Centre for Personalised Medicine podcast
Series 2, Episode 2
Why context matters in genetic testing

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 in today's episode, we're looking at why the same genetic finding can mean different things in different people. We caught up with Professor Anneke Lucassen, Director of the Centre for Personalised Medicine, at a recent workshop to ask her some questions about this. Anneke's research aims to support improved delivery of genomic medicine to people and families.

Anneke, thank you so much for joining us today.

Anneke Lucassen

Hello.

Rachel Horton

Could we ask you to talk us through a couple of examples where the same genetic finding might mean different things in different people?

Anneke Lucassen

Yes. I wondered if I could start by thinking about an analogy, this just came to me this morning as I was coming here, which is that if you think about certain words, they have different meanings in different settings. So think of a word like 'dear', you could hear the word and think you know what the meaning is. But it depends all about where it is in a sentence as to what its meaning is, it could be a noun, or an adjective, it could be 'Dear Rachel', or it could be 'that dress is very dear', or it could be about an animal galloping around in the park. So the word alone does doesn't stand by itself. It's in a context that gives it meaning. And it's exactly the same for genetic variants. And so a really obvious example might be that if you have a variant in a *BRCA1* or *2* gene, the *BRCA* gene, that that has greater significance if you're male or female. So the greatest risks that those variants give you is cancer of the breast and ovary. And if you're a man, you don't have ovaries. So that's an obvious example of the context in which that finding is found making a big difference.

Gabrielle Samuel

You talk about, say, the male and female distinction, but like, what other types of distinctions would geneticists need to think about?

Anneke Lucassen
So all sorts of contexts: the stage of your life, so a particular genetic variant might be significant if you're thinking about reproductive options, and obviously, if you're an 80 year old, that's not the same sort of context, but we, I think, should be thinking about genetic variants as depending on a lot of other factors rather than standing alone. The sort of textbook GCSE description of genetics, is of the variant is it and nothing else matters. But actually, we know now that it depends, for most variants, it depends very much on the genetic background in which they lie. So it might depend on your recent ancestry, but also on the environmental factors that you've been exposed to, or just the random factors that you've been exposed to like your immune repertoire and things like that.

Rachel Horton
That's such an interesting analogy, actually, like the word 'dear' but without the words around it, how can you know what it means? And I suppose, getting that context of what a kind of genetic finding really means when you can only in a way say that word? Yeah, finding ways to communicate the other words in the sentence is really tough. Can we talk a bit about how the meaning of the finding might depend on why a person had a test? Because I guess we've alluded to that a bit with if you find someone was a carrier, but they're in their 80s, it might have different meanings. But there's also- some things mean different things, don't they, if you find them in someone who doesn't have a family history?

Anneke Lucassen
Yeah, and that's also a point that's really often missed. So I think, partly, that's got a historical explanation, that the only genetic testing that was available until very recently, was on a very carefully selected subset of the population, i.e. members of the population who had signs and symptoms of something that made you suspect a particular variation in a gene. So you went looking at that gene to see whether you could find it or not. And so you really just homed in on a particular subgroup. And what we thought from that was, okay, now we need to spread out and find the other people who haven't got the signs and symptoms. But it turns out that actually, if you find those people, it doesn't predict the same thing, that genetic variant, as it did in the group where you first looked at, because they'd already shown signs of that variant. Increasingly, we are finding those variants in healthy people and realise that they're not as strong or as predictive of the condition in question, as we thought when we used that targeted approach.

Gabrielle Samuel
That's really interesting, because I've actually started reading a lot about that, right, about the fact that we are finding these variants in healthy populations, which means that they can't, or may less so be relevant for the particular disease. And it makes me think about how quickly we're moving with genetic technologies and trying to bring them into practice when we know so little about them. Just wondering how I suppose your work kind of reflects on that aspect.

Anneke Lucassen

I think that's absolutely right. It's really interesting how the discourse around the advances in technology has taken hold of our attention. And we, we like to think about genetics as, as an example of technology that's really producing fantastic results, and in many ways it is. But it's almost like the bottleneck has shifted. So we had a bottleneck of technology where we couldn't do the testing. And so we thought that once that was solved, it would all be straightforward.

Actually, now we've got to the interpretation stage, we've got all this, the technology producing all this data. And we suddenly realise that actually, the context matters so much that if you find, you know, there's one example of a particular type of diabetes that we thought had a really high, if you had that variant that you had a sort of 80, 90% chance of developing diabetes in your lifetime. And actually, now, if you look at it in big biobank populations that are doing genetic testing on a general population, rather than selecting because of signs and symptoms, then the chances are probably something like 10%. So that's just such a good example of how context matters, and where it's clearly the genetic environment and the other environmental factors that are affecting what that variant does.

And so it's, I think, really important to be aware of that. We've come across this very much in this expanding area of direct to consumer testing, where people think, if they have the test, it will tell them what they're at risk of. That's just a really good example of how if you're finding something in a different setting, it doesn't predict the same thing, yet if you act on those findings, in the usual way of chemoprevention, regular screening at an early age, or sometimes very drastic surgery of removing your breasts and your ovaries, when that risk isn't the same, that clearly has deleterious consequences that we need to think of.

Gabrielle Samuel
And I remember you telling me a story of a patient that you had about that, do you want to talk a little bit more about that?

Anneke Lucassen
Yeah, not just me, around the country, lots of people have found that now, where direct to consumer testing buys you a kit for, say, finding out your recent ancestry, you can find out how much Spanish blood you've got, and how much Neanderthal is in your DNA, which is very interesting. And I think you can buy that for somewhere between 50 and 100 pounds, or cheaper on Black Friday. And that tells you about your ancestry, but some people are then following adverts saying 'oh we'll also analyse your DNA for health consequences'. And one of the things that they then do is look for things like the *BRCA1*, *BRCA2* gene, and report variants in that.

So I had a patient who had come to me saying she wanted her breasts removed, and her ovaries removed as a preventative measure, because her direct to consumer test had shown a *BRCA* variant. And when we tried to confirm that in an NHS laboratory, it just wasn't there. First of all, we thought there'd been a sample mix up, or we thought that it might be a relative's sample. And then we realised actually that this was quite widely known in the sort of academic world, that the particular tests used to do the ancestry testing, relied on recognising common variants, multiple common variants, and they were really bad at calling rare variants, and they miscalled rare variants. So they had a false positive rate of calling

BRCA1 variants of, I think something like 85 to 90%. And that's just not what people expect. They expect the technology to be accurate. But again, the context of the technology matters. Here, we had a technology that was identifying common things, really bad at identifying, and actually miscalling rare variants rather than missing them.

Rachel Horton
It's interesting, because it sounds like context matters at so many levels. I mean, I suppose at the one level, there's the technology context, and was the technology used, good enough that you're sure that what you're talking about in the genetic code is actually really there, if you measured it in that person with the best technology? But also, in some ways, the more difficult question of if it is there, what does it mean for the clinical context of that person? And I think personalised medicine often is, in a way you think if you've got the genetic code, that's your medicine personalised, whereas almost it's like, what do you need to do around that code? To make it really clear what that means? Like, to use your first example, whether it's 'dear Rachel', or 'Oh, I just saw a deer'. Do you have any thoughts as to how we can communicate that more clearly?

Anneke Lucassen
Well, my answer to that would be that we really need to get more familiar with the amount of variation and noise in the genetic code and, and be aware that our first glimpses into it were a very sort of skewed glimpse. And that all the discourse around that of making diagnosis of rare diseases is fantastic in bringing support for genomics, and recognition that it can play an important role, but we also now need to look at all the people in, say the 100,000 Genomes Project that didn't get a diagnosis, because it's just too complex to recognise how their variation and their genetic code has an impact on their disease.

And I think if you sequence a whole genome, you're going to find about 100,000 rare variations in your genetic code. And a rare variation was in the past, something that we thought was a pretty good indication of a diagnosis. Now, we can't have 100,000 diagnoses each. That's very obvious. But I think the discourse around genetics just doesn't recognise that there's that amount of variation. And that when you start with a genetic code, it's so much harder to predict what's going to result from that genetic code than if you start with a set of signs and symptoms, and you use that genetic code to confirm a clinical diagnosis that you've made.

And I think that has really important consequences for thinking about programmes like newborn screening, because there you are endeavouring to predict what's going to happen to children, when they're just born, that have no signs or symptoms at all yet, and you're trying to say, well, your genetic code shows, you're going to develop this in the future. And for a very small proportion of children, you're going to be able to do that well. But for the vast majority, more than 99% of children that you screen like that, you're not going to be able to make any clear predictions. And I think that might run very counter to expectations. So I think we need to pay lots of attention to the conversations we have around this. And that's why I think podcasts like this are so important.

Gabrielle Samuel

I just think it's so fascinating, because when I did genetics, I was so attracted to it, because the way I was taught it was textbook, very logical, very very clear cut. And I didn't like biochemistry, or proteomics, because it was just so complicated. And as we've moved along, all I'm hearing you say is that genomics is so complicated, it isn't that clear cut. And it reminds me of some sociological work that I've been reading, about decentering to the technology? So rather than thinking about a technology, and about the ethical issues that are related to it, we need to decentre it and look behind. So deal with the patient. And take a more holistic approach, and see how the technology can work for you within that.

Anneke Lucassen
Absolutely. And that was what first appealed to me about the specialty of clinical genetics, which is a really small specialty that will probably disappear as it's sort of subsumed into medicine at large. But exactly like you, Gabby, I came from the laboratory thinking it's all about translating these genetic findings to patients so that they can have screening, treatment, et cetera, et cetera. And then I realised that the decisions around when it's right to be tested, and who wants to be tested, how it might be communicated in a family, how we might find out things that we weren't expecting- they were the interesting things, that was the stories that really fascinated me, and helping people to make sense of complex terrain. That was the interesting bit.

But I think you're absolutely right, that when we're trying to talk about genetics, in headlines and media articles, it's so tempting to go for the nice clear cut 'this is what technology can now provide you with'. But I think it's really important to shine a light on the bits behind that, or around the black box is the other analogy I sometimes use, that, you know, the technology has all been focused on getting this black box sorted. And then we need to pay much more attention to the bits around that. How can we really take meaningful consent from people? How do we ensure that when we do find a genetic risk, other people are appropriately alerted, etc.?

Rachel Horton
If you had to pick one message for people to take away from this podcast, what would it be?

Anneke Lucassen
That genetics, like many other things in life is complex. And that context is so important, we must look at the context of a genetic variation. And back to my analogy at the beginning that the word 'dear' will mean different things in different contexts. And we need to look at the sentence around the word to be able to make sense of it and it's exactly the same with a genetic variant. You need to look at the code around it but also the environment in which it arises.

Rachel Horton
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.