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 23 March 2025

Expert: Clinical Prof Kristi Jones, Department of Clinical Genetics at the Children's Hospital, Westmead

Title of presentation: Genomic Newborn Screening: What are the risks, challenges and unintended consequences? Why might we be concerned about doing this?

PART 1: Q&A TRANSCRIPT

Juror (via chat, read by facilitator): So the question from [juror] is that there's been quite a lot of concern from the jury generally about the lack of information on the genome, on lack, lack of genomic information from First Nations people and other minority groups in Australia. And a question about whether actually that might be a good reason to include genomics in newborn bloodspot screening in NSW, because that would allow us to build that database and perhaps even whether those people would be first place to start with genomic screening.

Kristi: Yeah, I think it's a really interesting point. Certainly the data will be there which can be which can be used to put into databases to improve the data knowledge in various different groups. I'm not personally aware of a research project that is looking at that specifically at this point. Because of course, when we get information about the children, the babies that we're collecting the data on, we don't have information at that point about their background. So it would need to be a specifically planned, but I think it's a really good thought. I'm not aware of anybody doing that specifically. There might be. And we obviously would need to collect specific consent and specific background information on those individuals to do that.

Juror: I have two questions because I, I'm getting the impression that the whole field of genomics itself is kind of in its infancy. We're at the very sort of beginning stages of it and as technology progresses. But my main concern is like with the false positives and false negatives, how are they actually detected that they are in fact false positives or false negatives? And what processes and procedures, you know, will they be put in place to actually detect them and improve and update those processes as data comes in?

Kristi: I think your, observation about genomics being in its infancy, I think is really interesting because on some levels, you know, we've been working with genomics for decades. But on the other level, the more we learn, the more we realise we don't know n. I think you could say we're, we're moving through rapidly, but there's just so much we don't know and still have to learn. False positives and false negatives are a complex thing. So there are the false positives and false negatives that are due to system failures to, to errors that are preventable. And then there are those that are inherent in the, the newborn screening process and in, in most of the testing that we do. And that data is actually very well collected and followed up in general and will continue to be, I think the things that are most relevant to this are the ones that are inherent to the specific test. So there will always be false positives and false negatives because of the type of testing we're doing and the nature of the genetics of these

conditions,. And I think finding the 'sweet spot' where over-calling versus under-calling is, ' is something that we need to work out over time. So a lot of the research projects that are going on right now in the current round of government funded research grants are to try and help define that sweet spot for overcalling and under-calling false positives, false negatives. But a lot of that will be collected over time, over decades, as the data that we have and the experience we have increases. So one of the things that we discuss a lot is how are we going to collect this data in an ongoing way? We need to be collecting this over the next decade or more, not just in the short term, and then learning from that. That's been very much the case in the current genetic newborn screening that we're doing anyway. So for example, cystic fibrosis, the way in which we're doing that has changed a lot over time in response to the data that's been collected as the programme been rolled out. So it will be an ongoing process. And then obviously as new treatments come up.If you've got a condition where missing a case of a particular condition is much worse than telling someone that you think that they have a condition when they don't because there's a lifesaving treatment that you need to institute immediately. Then you might want to 'overcall'. So a false positive is actually not as bad as a false negative. But if you've got a condition that isn't immediately amenable to a lifesaving treatment, then actually you may not want to be over calling. You may want to make sure you only get the ones you sure have that condition.

Juror: There's been some talk about if we introduce a whole large range of new tests to detect these new conditions that it might put increased load on the health system because there's all these new cases and treatments to deal with. I was wondering if the early detection of these new cases might actually cause a lessening of load on the health system because the treatment can be taken on earlier rather than being are implemented later on when the conditions already started to manifest.

Kristi: Yeah, that's a very good point, [juror]. I think in some conditions, all it does is shift the timing so these children are going to present anyway. When they do present, they might actually have more problems and create more strain on the health system. And picking them up early, they may prevent problems in some cases. You know, looking at this, in a purely financial sense, these are children that might have died otherwise, and we're saving them and treating them. So that might increase cost and strain on the system. But in general, the idea is that if we pick up these conditions early, we prevent illness and irreversible problems and actually ultimately reduce the strain on the child, the family and the health system. But yes, it certainly changes the touch points at which we are intervening. And you know, it might actually mean that we for a while have quite an increased load on our on our system.

Juror (via chat, read by facilitator): So [juror] has actually asked about our readiness to deal with genomic testing for so many babies a year and what would be required in terms of staffing for the labs and how the system might be able to deal with peaks in births as opposed to times when there's fewer births, whether that could cause problems for babies that are born in those peak kind of periods. Have you got any thoughts about that?

Kristi: Yes, very important point and this is very much a part of the research projects that we're currently doing to try and understand the resourcing that is required and how those workflows might change. And you know, you're probably seeing in the media all the time that the health system's under enormous stress. Howare we going to manage this? You know, ultimately I think as we were earlier discussing, the aim is that overall the health system will benefit from these advances, but there's a shift. So you know, you've got all these people now doing genetic testing in in the newborn screening labs rather than in the diagnostic labs, for example. And how are we going to manage that? One of the big parts of these research projects is to try and understand the resourcing required for the newborn screening system – which is already an excellent well-established system in Australia and particularly, in NSW in terms of managing those ebbs and flows in in demand. So I think that's something that is

well recognised and relatively well understood, but how genomics will respond to that is something that we need to manage moving forward.

Juror: So there's two other questions that are connected 11 is this question about indigenous and non-North American people not being well represented in the data and just trying to understand why that's the case. And then relatedly, a question about the reach of newborn screening in for example, remote communities now and whether including genomics might make it more difficult to ensure that those communities were included. So the first question, why are certain groups under represented?

Kristi: That's a complex question. Some of it is purely because a lot of this research is out of Europe and North America and the populations represented there are different. I think research is often done in big in big urban centres where the population may be maybe not quite so representative. Thinking more about First Nations people, I think that is relates to First Nations people in various countries around the world. I think that there's been a long-standing mistrust, well founded in many cases of the establishment and the research establishment. So I think many First Nations groups have actively avoided being involved in research. And I think that's something that many groups are actively addressing now to try and address that, that mistrust and work together with and alongside First Nations groups worldwide to develop new trust between those groups and try and build the relationship, to increase the research in those groups. So some of it is purely historical and some of it is because of actively of certain groups actively avoiding being involved in research because of mistrust.

And the question about access for remote communities and whether including genomics might make that better or worse. I don't think including genomics will make the access to newborn screening any different. Where I see it might increase inequity is that if you are introducing new, rarer and rarer diagnosis,access to experts in that field might become harder and harder in remote areas, then that makes that divide more difficult. So now if you've got someone talking about relatively common conditions in childhood that have been around and screened for, for the last, you know, multiple decades, then that expertise is going to be present and spread out through more remote communities. But for example, spinal muscular atrophy, which is already on the programme and is a genetic condition, one that I referred to throughout my talk, in terms of getting access to information about spinal muscular atrophy, that's not easily going to be available in remote areas. And the treatment certainly isn't. So if people in remote areas can't travel to a few major coastal centres, big cities, then, you know, I think that is potentially going to increase inequity. I think we have control over that to a point, but it is difficult. So I don't think access to newborn screening will necessarily change, but maybe the inequities in the treatment, and what happens after that may become more different. Or it may become better because actually many children and babies in remote communities miss out on the diagnostic part in the first instance. And by the time they come to medical attention, they're already a long way down the track of their condition. So, you know, I suppose the other way of looking at that is that introducing newborn screening may actually make the diagnosis earlier and make it more possible for remote communities to access treatments, if that makes sense.

PART 2: RESPONSE TO ADDITIONAL QUESTIONS

Q: How late can a genetic condition or disease onset. Will it all have happened before 18?

Answer: Genetic conditions can have onset throughout life. We are targeting the NBS genomic testing to conditions that are predicted to have onset in early childhood. Whilst we are trying to choose conditions that are reasonably predictable, it is not always possible to be 100% certain when a condition will present in an individual.