Expert Q&A Sessions

Researchers' note: *This document contains materials generated during the Zoom session with the experts. The first part is the transcript of the live Q&A session. The transcript has been de-identified, and slightly edited for ease of reading. The second part contains the expert's response to additional questions that were not responded to during the Zoom session. After the Zoom session, these questions were collated and sent to the expert who was given a few days to provide a written response.*

Date of Zoom session: Sunday 16 March 2025

Expert: Prof Zornitza Stark, Murdoch's Children Research Institute

Title of presentation: Genomic newborn screening: benefits

PART 1: Q&A TRANSCRIPT

Juror: Hi, Professor. My question is at the moment, we've watched a couple of videos, but there was one, the SCID was one that was added to Queensland newborn recently, well within the last few years. Are states have all the same current testing applied or does it differ state to state?

Zornitza: Currently with the newborn screening we are trying to have national consistency. So at the moment the newborn screening is the responsibility of states. But there has been a lot of work done over the past, I want to say two or three years to try and achieve national consistency. So there is a nationally agreed list and a process that runs nationally that decides which conditions should be included or not included. But once that decision is made, there's still a bit of variability at the moment because each laboratory that delivers the newborn screening has to be sure that they can add the new condition. So in in reality, what happens is sometimes there's a lag between different states in terms of how soon they roll out a new condition once it's been agreed. So in practise, it can end up the different states have slightly different programmes at a particular point in time. But the intention is for it to be nationally consistent.

Juror (follow up): And is the time frames then for the laboratories the same? Or could one, they say, if there was a disease in New South Wales that may take X amount of time in Queensland, if it's already ingrained, could they actually get a result a lot sooner?

Zornitza: Sorry (delay) for the baby? Yes. So there's variability at the moment. So it depends on where your baby is delivered. And so a condition may be included in Queensland at the moment, but not included in NSW.

Juror: The main thing I wanted to ask is if we're like suddenly screening for so many more like conditions and getting much more like diagnosis, can we expect like the, the strain on the health, the rest of the healthcare infrastructure will go up? Can we like expect the, can we expect it to be like more or less expensive? Like we have early prevention, right, which will I guess save costs, But then there's also more strain because there's more diagnosis. I hope that question makes sense.

Zornitza: It absolutely makes sense. It is one of the core problems or issues that we would need to work through with rare conditions. Yeah, it's difficult. I guess one thing that's not answered is whether by adopting a screening approach, are we going to pick up exactly the same children that would have presented in the first year of life being quite unwell with the same condition? So we're going to pick up exactly the same children. Are we going to pick up a bunch of extra children who never get that unwell and don't actually need the healthcare system? So everyone's worrying about the latter

possibility because if all we're going to do is just shift forwards exactly the same children that the healthcare system already has to look after and just shift them forwards to picking them up before they get sick. And then there isn't necessarily an added strain except for that shorter period of time whilst they might have otherwise been in the community and before they got unwell. But what we worry about is whether we'll pick up extra children with milder conditions or milder manifestations of the condition and that may overwhelm healthcare services. But ~~the only~~, yeah, we don't have a way of answering that question or working out those numbers until we've actually tried it. That's why it's really important for us to do the research studies at the moment. And what's also really important is that we don't just do 100 babies or 1000 babies. It's very important that we try and do it at scale to try and understand exactly what it is that we're going to pick up and what the downstream effects on the healthcare system are. So I don't think we actually know the answer to that question, but it's a very important question. That's what everyone worries about, not just the cost of the new test, but also the downstream consequences and whether the healthcare system can cope with that and also ensure equitable outcomes -- that we look after all those children in an equal way regardless of where they are. So a lot of these conditions are very complex and very rare and can really only be looked after in specialised children's hospitals. So that obviously has a big implication as well. So but we think that's maybe something that we could answer a bit better after like a really good study on it. And a really large study is the important part because just by doing 1000 babies, we won't actually understand the full implications.

Juror (via chat, read by facilitator): So [juror is] saying these are rare diseases. We know that about one in 1000 babies at the moment is picked up in the newborn blood spot screening programme with a rare condition. What how would that change do you think if we implemented genomics, what kind of ratio would we end up with? How many babies per 1000 would we expect to be picking up?

Zornitza: Now I have a really good answer to that because I lead one of the current studies here in Victoria and we've just finished testing 1000 babies. So we've picked up 16 babies through genomic newborn screening and we let standard newborn screening run its course in the background as per usual. And that as expected picked up one baby. So that that seems to be a reasonable ballpark. So there's been a couple of publications recently, one from the US and the other one from Belgium. And again, the numbers were in that ballpark as well. So we're looking at something like 16 per thousand. Having said that, about half of them had a relatively minor condition for which we just provide advice about things to avoid rather than needing medical care. The same condition has been picked up again very commonly by the other studies that have run in other countries. So there's a range of severity of the conditions that we pick up.

Juror: Someone said before that the different states, they're all not uniform. Who decides to actually make the states uniform? Because some states might take a long time to do a test, while another state might have already achieved that. But they're not uniform and sharing their news, so who decides?

Zornitza: Yeah, there is now a national body that looks after that. The name escapes me, but there is meant to be a nationally agreed process about which conditions to be added. And yes, some of it is about sharing know how, but some of it is about buying new machines and things like that. So all of that can take different lengths of time and obviously a state has to be confident that they can add a new condition before it goes live. So it is a complicated process at the moment, adding a condition, because each new condition requires a new separate test and often requires a new machine, often requires retraining the scientists to do something completely different in addition to what they're already doing. So the current process of adding new conditions is very inefficient.

Juror: My question kind of ties into that. Is there any consideration that this could become a federal programme rather than a state-based programme?

Zornitza: I don't know about that and I can't answer that. I find the Australian healthcare system is complicated with the division between responsibility, between the federal and the state governments. I think everyone who works in the Australian healthcare system is conscious of that. So there's definitely a lot of work that's been done at federal level to try and align the state based programmes, but whether there's any appetite to have a national programme, I cannot answer that.

Juror (via chat read by expert): And is there genome screening done anywhere in the world today?

Zornitza: No, it's only research studies at the moment to the best of my knowledge. I think there's a couple of commercial providers now in the US that are offering it as a fee-for-service to parents, but there's certainly not a public healthcare system that has adopted it. And my own personal view is that we're good at least 10 years away from that. So it is very important to appreciate that we are discussing this now at a very early stage and the research has not really been done to show whether it's worth doing or not doing. So we are at a very early stage in terms of considering how this should be done and building the evidence. So I'm not actually expecting any public healthcare system to approve this in the next 5 to 10 years.

Juror (via chat read by expert): Were there any false positives in the 1000 that we tested?

Zornitza: No, we were very, very careful. So the way our study was run is to integrate it very closely with our standard newborn screening programme. And it to some extent it also depends on how much automation versus human review you have. Sorry, to the best of our knowledge we have not had any false positives and some of the other studies, particularly the one that was run in the US had a number of false positives and some of them were slightly silly ones. So they had false positives for cystic fibrosis. So cystic fibrosis, something that is included in standard newborn screening. So all they they should have done is cross check the results before putting those results out, but they didn't because of the way the US system works in a very disjointed way.

Juror: was the entire exome considered to find the 16?

Zornitza: And so the way this works and is we sequence the entire genome, but we limit the analysis to a list of target conditions that we're interested in. So for our study, we selected 605 genes that we were interested in and that are all associated with severe early onset treatable conditions in children that typically manifest under the age of five years. So we have the underlying information for the entire genome, but only analysed the genes that we were interested in.

Juror (via chat read by expert): Is there collaboration between countries and improving newborn and genomic screening?

Zornitza: Yes, there's a large international consortium, so there's multiple of these studies running at the moment around the world. And I showed a map of them at the end of my talk. All of them have actually gotten together to form an international consortium and we'll talk to each other usually at horrendous times of day for us here in Australia. But we meet regularly and there's also multiple working groups. So people are sharing experience. And we've also worked particularly closely with the UK because it's another public health care system that's at exactly the same stage in terms of considering this, except they're running a much, much larger study than we are.

Juror: how are we storing the data?

We are running this as a clinical accredited test through our genomics laboratory. So with any clinical testing and there are regulations about us storing the data. So we're storing it in exactly the same way that we would store data from any other genomic tests. It's kept help completely private and in our laboratory and we I don't know how long we're going to store it for. We've only been doing genomics for 10 years, but we so far have not discarded any data. It's very expensive to generate, so we don't want to be throwing out thousands of dollars' worth of publicly funded testing. The data has been accessed twice so far for babies who then became unwell and their medical doctors had additional questions about ruling conditions in or out. So it was very useful to have that data available for them.

Juror: I was just like how much more data was there compared to the NBS screening?

Zornitza: Oh, huge amounts, but I mean, NBS doesn't really generate much data at all. Genomics generates huge amounts of data and that's definitely going to be, it's already a problem for us and will continue to be. So the infrastructure that is required to carry out the test, but then also to store the data is massive. It's massive. ~~So like you said something like 10 years, we're looking at 10 years before all this.~~ So far our laboratory has been doing genomic testing for about 10 years So we've got stored data and from all of that time. At the moment we're not discarding any, any data. It is a something for us to consider like how much of it should be stored? Can we just store some of it and discard some of it to balance? I guess it's a balance between the expense of keeping it versus trying something out that's actually been, it's very expensive for us to generate. So millions of taxpayers dollars have been spent on generating it. So we feel it is a precious resource. It's not something that we want to discard.

Juror (via chat, read by facilitator): There's a couple of more follow up questions about your studies and it's the one from [juror] a while ago was you, you did say that we need more evidence about cost, but [juror] was worried if your study has shown anything about the cost that might be helpful. And then [another juror] asked about consent, whether you had any challenges with getting people to agree to participate in the study that might be informative for us.

Zornitza: The cost question first, that's really going to be really important. We have got the main results to study at the moment. We just finished at the end of December. And so we've put those together. But the next thing that we'll do is look in more detail at the costs. And for that, we're getting historical data, for example, for babies and children with exactly the same conditions that have been treated in the past at the Royal Children's Hospital to see what their trajectory was in the absence of us picking up these conditions. And then compare that to the cost of the babies that we picked up through our study, for example. And that's going to take another 6 to 12 months. So I, I don't have good data on that at the moment, But here in Australia, we've actually been very good at generating health economic data in relation to genomics. So if anyone's going to do it, it will be us. So watch this space.

And what was the other question? Consent and 1000 sounds like a lot, but it isn't. So I suspect we still got people who were very enthusiastic about learning things about their baby, technology, etcetera. So we had good uptake and the way we chose to do consent was using an online platform during the third trimester of pregnancy. And so that the content can be tailored much more to what sort of person you are. Some people need very little information to make a decision. Other people need quite a lot more detail or would like a deep dive into various components on online platform actually caters quite well to that. So on the whole, we've done surveys with the parents that went through that process and the feedback was very positive. But yeah, I do want to kind of highlight that it is probably still, we're still getting the people who feel quite enthusiastic about something like this and that a study like ours at that scale would not reach people who have more concerns or for example haven't got access to digital platforms or English is not their first language etcetera. So I think quite a lot more work needs to be done in that space. We can't necessarily extrapolate from the first 1000 parents who put their hand up.

PART 2: RESPONSE TO ADDITIONAL QUESTIONS

Q: Is there any research being done in Asian countries?

Answer: Yes, there are multiple genomic newborn screening studies currently underway, principally in China.

Q: Have any of the studies consider testing that isn't whole of genome sequencing, maybe just a targeted set of genes? to reduce the info risk and burden

Answer: Yes, this has been considered extensively. However, most international experts are keen to explore genome sequencing for this application. The number of genes associated with treatable rare conditions are still rapidly evolving – if a targeted panel was used, this will need to be updated frequently, which is laborious and time-consuming. We also know that genome sequencing identifies an additional 8% diagnoses compared to exome sequencing. So we are trying to future-proof the current research studies, particularly in the hope that the cost of genome sequencing will drop further over the next 5 years. Please note that even when we sequence the whole genome, we still target the analysis to specific pre-selected genes that are relevant to the life stage. The principal additional burden (but also potential additional value gain over the years) is the data storage.