needs to be, and also just the practicalities of delivering the screening programs and also following up and tracking how effective they are.

So, it is clear, and we include this in the article, it's really well recognized how much of an impact overall newborn screening has had. And it's quite often quite hard looking at individual conditions to be confident of the difference in the long-term outcomes, because these conditions that we're looking for are really quite rare and it's really hard to do that follow up in a way that perhaps is more easily done in more common conditions, sorts of things that are screened for in adults, maybe cancer screening and so on.

**Naimah:** You touched on a few points already, but I wondered if you could delve a bit deeper into more of the benefits of adopting a genomic sequencing approach to newborn screening.

**Zornitza:** A genomic newborn sequencing approach to newborn screening would open up the possibility to screening for many, many more conditions using as single assay. So, at the moment, newborn screening is largely limited, screening for conditions for this biochemical markers. Whereas adding a genomic sequencing approach to this would allow us to screen for potentially hundreds of different types of conditions. So not necessarily just metabolic disorders, but also immunological disorders or cardiac disorders or neurological disorders.

The other advantage is the use of a single assay, which means that the same type of test is run on each baby, but over time, we can change our mind in a much more dynamic way about which conditions should be looked for or not. So, for example, if an effective treatment becomes available and the evidence for that builds, actually adding that to a genomic newborn sequencing panel, so analysing for that additional condition, is a much simpler proposition than adding a new biochemical test to the current programs. So, at the moment, for example, it is not unusual to take many, many years to add just a single condition to a newborn screening. So, I think there's a statistic from the US that it takes about nine years to add a new condition to do universal newborn screening program. So we're now in a completely different situation in that over the past 10 years, there's been an explosion in the number of effective treatments that have been developed for rare diseases, and the current approach that we have to adding new conditions, it's just not dynamic enough and it hasn't really kept up with the pace of development of treatments for rare conditions.

There are other advantages to adding genomic sequencing to newborn screening. So once the data is generated for each baby, it can be stored and can be used over the lifetime of that individual as a healthcare resource. So, for example, it may be relevant to look for a particular set of conditions in newborn babies for which there is effective treatment in early childhood, but the data can be interrogated over time. For example, for adult-onset conditions or for reproductive carrier risk or pharmacogenomic variants as the child becomes an adult.

**Naimah:** You mentioned keeping and storing this data for over 25 years. Are there ethical considerations or challenges associated with this?

**Rich:** I think working through some of the questions related to the potential use of genomics in the newborn setting is just as important as the clinical aspects and the scientific aspects, and that's something that Zornitza and I have spent lots of time talking about in the paper.

The program that we're running here in the UK, the Newborn Genomes program, is going to be looking to develop the evidence across the range of questions. So, we're sequencing a hundred thousand babies genomes to understand how this would work in practice to track the outcomes of babies. We are also engaging with the public on all sorts of different questions and participants in our programs.

Because the big question here is whether you should do it. And if so, how? And for that, I think there's a lot of questions about what the expectations are on how you would store data, what people would expect to know about what they might be told before data was used for another purpose, who they might expect to have access to that data for what purposes.

And that's as important for us as, as I say, the clinical and scientific questions, and it's also important to recognize there's a quite diversity of views even amongst any given country's population, and so really understanding those views is really important. At the moment, there's been a fair amount of work done with professionals to understand professionals’ views, which are often quite cautious, and there's also work that's been done understanding views of people in the general public or participated in programs. One of the things that we've really learned during the early phases of our program is really taking people on the journey and understanding some of the nuances here, some of the complex questions. It's really important because often, if asked very quickly and simply, people give one view and with the public often really very supportive, working through some of the nuances of some of the really key questions is important here, rather than just stopping as a sort of a simple answer and understanding quite how this would happen.

**Zornitza:** There's obviously a balance to be strapped here between data security and privacy, and maintaining the trust of parents and of participants. But also a moral imperative to make the most out of the data in terms of benefiting health over the lifetime of an individual and trying to integrate that as much as possible with the healthcare system and in particular electronic health records, so that it does become a resource that can be used over time to benefit health much more generally.

**Naimah:** Can we talk a bit about what evidence currently exists to support the use of genomic sequencing in newborn screening?

**Zornitza:** That's a really interesting question because the issue about whether to offer genomic newborn sequencing has been discussed now for about 15 years in the medical literature, but most of what has been written is opinion pieces and lots of detailed discussion of the pros and cons of adopting this approach.

But actually, when it comes down to it, there's very little in the way of empirical evidence about how this might be made to work in practice. So, for example, there are actually only a couple of cohort studies where genomic newborn sequencing was performed in a prospective manner and there were each of about a hundred patients.

So obviously that's clearly not anywhere near enough to inform public policy decisions. And similarly, in terms of exploring healthcare professional views and the views of prospective parents, the choices that have been offered as part of those studies are hypothetical choices. And what people would report that they're planning to do does not necessarily translate into what they're actually going to do if it was offered as a real choice.

So, what we really need to be seeing now, and this is the reason why this is quite an exciting time, and the reason for the review, is that we need to be seeing much, much larger studies across different healthcare systems totalling hundreds of thousands and potentially millions of babies to help us develop a robust evidence base to inform those sorts of policy decisions in the future.

**Naimah:** And given that there's not a lot of evidence, why have we decided now is the time to incorporate genomic screening?

**Rich:** Going back to what I was saying early on about the journey that we've been on internationally and both in Australia, in the UK and elsewhere, in terms of the potential for genomics in healthcare in general, and particularly in the area of rare conditions, a number of different things actually have changed alongside each other. One thing genomics has changed completely in the last 10 or 15 years with the availability of these next generation sequencing technologies, which have made it possible, and also within the bounds of healthcare costs to sequence at scale, whether that's the whole exome, so all of the genes, all of the coding region of the genome, or in fact the whole genome.

That's just become possible. Our knowledge on how to do that has really improved as well. There's been really a lot of studies thinking about using that to diagnose rare conditions. So, in a setting where you've identified people who you think may well have a rare condition and making the diagnosis, so we've got a lot more know-how and knowledge in terms of the types of genomic variation that you can confidently interpret and say to someone, this is highly likely to only be present in someone who has a very high chance of developing whichever condition you're talking about. Alongside that has come the ability to deal with data at scale and that's something which has happened in multiple different ways. But something we've spent a lot of time, in the UK, investing in infrastructure that allows you, again, to do that feasibly within a healthcare setting. We’re just also on the cusp of what feels like a really potential game-changing period in terms of the availability of treatments and interventions for rare conditions. The moment when I sit in clinic, and I'm sure it's the same for Zornitza, we’re getting better, it's still not great, but we're getting better at making diagnoses in rare conditions. Where we really fall down is turning that into a really meaningful intervention where you can make a substantial difference to the outcome of that person or for that family. So now we think that probably a bit under 10% of rare conditions, is there some sort of intervention where it does make a sort of really substantial difference?

We also can see around the corner, there are a number of much more targeted treatments becoming available where we hope that in the coming years, that number, that just a bit under 10% number, will really change. So, a rising proportion of people with a rare condition, there is some meaningful difference one can make.

And I think that means two things. It means now we have the technology and the know-how to think that we could potentially move the dial for the 10 or so percent of rare conditions where there is an intervention that we could make and we could make that early in childhood, just like the existing conditions, use the today's knowledge to open out the number of conditions that you can look for. So rather than it's in the tens, it's maybe in the low hundreds. Through these programs and through other work, stimulate research to say, we're not happy at being that many conditions that actually have an intervention. How can we make sure that we're increasing the number of conditions where there is an intervention, where there is good evidence for it? I think that's why now is a time where we, in the UK and Australia, and as we set out in the paper, a number of other places in the world, there are programs launching to address exactly those questions. To go back to what Zornitza said, there's a moral imperative, we feel there are really urgent questions that we shouldn't just sit here and leave unaddressed. Often in medicine and in science, it's easy not to ask the complex questions. We recognize this as a set of questions that are really urgent to address because of the many, hundreds and thousands of families who are out there who could potentially benefit.

We also recognize that these are really complex questions. It's not a simple, let's just get on and do this. This is about developing really robust evidence and understanding of people's views on if we do this, how should we do it? Which means that we need to balance that urgency of asking the question with a sort of caution in the way we navigate it and develop really robust evidence that policy makers, not people who are carrying out these studies, but other people, policy makers, can then help make the decision on whether this is something that should be adopted.

**Naimah:** I wondered if you could comment on, with rolling out this population level testing, what kind of burden or does it reduce the burden on healthcare systems or could it increase it? What's your thoughts on that?

**Zornitza:** That's a big unknown and it's obviously very important that we measure that and we measure that from several different points of view. I guess one of them is patients and families, and obviously what we hope to see is that a diagnosis is achieved much earlier, treatment is started at an early stage of the disease or pre-symptomatically, and that significantly alters healthcare outcomes that obviously needs to be balanced against the cost of some of these precision treatments, which can be high.

The other consideration to take into account is the whole family unit and how that information then impacts on family functioning and on decisions by parents about having subsequent children. The other thing that will really need to evaluate really carefully is the impact on the healthcare system as a whole and in particular on healthcare professionals. So both in terms of the laboratory staff who will deliver this new type of testing, but also on clinical staff and what the impact will be of potentially detecting many, many more individuals at an early pre-symptomatic stage and offering them these treatments.

**Naimah:** I wondered if you could talk us through some of the genomic newborn screening studies that are currently being launched internationally. With regards to what country, what kind of size they are, and what approach is being used.

**Rich:** Sure, there is a growing number. In the paper, we highlight some of the studies that have either launched or are talking publicly about their work they're doing, and one of the things that's striking is the spread geographically. Zornitza has talked about the study that she's launching in Australia, in Melbourne. I told you a little bit about the study that we are launching in the UK. There are four studies that we talk about in the US in the paper. So there's a study based in New York that has already launched and is beginning to share some of their early findings called the Guardian Study. Which ultimately is aiming to, like our study, look at a hundred thousand babies.

There's also a study called BabySeq, which is a follow up to one of the real pioneer studies in this area that is led out of Boston. There's a study called Early Check, which is going to look at 10,000 babies again in the US and a further study called Beginnings based in San Diego, led by the Rady Group and Stephen Kingsmore, who really pioneered the use of whole genome sequencing alongside Zornitza and team in the neonatal intensive care unit settings.

In Europe there are a number of studies, the ones that have we had talked most about in the paper. It's a study in Belgium called Baby Detect, it's ultimately going to look at 40,000 babies. There's a European Union study called Screen for Care that's going to look at 18,000 babies and then one in France called Peri Genome Med.

If you look across those studies, there is quite some variation between them. So for example, most of the studies are going to be using whole genome sequencing, but a couple of them are using panel sequencing, so looking at a predefined panel of genes. Those ones aiming to develop particularly evidence on genes where we know the cause, whereas those focusing on genomes are also aiming to do that partly to learn more about genes where there's not currently evidence.

There's obviously quite a variation in the size of the study and one of the things, Zornitza had alluded to it earlier, but actually the power here comes from scale. These conditions are individually very rare, so actually, the fact that these studies are working together and talking to each other is really important so that we can get commonality in some of the evidence that's generated and all but one of the studies are observational, so watching the use of these approaches in babies, in a group of babies that you can track over time in our study are going to compare the babies that join our study to babies born at similar time in the UK and track the outcomes that way.

There's one, the BabySeq study is going to carry out a randomised approach in a smaller number of babies. But that's something that's really challenging in a rare condition setting. The other thing that varies between different studies is the number of conditions that will be looked for and that's something that is quite dependent on the availability of treatments in different countries, the capacity of clinical pathways, but also just judgment on the level of evidence that people want to use to take a condition into the study. I think a common theme here is balancing that urgency and the need for caution.

Ultimately it may be that the number of conditions grows over time if this were to be adopted. But at the moment, the range of conditions at the lower end is a 125 or so in the study with the smallest number, most of them clustering around the low hundreds. The BabySeq program are looking at more like a thousand conditions.

**Naimah:** You alluded to it a bit there about the availability of testing in different countries. What can be done to ensure equitable access to testing?

**Rich:** Equity is a really important word across a number of different dimensions. At the moment, if you think about the studies and the locations of those studies across the world, this is something that's being explored while it is worldwide in only a handful of countries, and there is considerable investment needed to explore and develop the evidence here. Equity is really important as well within countries and within studies and understanding different ways in which equity might play into how the benefits or disbenefits of genomic newborn screening is a really important part of all of the studies and definitely of ours. For example, thinking about how important it is to make sure the knowledge you use to interpret genomic data is reflective of the populations and the communities who are included in the studies, and understanding what impact that has on the findings. Also, thinking about the way in which conditions are selected, thinking about overall the benefits and disbenefits that come from the use of genomic newborn screening, but also thinking about questions of access and how you make sure that people understand what's available, are able to make the right choice for them, is a really important question as well from an equity perspective, as well as just generally.

**Zornitza:** As well, of course, after potentially a baby is diagnosed, ensuring that there's equity of access to treatment, particularly in healthcare systems that are not publicly funded and ensuring equity on a global scale. At the moment, there's a real danger that in North America, the UK, Europe and Australasia will faster through this and leave behind many middle or low income countries.

**Naimah:** Definitely sounds very challenging. On that, I wondered if we could discuss any of the other challenges or even opportunities that are presented by incorporating genomic screening.

**Rich:** It comes back to this point about the many layers of complexity here and walking slowly through each of the different elements. One of the really important reflections that I've had as we've been thinking about and designing and now getting ready to implement our program is that newborn screening is hard. These are rare conditions. Understanding even the natural history, the typical pattern during someone's lifetime with these conditions is challenging. Each of the different lenses with which you look at the evidence for screening in a newborn setting are hard, irrespective of whether you do that with a genomic test being the first way in, which is essentially what newborn screening in the setting we are talking about is, or other types of newborn screening, it's always challenging. A big thing here is making sure both that the evidence we generate is meaningful and recognising that even if in 5/10 years’ time, policymakers in different governments make a decision one way or another, if in some part of the world this is something that's adopted, then we also make sure that we set up systems to continue to collect evidence on how it's playing out, how things are changing over time. Because this is very much a long game about making sure that we don't just think we get a bit of evidence, we've got all of the answers and then we move on. Then there's another lens and Zornitza and I thought through this in writing the article, one of the things that we have done is think end to end through the process of the different steps, what the different challenges and opportunities are.

For example, if you stop right at the beginning, making sure that people understand this is a new type of testing, understanding what it is that they might be saying yes to, while also making it something that's accessible, because this is something that we believe may well bring benefits and getting that balance at that stage, as with all other stages is really important.

For example, explaining that this is screening as with any screening test, this isn't actually terribly different potentially in that they come with potential upsides. We know that screening tests do identify people who one on the first test think might be at risk of the condition and you do your follow on testing and either you are very clearly then saying, no you're not at risk. that first screen was useful, but we've now been able to rule that out. There are sometimes uncertainties and conveying that, which is very much part of screening in general, but making sure that you can have those conversations is really important.

**Naimah:** Finally, just to finish off, where do you see the incorporation of genomic sequencing and newborn screening in five years’ time?

**Zornitza:** I definitely want to write this review again in five years’ time, and I think it will look very different to what it looks like now. It will hopefully include the results of all of these studies, and we will be able to have meaningful comparisons about the different choices, the different studies made and link that to particular outcomes, but also to be able to bring that together into some sort of a coherent summary that will then influence policy makers worldwide.

**Rich:** As well as having that updated evidence, I think we'll have quite an interesting and more informed perspective on what the future looks like overall with genomics and this concept that these sorts of programs bring into your mind of the concept of lifetime genomic data. Zornitza again touched on it earlier, about the potential to reuse genomic data at multiple stages during your life.

These programs will help us understand some views around that, particularly around that starting at the beginning of life. But I think also the conversation on that will also have moved on a lot more generally because that's something that's potentially really useful at multiple stages of life.

We'll have a better understanding of ways in which that might happen practically, but also of people's views in the public and in particular patient groups and so on. That will also be a really interesting change, as you say, Zornitza, let's do it again in five years.

**Naimah:** That's all for today's episode of The G Word. That was Zornitza Stark and Richard Scott discussing newborn genomic screening for rare diseases. If you enjoyed this podcast, please subscribe to The G Word on your favourite podcast app. Thank you for listening.