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 9 March 2025

Expert: Prof Bruce Bennetts, Sydney Children's Hospital Network

Title of presentation: Genetics and Genomics

PART 1: Q&A TRANSCRIPT

Juror: I have a question around you mentioned in the presentation that you won't test for adult-onset diseases, but will there be diseases that you test for that manifest later on in the child's life? And what would then be the support around that family? So say you've got the disease that manifests when a child, you know, hits their teens or you know, so then a parent's got, you know, 12-15 years of anxiety knowing that their child is going to then develop this condition. What, what kind of support mechanisms will be around that?

Bruce: I think the choice of the gene list, you know, what genes we actually study is an incredibly important one and one that needs to be worked out in terms of that. Generally, in the research that is occurring, most of the studies are looking at disorders that manifest symptoms prior to the age of five. So that would be where people are looking at. We would also be looking at, you know, there are variants, you know, you could look at a particular gene and go, no, that is an adult-onset variant. We aren't going to report that. So within genes you could have variants that are going to give a childhood presentation and some that will present it as adults. So a lot, you know, it is about how we set the policy. You know, what do we report? What don't we report?

Juror: Which group will be deciding what are the thresholds for this? What is it the accuracy and the specific? No, the sensitivity and the, I can't say specificity, whatever that is. So who sets those benchmarks so that we can then or you can then decide which conditions to choose because the impacts of that not being right is going to impact lives. How do we decide whether it's worth telling somebody if the sensitivity's not there, how do we who's going to make those decisions?

Bruce: So that that's what laboratories are good at in terms of working out how to determine what you know, we spend a lot of our time in terms of determining variants, how they're going to present. So we look at variants and go "that variant is going to cause a particular disorder phenotype as such". So one of the key tenets in the research that's going forward is because this is screening you would not be calling variants that you didn't know what the outcome of that variant was As such, hopefully that's answering your question. It's to say I think there is only a lot of international evidence and effort to work out what gene should be screened. And then within those genes there is also then -- a lot -- a strong community working out how do you determine whether a particular variant causes a significant phenotype or a child-onset phenotype as such. So we would be working and all labs would work closely within those boundaries as such they would be in this process in a variance that may cause disease that we're going to go, we don't know and we're going to let that go.

Juror: So you wouldn't call that if you've got evidence enough, hard evidence enough, you'd include it. And if you're not sure, it would have to wait till you had the evidence that it's a good one to test.

Bruce: So certainly, in terms of genes, one of the things is which genes to choose. We would only be choosing those genes that have strong evidence that that causes a significant disease because there are genes where people go, well, what does that do? We think it causes intellectual disability? We don't know, but you would wait until you've got solid evidence and that would be a big part of it. It would be a conservative approach moving out and going: This gene causes this problem. We have treatments and the likes.

Juror: Sorry, this might have been on the video. It was just there's a lot of information in that video. I was just wondering this genomic testing, can it tell the difference between someone who's just a carrier or someone who is going to be affected by the disorder?

Bruce: Certainly I think when you have genetic sequence, you can determine if someone's a carrier or not. I think all the screening projects, all the research projects moving in this space are not going to call carrier screening. That can be controversial, particularly for X-linked disorders. But in our research we would not be calling carriers as such. But you can pick up a carrier and say that, but again, those would not be, called because that would be something you could do later if you wanted to.

Juror: I mean, like just a follow up question. Would it not be ethical to let them know that their future children have the potential to have the disorder or they just have to find out when they're having their future children?

Bruce: I think there are systems in place. There is something called, you know, expanded carrier screening. So that is being offered to people now. So the feeling would be is because you're as a carrier, you're not going to have a disease, a disease phenotype disorder. So I think it would be the feeling is that if you were interested in that, then you would do that separately. One of the questions would be is could you use the data to do that later and could reconsent someone to do that.

Juror: So my question was related to the carriers as well. So where sometimes you might find the gene is present in someone and is not causing that disease, why do you take that into account when you're doing the testing as well? Or do you just disregard that completely?

Bruce: If there's just a carrier, then we would let that go that we'd not report them.

Juror (via chat): We've heard about whole genome sequencing. Is there such a thing as a partial genomic test that's kind of halfway between a genetic test and and whole genome sequencing?

Bruce: Absolutely. So there are different ways and there are many ways you can do it. You could do a capture. So one of the ways that you can do genetic testing is by taking a set of genes and designing things to capture those particular genes and only to look at that, so that may happen. And there is some cost benefit of that. The problem often with a capture is once you've made a capture panel and then you go, oh, hang on, we want to add one more gene in, then you've got to go back and redesign it as such. The advantage of doing a genome is that you have everything available. And then we what you can do is do a bioinformatic capture and information capture. So you're only looking at those particular genes. But it is also possible, as I said, just to only sequence the genes that are on a particular list. You might be 400, might 550 genes as such. Hopefully I'm explaining that they're quite complex.

Facilitator: So, can I clarify just to make sure that we're understanding correctly. So you could have a list of the genetic tests that we've agreed that we do and only those genetic tests happen. Or you could sequence the whole genome and only report certain things out of that whole, that whole sequence genome. Or you could sequence the whole genome and report absolutely everything that you can possibly report out of it. Is that the range?

Bruce: No. No one is thinking of reporting everything because it's just too much to report to everyone. If you were doing a genome, you would be having a selected list of genes that are well established and with reporting policies and you would only look at those genes, you'd only analyse them, so you wouldn't even see the rest of the genome. The rest of that genome would be hidden to those who are doing the analysis. So that is that is one option. The other option is to actually only sequence that listed defined genes. So therefore the only sequence available is those that are within that list of genes. So those two options available, genomes gives you all the information, but you only look at that small part and everyone would only think about that in newborn screening. You don't want to look at everything because a), you can't interpret it and b), there are many things, such as adult onset disorders that are just not appropriate for newborn screening.

Juror: Just a quick question where you're screening people and they're coming back as carriers only and they're not exhibiting, I guess whatever the condition may be. Has there been research into why that is the case and obviously possibly linking to something else?

Bruce: So carriers why, why are people just carriers and carrier not exhibiting? So a lot of genetic disorders, you know, if you've got one good copy, that's enough. You're not going to do that. All of us, everyone in this Zoom meeting has recessive disease disorders. We're all carriers of something.

Juror (via chat): What exactly you're picking up when you're doing genomic or genetic tests. So is it about chromosomes being like too many or too few compared to usual? Is everything that you're looking for about non sex related genetic conditions? Are there's some things that are linked to X or Y and and other things that are not.

Bruce: When you're doing the testing, when you're doing testing and I'll speak about the whole genomes at this stage you're looking for changes in the code. So then the you have the four bases of A, C, G and T. So sometimes you'll go, OK, the code has changed at a critical spot. So we're looking for those sorts of changes to go, OK, that's going to stop the protein halfway through and you're not going to get an effective protein because it stops. We're also looking to see where there is deletion so that, you know, a big piece of DNA is missing, so sequencing can actually pick that up. We're also looking at where your pieces of DNA get moved around and so you can go, OK, that DNA is now in a different spot. So it's a structural change there. We're looking also to pick up duplications. So often DNA can get copied and that doubling of DNA is a problem. So we're looking at all of those types of things. We're looking at the chromosomes 1 to 22 and any, all of the various changes on those. And we're also looking at the changes on the X chromosome-- and the Y chromosome generally doesn't have a lot of disorders on it. With the Y chromosome the only main thing is about whether you're going to be a male or not.

So this sexual dysmorphia is, is an issue there. You can also pick up when you're doing whole genomes mitochondrial changes and there's some of those are relevant to newborn screening. There is a common mitochondrial variant that if children have certain antibiotics, they will lose their hearing. So that would be one that you'd potentially want to look at and say, OK, that child, the treatment for that child is to avoid that particular antibiotic. So we can also look at the mitochondria, which is a separate genome that you inherit solely from your mother. So those are things there. So you could you

get a lot of information out of a genome. Having said that, there are things that the current genome sequencing cannot easily detect. So expansions of triplet repeats, things like Fragile X can be difficult to do with gene with current genomes.

Juror: What do you think is the right answer? Is it better for us to sequence the whole genome or is it better for us just to sequence the list?

Juror: if we sequence the whole genome, would that mean that in future when there was new science, we could loop back and look for new conditions based on that stored information?

Bruce: I, I think the value of the genome is that you, you're always ready. So if there is a new treatment coming up, you don't have to scramble and design a new, a new test to put that gene back in. It's just a case of switching it on. So I think genomes have a lot of advantage about that. I think one of the challenges would be in newborn screening is that I think it'd be difficult to, in the screening stage to loop back and to do that. Having said that, what you could ask families is do they want to re-consent for a re-analysis at a certain point of time? Consent is a huge and important part here. So one of the things that we're interested in our research is this idea of re-consenting throughout life for different things. So you might get to the age of 16 and you go, I'd like to consent now to my carrier status because I'm in my reproductive years. I didn't need to know about it when I was 3, but now I do. So I re-consent that and I'm using that potential same data. Some would argue it may be better just to retest, but there is a lot of advantage about newborn screening is that it's capture, it's reach of people is vast.

PART 2: RESPONSE TO ADDITIONAL QUESTIONS

***Q**: How are people from different backgrounds treated in this process, in particular where English isn't their first language? Also, how are people who do not give birth in hospital captured in this process, in particular indigenous women who give birth on country?*

Answer: These are important questions. Currently the NSW Newborn Screening Brochure is translated into a number of languages on the NSW Health web site. If genomic newborn screening were to proceed, consenting information and education would need to be translated into a variety of languages. Exploring ways to consent online and have educational material online is part of the current research. This would help in the home birth setting though access to online material is always a potential problem.

***Q**: I would like to know if extending the amount of conditions tested will this impact the timeframes of the results, thus impacting treatment to early conditions such as pku, also will rural areas be able to access this same testing in suitable timeframes?*

Answer: Genomic newborn screening would not alter the existing newborn screening. Testing for conditions such as PKU would proceed alongside genomic screening and would likely have a faster turnaround time. A key component to newborn screening is getting a result in a clinically relevant time frame.

***Q**: To what content can we obtain information from genomics besides health information, such as personal information?*

Answer: It is not envisioned that genomic information obtained through newborn screening would be used for non-medical/health purposes. There are other avenues to people to explore this if they felt it were relevant.

***Q**: So it seems to apply that there are possibly extra or less chromosomes in some people? So are there non-sex xy genes? are all the chromosomes identical and genes and genomes all the same? What is an x-linked disorder?*

Answer: The genetic makeup of individuals is highly variable. However, most individuals have 46 chromosomes, made up of 44 non-sex chromosomes and 2 sex chromosomes (either XX (females) or XY (males)). Some individuals may have more or less chromosomes such as Downs syndrome where these individuals have 47 chromosomes (including an extra copy of chromosome 21).

Within a chromosome some people have deletions of part of the chromosome or duplications. These variations may or may not result in a disorder.

An X-link disorder is a genetic condition where the responsible faulty gene is on the X chromosome. Males are more at risk of an X-linked condition as they only have one copy and the faulty version is likely to cause a problem. Women, on the other hand, may not be affected as they have two X chromosomes and the non-faulty copy can usually cover for the problems caused by the faulty copy. However, these women can pass on the faulty copy to their sons (1 in 4 chance) and those boys are likely to be affected.