

Centre for Personalised Medicine podcast

Series 2, Episode 4

Newborn genome screening

SPEAKERS

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Rachel Horton

Welcome to the Centre for Personalised Medicine podcast, where we explore the promises and pitfalls of personalised medicine and ask questions about the ethical and societal challenges it creates. I'm Rachel Horton, and I'm here with Gabby Samuel and Lisa Ballard from the Clinical Ethics, Law and Society group at Oxford and Southampton.

Today, we're talking about newborn genome screening, the idea of analysing the genetic code of babies who seem healthy, to try to detect and treat health problems early. This relates a lot to my own research interest of how do we make sense of our genetic code? When and why might different variations in our code become results? So I'm really looking forward to discussing this.

Gabrielle Samuel

Hi, both of you. Rachel, it's so nice to be able to ask you some questions about your own research. Could you just start us off by telling us a little bit about the current situation related to newborn screening in the UK, and then maybe also internationally as well as a comparator?

Rachel Horton

Sure, so it's done via a heel prick test that's typically done when a baby's five days old. And it checks for nine different conditions here in the UK. And those conditions are chosen by the UK National Screening Committee as being ones where there's a good test to detect it. And it's very much in the child's best interest to have that picked up and treated early, before the baby becomes symptomatic.

It's quite conservative here in the UK. For example, we only test for six metabolic conditions as part of the newborn screen. In the US, their Recommended Uniform Screening Panel has got 20 metabolic conditions on it. And there is some criticism of that, in that for very rare diseases, it's very hard to build up information on the natural history of the disease and the benefits of early treatment, and that kind of thing. So I think there's quite a compelling argument that it's important to look a bit wider and consider what else needs to be screened for.

At the moment, the test is ostensibly done under parental consent, in that parents are asked to consent to their baby having the test. But there's lots of research on the topic that shows that typically it passes in a bit of a blur, it's seen very much as a routine thing that's

kind of expected. And often it's only actually when an unexpected result comes of it, that it's then sort of revisited and becomes visible in a person's experience.

Gabrielle Samuel

So the tests that are being done at the moment, are they genetic tests, or do they just test for particular proteins?

Rachel Horton

So they're generally biochemical tests. So testing for particular proteins. And actually, the test at the moment that involves the most prominent direct genetic element is a screening test for cystic fibrosis. And that's probably the one that currently introduces the most uncertainty in the newborn screening programme that we've currently got.

So the first part of that is they'll test for immunoreactive trypsinogen. But depending on the levels of that, they might then go on to do some genetic testing. And that genetic testing, the kind of inclusion of that in the screening programme, has led to a few people getting this inconclusive result that's called 'cystic fibrosis screen positive, inconclusive diagnosis'. So currently, the element of the screening programme where we've introduced genetic testing on a very well understood, very well characterised gene is the one where currently a few families end up in this very uncertain situation where they get a result for their child and it's not really clear what it's going to mean for that baby growing up.

Felicity Boardman and a colleague did a really interesting paper talking to parents who'd had children diagnosed with cystic fibrosis screen positive, inconclusive diagnosis, which is called CFSPID for short. And they described this sort of issue of almost being like genetic nomads, where people didn't quite know if they fitted in the kind of healthy child world or the cystic fibrosis world, and sometimes would travel between the two depending on what was going on in their child's life at that time.

Gabrielle Samuel

I think that's so interesting. Cystic fibrosis was always something that seemed quite definitive, like out of all of the genetic conditions that you look at, you either had cystic fibrosis, or you didn't have it. But in this sense, you're suggesting that it's kind of like nomad territory, is that right?

Rachel Horton

I think certainly in, in some cases, that's, that's right from newborn screening. There'll be some diagnoses that are made that are solid and clear. But there are just a few families who are left in this really uncertain territory where there's this anxiety that's been raised about their child's health, but it's not really clear whether that's going to turn into anything. And historically, the care that's been provided to babies in that situation has been really variable. It's ranged from kind of almost nothing to full on care, such that you'd get with a solid diagnosis of cystic fibrosis. And there are now some European consensus guidelines that have tried to bring a bit more consistency and, and structure to that process.

But yes, I think whilst most of the diagnoses made by the newborn screening programme are very solid, there's certainly a few situations where people end up really in limbo, unsure

whether the anxiety that's been raised about their baby's health is ever going to turn into anything. And that's just with nine conditions.

Lisa Ballard

It's just so interesting, Rachel, you're talking about that nomadic status and that kind of limbo, and it makes me think about, some researchers have coined a term 'patients in waiting'. So patients that have had a genetic test result that might indicate something happening in their future. I just wondered how that fits with this new proposal, and you've kind of talked about cystic fibrosis. But I wonder whether there are other conditions that are being discussed as well?

Rachel Horton

So I think that's a hugely interesting question. And it depends a lot on what newborn genome screening is actually going to end up involving. Because I think there's potential that we could create a huge number of patients in waiting. But genome screening could cover a multitude of options, really.

So it's going to start with genome sequencing. And that's sometimes described, like when you read about it in, in the papers or things, as reading all 3 billion letters of a person's genetic code. But in some ways that reading analogy is quite misleading, because it's more like getting a printout of that genetic code, and getting a printout of that person's 3 billion letters, but with no guarantee that anyone's going to even try and read it. And if they do, be able to understand it. And I think the consequences of the Newborn Genome Programme will essentially depend on how much of the 'genome book' for a person, the programme tries to set out to read. Because the wider we look, the more uncertainty we're going to generate.

So there's research that looks at genomes of healthy adults, or people who we all kind of consider to be healthy at this stage and finds that if we did a genomic test, on any one of us, we'd probably have about 50 genetic variations that if we ran it through a database of disease-causing genetic variations, they'd be in there. So we've all got stuff that looks a bit worrying and concerning in our genetic code. And there's a study recently on UK Biobank that shows that, once you start to look at very large numbers of genes in one go for a person, you know, odds are, you'll find something that looks concerning. So we've each got about 23,000 genes, they found that once you look at 500, or more disease genes, most people will have something that looks at least kind of hypothetically, a worry.

And in studies like that, in biobank, or in studies of adults who seem healthy, we've got the reassurance that, well, they've grown into healthy adults. So it's unlikely they've got lots of different very rare genetic conditions. It's really so much harder to make that call on a baby, because they won't have had time to grow into loads of the features that might kind of steer you clinically to thinking they've got the condition or not. And I think it just highlights really how little we know about a lot of the genetic code and how it works.

The variations that I mentioned in the database of disease-causing variation, you know, some of those will be in and that will be incorrect, in that that variation won't truly be linked with a disease. Some will be because perhaps it is, but in certain contexts or on a particular

genetic background, or when you're exposed to a particular risk factor. And I think there's a whole load of subtlety in that and in its interpretation that we are still unpicking, and that has yet to be understood. So I think it's going to be very hard to make sense of what you might find in a newborn baby, unless we're looking at very well understood genes in quite a restricted and conservative way, really.

Gabby Samuel

So, given that, I mean, I really like this idea of reading the book, it's a really nice analogy. But given all of this complexity, what's the idea? Is it to read like quite a lot of pages of the book, or just to pull out, you know, specific areas of the genome and look at those in a lot of detail?

Rachel Horton

That's a really key question. And I think it's kind of unknown because the Newborn Genomes Programme is still very much in its infancy, and is being co-designed with parents, people across the NHS, and other experts. But I think the consequences of the programme will be massively different depending on how much of the book they try and set out to read. If they decide to look broadly, that's going to introduce a lot more uncertainty than we currently have from the newborn screening programme and potentially create a huge number more 'patients in waiting', like you mentioned, Lisa.

There have been some studies in America, the NSIGHT studies, that have looked a bit at genome screening and babies. They tried genome screening in a few hundred babies and with the sort of amount of 'the book' they chose to read, 3-8% of babies had some sort of finding fed back from that.

And from those, you know, there were several findings that probably were very much in a baby's best interest to know about early. But there are a few others, which were perhaps a bit more of a grey area, like, for example, a potential predisposition to developing a heart condition where no one can put a number on it, no one knows if it's that solid a risk. And that baby could potentially have screening. And in all cases, actually, those variants had been inherited from a parent, that parent could have screening, perhaps if it came from a grandparent, they could have screening too. But you just think that's a whole lot of screening, escalating out to a whole lot of people. That's going to cost money, and cause anxiety, and needs kind of thinking and planning about.

A lot will depend on how much they choose to look at of a person's genome. And you wonder if they might be likely to take a more conservative approach and look at substantially less of it. But then it would be possible to get the data you need to do that sort of analysis without looking at a person's entire genome.

Gabrielle Samuel

That sounds like quite a good idea. Because otherwise, it sounds like this massive risk society, which to me I suppose as a sociologist raises quite a lot of social questions.

Lisa Ballard

I guess, as a psychologist, I'm thinking about the psychological burden of results on parents, and then how they can communicate that to their children later on?

Rachel Horton

Yeah, absolutely. I think it needs so much thinking about really, because those projects I mentioned in the US, that was a few hundred babies, the Newborn Genomes Programme is setting out to provide this analysis for 200,000 babies. So that's a lot more babies than we were talking about in the US. And I think the consequences of it, for the health service could be very significant.

I think doing health economic analysis on this must be really challenging actually, because obviously, the hope from detecting and treating conditions early, which I think is a great aspiration, if you know that there will be benefit in doing that. But I guess the hope would be if you do that successfully, that both the baby and family avoid them becoming really ill. But also you save money for the NHS in the longer run, because they don't then become really ill and need all sorts of admissions and things because it's been picked up and proactively treated. And I think that's a great aspiration.

But in practice, actually, you know, how often will we end up in that situation? And how often will we end up in situations where people are needing recurrent medical visits, or investigations like heart scans or something like that periodically, perhaps for a condition that's never going to show itself and will never cause them any problem? And that decision will very much depend on where they draw the line, in terms of reporting results from this kind of thing.

But the knock on effects for the rest of the health service, for example, babies who are born and clearly do have a very significant genetic condition that needs diagnosing early, if their genome test is pushed back, because labs are dealing with all the kind of work on screening healthy babies, or if their clinical genetics appointment takes longer, or they have to wait longer for it, because so many appointments are filled up with people needing to talk about relatively uncertain or tentative findings. That's a real concern.

So I think trying to find and treat babies with serious conditions early to improve their outcomes is a really, obviously a really important and positive thing. But making sure that the services downstream are resourced, such that that doesn't disadvantage a lot of other people in the process, I think is going to be hugely important.

Lisa Ballard

So my question relates to what you said, Rachel, at the beginning, when you were kind of talking about how the consent process is a bit of a blur, and it kind of appears like it's, you know, routine care. And I'm wondering now, if this new screening is introduced, and the things that parents will have to think about the implications, and the kind of the amount of information that parents are going to have to be given to kind of consent to this new test? Is that something you can comment on?

Rachel Horton

Obviously, babies can't make these decisions for themselves, parents are going to have to make the decisions in their baby's interests, but it's the babies who are going to have to live with that decision and have their genome, you know, as part of this initiative. And I think there are huge challenges. And when is the best time to ask parents about it? I think there's a lot of thoughts about maybe having those conversations during pregnancy where you perhaps have more time to reflect on it and to engage with all the complexities of it. But perhaps the person who you're making those decisions for is also a bit less, less tangible at that stage.

My biggest concern is will this just be seen as like a better version of the heel prick? Because I think on face value, if you're like, "Oh, you could have this standard test for nine conditions, or you could have a test for a whole load of extra conditions", it might seem like fairly obviously, it's better to be tested for as much as you can be tested for, and that's the way it's often described when politicians are making announcements about it or when it comes up in the news. Like the health secretary and things saying, "we want every baby to have the best possible start in life by having their genome sequenced as soon as they enter the world. And, and that's the future, personalised preventative medicine".

And obviously, that's a sort of very powerful image. And, you know, if, by getting a genome sequence, you could do that, you know, I think many people would want to, but I think... And the complexity of undertaking this doesn't mean that it's not, not a good idea where we can to try and diagnose and treat rare conditions early, to try and use genetic technology to do that. But I think we have to be really explicit that trying to use technology to make diagnoses earlier comes at a price. And that price is a lot more people living with uncertainty and living with questions raised about the future of their baby, and all sorts of potential downstream implications in terms of, you know, will that affect their prospects growing up? Or what kind of activities people are comfortable with them engaging with at school, and all that kind of thing, if some concern has been raised about their health, that might actually never turn into anything?

Gabrielle Samuel

So how is the Newborn Genomes Programme going to decide what to report? Like, where is it going to place those thresholds in terms of what to report back and what not to?

Rachel Horton

It's a really difficult question where the threshold should be for saying, "Yes, this is a useful thing to report back from this genome test". And I know, it's something evidently, that the Newborn Genomes Programme is, is considering very deeply and involving a lot of people in the co-design process. I guess, you know, my question, in some ways would be: are people who've had uncertain or potentially unhelpful results from genetic testing, being included in that dialogue as well? In that, you know, are parents of children with CFSPID, or parents who've had uncertain findings from genetic tests being included in those conversations? Because I can absolutely see the argument that for, you know, for example, if you have a baby with a rare condition that would have been picked up via screening, if you were born in the US, that hasn't been because you happen to be born in the UK, that you know, that- it feels like that, you know, that aspect of things you can see, we need to improve from where we currently are. But what we're kind of opening up in, in trying to make that step into using

more extensive genetic testing, the capacity to introduce more uncertainty needs to be really kind of headlined in that.

And if a response to that is, actually we're going to take a much more conservative approach to this, and we're only going to look at a very limited amount of the child's genetic code, i.e. only read, you know, a few lines of the 'book of the genome', then I think it needs to be really explicit that these genomes are being collected, but only a tiny bit of it is actually being looked at for the child's direct benefit, and really clear conversations as to what's happening with the rest of that data. And what's the future going to be around how that's used?

Gabrielle Samuel

So just to finish up, if you had one take home message that you could tell people about newborn screening using genomes, what would it be?

Rachel Horton

I think it would be that issue that breadth and clarity are in conflict when it comes to genome screening. And the wider you look, the more uncertainty you invite, and moving from nine conditions to many more conditions isn't a sort of simple upscaling of a heel prick test, the wider we look, the more kind of 'patients in waiting' we're going to create. And the more carefully we need to think about- have we planned for that? Are people prepared for that in consent conversations? Is the health service funded to deal with all the extra medical interventions that we're going to need?

Thank you for listening to this episode of the Centre for Personalised Medicine podcast. If you'd like to find out more about personalised medicine and its promises and challenges, please visit the Centre for Personalised Medicine website at cpm.well.ox.ac.uk.