Conditions list – The Generation Study

The G Word transcript

**Vivienne:** Hello and welcome to the G Word. My name is Vivienne Parry and I'm Head of Public Engagement here at Genomics England. On today's episode, I'm joined by David Bick, the Principal Clinician for our Newborn Genomes Programme. Hello David, lovely to have you with us.

**David:** It's great to be here, thank you.

**Vivienne:** And loyal listeners, and I know that we've got many right across the world, if you particularly enjoy the next half hour with us, do please link, share and rate us wherever you listen to your podcast.

Now, we've got really exciting news haven't we David, because we recently announced the conditions that we'll be looking for as part of the generation study. There are hundreds and hundreds of conditions that you could look for. So why have these been chosen? David's going to take us through how they were selected and how we'll continue to review and update this list.

But before we plant into the details David, just tell us a bit more about the Generation Study and why we're doing it.

**David:** So the Generation Study, to really understand that, the first thing you need to know is that there are lots and lots of children born with genetic conditions. And it turns out that quite a number of these genetic conditions are treatable. This research study seeks to find and treat those children before they get sick.

**Vivienne:** And how many babies are we talking about?

**David:** So, in the generation study, we plan to screen 100,000 newborns. It's important to know that we don't expect huge numbers. We think that there'll be perhaps 500 or 1,000 children who will screen positive. And we can go into that in a bit more detail.

**Vivienne:** And where will these children be found. Where are you going to find all these babies?

**David:** The generation study will be going out to a number of trusts around England. What we plan to do is ask mums and dads during pregnancy, in the second trimester of pregnancy, and so nurse midwives will be introducing families to the possibility of this study.

Then, we're going to provide a lot of material to help them understand what the study is about and we're hoping that they'll sign up. Once they've agreed to join the study, we'll go at birth and take some umbilical cord blood, and because we know that the placenta and the umbilical cord are thrown away, this is no problem at all.

We'll then take those samples, we'll run DNA sequencing on them, and we will look for these treatable genetic conditions. At that point, when we find those, we will ask specialists to then contact those families with those results and bring them into clinic, where we will do follow up testing to confirm what we suspect and get treatment underway.

**Vivienne:** We should say that these trusts, and in case you're not from the UK and you're listening, trusts are hospital administrative units, I guess you could call them. But these NHS hospitals, they've all volunteered to be part of this, haven't they?

**David:** They are very excited. In fact, there's a bit of competition going on among them right now, because they all really want to get going with this study.

They all recognise that at the present time, with children with rare conditions, they'll often go many years before the condition will be established because the symptoms might be vague, or they might not be clear cut. And so for these trusts, they see this as a way to really help the health of these infants and help these families identify these children before they get sick.

There's a great deal of enthusiasm, not only among these hospital systems, these trusts, but also among the hundreds of specialists that I've spoken to who are going to become involved in this program.

**Vivienne:** Because a lot of people say, goodness me, the NHS's maternity services are overwhelmed at the moment.

Is this not going to add to their burden? But what you're saying, and what I'm getting very strongly from you, is that this is people volunteering to be part of this study.

**David:** Exactly, because these specialists, these are the ones who take care of the children with these rare conditions, they've all had the experience of going to the hospital, finding these children who are quite ill, and doing the best they can.

But what's going to happen instead is that we will find these children, and it's important to realize that the children that we identify, they are going to get sick. They're just not sick when we find them. If we can find these children that are going to get sick, we can get to them, we can treat them, and we believe this will actually relieve stress on the NHS.

Let me give you an example. There is a condition called biotinidase deficiency. These children have a genetic condition which prevents them from recycling biotin. It's a vitamin you can pick up at the health food store. And because of that, these children, they get low muscle tone, they can develop seizures, skin rash, but if you can give these children extra biotin right from birth, they'll never develop these symptoms.

Finding these children will have an immediate benefit to the family and an immediate benefit to the NHS.

**Vivienne:** Okay so let's now dive in, straight into these conditions. So, how did you decide which conditions? As I said, there were hundreds and hundreds and hundreds that you could have chosen. What was the process?

**David:** This is a fantastic question. I think to answer that, I'd like to go back just a few years. A number of years ago, Sally Davies, who is then the Chief Medical Officer of England, had the idea, would it make sense to sequence all the genes of a baby as an adjunct to the current, very successful newborn screening program to look for genetic conditions that we need to treat?

When that idea for a research study was developed, Genomics England and the NHS, as we were considering this, said, what we need is a public engagement, which is very important early in this program. And we really asked the public, what would you think of this? And what came back to us were two things.

Number 1: If we were going to do newborn screening this way, they wanted those to be treatable conditions. And they wanted particularly that those treatments really needed to be initiated in the first few years of life. They were not interested in late onset, adult-onset conditions. So from that public engagement, we brought together a group we called the Conditions Framework Workgroup.

And this workgroup involved physicians, nurse midwives, scientists, other specialists, but also the public and individuals from patient support groups, to develop principles for choosing the conditions. And then once we did that activity, we took those principles and we applied them to more than 900 different genes.

We got these from different websites such as Rxgenes.com, but other sources. Once we had sort of carefully gone through all of those conditions, using those principles, we then reached out to specialists in all the paediatric subspecialties, we spoke to immunologists and cardiologists and so forth.

But in addition, we spoke to a very special group, what are called the clinical reference groups. This won't be recognizable to [00:08:00] a lot of people, but these are specialty groups brought together by the NHS, specifically to improve patient care. By consulting with these specialists and specialty groups, we got clear direction on which conditions were highly treatable.

Additionally, we then turn to what are called commissioners. These are individuals in the NHS who are very careful to think about; “Is this treatment for this condition widely available across the NHS?” And so following all of that consultation, we then turned to NHS England and a group they brought together called the Condition Assurance Group, because they wanted to be certain of two things.

Number 1: that the treatment was widely available across England, but also number 2: that there was the clinical capacity across England to carry out such a program. That's really the process. It was really an extensive engagement.

**Vivienne:** So, what I'm hearing from that is that it wasn't just launching this whole project into the air and then just seeing how it would land. You needed to be sure every single condition that's chosen had not only something that could be done, but the NHS was able to do within its current constraints and staffing and all those kind of things.

**David:** Exactly right.

**Vivienne:** And I guess the other thing and you mentioned it before, was that you had to double check whether this condition was really what you'd found. So in other words, you do your screening, there's the particular gene, but then you do another test, not a genetic test in any way, to double check whether it's there or not.

**David:** Exactly, because we are really a partnership, this research program is partnered very closely with the regular care of children in the NHS so that the clinicians, the specialists that we contacted were very clear about what they would do and how they would go about confirming the test because they will in fact be the same individuals who will receive the results and therefore see the families.

And so they wanted to be, and they were, very comfortable that the condition needed to be treated. They were clear about the condition, but they were also clear about what testing they would do to confirm that this condition, in fact, does exist in this child.

**Vivienne:** And that's super important, because if you’re the parent of a newborn baby, and the baby is utterly gorgeous and looks incredibly healthy, and then somebody comes along and says, “actually, it's got this condition”. Your natural inclination is to say, “But look, they're perfectly fine. Are you sure?” This is why it's just so important that you have this double-checking service, as it were.

**David:** Exactly right. And I will say that before I came to join Genomics England, I helped to run a newborn screening program in the United States.

I'm very familiar with what it is like to call up a family, even a family that has a pretty good idea that they might get called. Now, I will also point out that the chance of our finding something with this is small because even though we have lots of conditions on the list, the individual conditions are quite rare.

We don't expect many tens of thousands. We only expect perhaps 500 or 1000 positives. But even for families that know that this is a possibility, and we plan to communicate very carefully with the families that join the study, it will still be a shock. I think having clinicians who are experienced with the disorders be the ones to be involved in making the initial phone calls [00:12:00] and then having those in those children and be able to get into those clinics quickly and then do confirmatory testing, will keep the amount of uncertainty time as low as possible.

And we have spoken to families as part of this program, even now, to get some ideas of what is the best way to speak to families about screen positive conditions. We routinely hear that families are concerned, but then they realize that this really is a blessing. They were able to take action before their child became ill.

Nobody wants to have a sick child. Nobody does. But on the other hand, if this is going to happen and you can do something before the child gets sick, that is wonderful.

**Vivienne:** So let's talk about some of the conditions that are on the list and the type of things that might be done to help babies. [00:13:00] You've already mentioned biotinidase deficiency.

What are some other conditions? For instance, you mentioned immune deficiencies. Are there many of those?

**David:** Yes. So, I gave an example of a relatively straightforward condition to treat. There are some conditions which will be more complicated to treat, and yet it's quite important that we find them. There are certain children who are born who don't have an immune system, or an immune system that doesn't function properly.

For those children, there are a number of medications that we can employ that can keep them healthy, keep them out of the hospital. And for some of those children, their immune system works so poorly. They're going to need what's called a bone marrow transplant.

And yes, that's a potentially dangerous procedure, but we also know that if we can carry out those bone marrow transplants while the child is healthy, then our chance of success goes up enormously. One of the great frustrations for the immunologist is a child who doesn't know, where the family are not aware that the child has an immune condition. They start to develop various infections.

They end up with some severe infection in the hospital. And now it's difficult to carry out a bone marrow transplant on a child who's so weakened.

**Vivienne:** Many people think of this about rare disease where there's going to be a drug available. I was thinking of something like spinal muscular atrophy, for example.

**David:** Yes, so that's another perfect example of a condition which only in the last few years has become treatable. Spinal muscular atrophy is a very severe neurologic condition where the nerves that control the child's muscles stop working and in fact die off. Those children after not very long have to be put on a ventilator and their life is quite shortened, but there are new treatments.

These are in fact gene therapies which can be administered, but it is critical that we get to these children very quickly after birth within, say, the first month or so because we know that we need to stop this nerve cell death that's going on before they get into real trouble.

**Vivienne:** So it's a window, I guess, that we're making.

A window in which you can, you know, do these interventions before the child gets so sick that actually a lot of the damage then becomes permanent. You were saying that you need to take action quickly. How quickly will the parents get the results?

**David:** That's a very good question. So, what we anticipate is we will be speaking to families in mid trimester, in the second trimester of pregnancy. We're going to ask them to sign up then.

We're going to take cord blood, as I had mentioned, and we plan to have a result within two weeks. Now, we recognize early in the program, it might take a bit longer than that just because it is such a complex program. But what will happen is, we will be able to identify and return results in an amount of time where we can get to these children before they get sick.

**Vivienne:** There will be people listening to this podcast who will look at the list and say “My condition is not on it. Why isn't my condition on it?” How would you answer them?

**David:** First of all, all genetic conditions are important. All genetic conditions are important. They cause suffering for the child, suffering for the parents.

They are all very difficult. In the beginning of our program, we took a very conservative approach. We said, “let's start with conditions where there's no doubt in the specialist mind as to what to do, how to follow up.” There's no doubt in the commissioner's mind that this is a treatment which is widely available across the NHS.

Once we get started, we expect to add conditions as we move along. And so, in the coming years of this program, we will be reaching out to clinicians and others to identify other conditions that make sense to add to the list. As I had said, this is really a very complex program to get started, but once we get started, we know we can add more conditions to that list.

**Vivienne:** So what's the program timetable? I guess we're going to start it later this year. In how many hospitals?

**David:** We've probably spoken to 30 of these trusts or hospital systems around the country. There are perhaps five that are going to be sort of early in the program starting in December, but we expect to add more very rapidly over the course of the following year.

We would like to see, perhaps, 20,000 children screened next year, and then 80,000 the year after that. So we need to ramp up very quickly with lots of these programs around the country, and that's why we're starting now to speak to such a large number of trusts, even though there'll be just a few.

**Vivienne:** And then what? What happens when you've got 100, 000 babies sequenced?

**David:** So the central question of this research program is, does this make sense to do long term? What would help us make that decision? Well, the most important group that we'll need to ask are these 100,000 families to say; “Was this good for you? Did this help you? Do you feel like this was an appropriate way to go forward with newborn screening?”

And I will also just say, parenthetically, that the Newborn Screening Committee of England has been deeply involved in everything we've been doing.

**Vivienne:** And of course the heel prick test is going to continue. This is not going to supplant the heel prick test.

**David:** This will never supplant the heel stick test. We're wanting to do this as an adjunct because we want to increase the number of conditions, find more treatable genetic conditions as quickly as we can. And we, and actually other groups around the world, there's probably another 15 groups like us worldwide who are carrying out the same sorts of program.

So there's, first of all, the parents, second, very importantly, are the physicians. Did they see this as valuable?

**Vivienne:** Or doctors, as we've called them.

**David:** Thank you. Do the doctors, do the specialists find that this was really helping them? help children really avoid medical conditions, really lead healthier lives?

And then very importantly, did this make economic sense? Did the cost of the program and the concern that we're going to raise with some parents, when you weigh that against the benefits of finding these children early, will that be sufficient for the NHS to make a decision to really do this long term?

And so it will take a number of years of follow up. And that's one of the things we're asking families is to stay with us for a number of years with this program.

**Vivienne:** We've asked them to keep their children's data with us because of course we absolutely have to know what happens next to those babies. And to be able to look back at their genetic data to double check what's going on.

**David:** Exactly. So we want both for children that screen positive, how did they turn out? But there will be children who will screen negative. And remember, this is a screening test. And like all screening tests, it will miss some of the children with conditions that we're looking for.

That's in the nature of screening tests. And so we're going to want to know which children did we identify where we got the right answer, and which children did this screening test not identify. And so that's a very important part of this. One of the questions that we're asked sometimes is about data access, who will be allowed to see this data beside us, making these determinations that I was mentioning.

We expect that this information will not only help us think about whether to have this be a long term program and allow the NHS to make that decision, but also to improve diagnoses and improve treatments. Now, I will just say that the data will be very carefully controlled. That we [00:22:00] take data protection to be a very serious issue and is a very high priority for us.

But what we want to see happen, is we want researchers and the pharmaceutical industry to develop drugs for conditions we can't treat. And so if we could use the information that we learn from this program, not only to help the children we can help, but just as importantly, help the children that we don't have a treatment for.

**Vivienne:** Because that's the experience of the 100,000 Genomes Project, is it was directed at people with cancer, but also people with undiagnosed rare disease. And you can have your rare disease diagnosed, but of course the question that comes next is, what's the treatment? What's the cure? And that's where you need to have the researchers come in, and that's where you need to have the pharma companies come in to develop these new treatments.

**David:** Exactly. We have a great need in genetics for more and better treatments, and researchers in universities, laboratories will not have the resources to make that happen. But our partnership, with those researchers in university, but also with pharma is what's going to allow us to make great strides.

And if you look at the treatments, for example, you had given the example of the treatment for spinal muscular atrophy. That was a wonderful partnership between academic institutions, but also the pharmaceutical industry, to make those things come about, to make those drugs get to the market, because it's a phenomenally complex process.

Given that the conditions that we're talking about are quite rare, gathering enough of those children together to try out these things is quite a challenge.

**Vivienne:** You are a gentleman, I get to say, in the prime of your life. So [00:24:00] you've been in genetics. You've lived quite a long life already.

How is this program for you in terms of its excitement? Because when I'm talking to you, I always get the kind of bubbling enthusiasm that you have..

**David:** I'm doing this because I imagine a day when all over the world we will find and treat children before they get ill. This is one of the most wonderful programs to be involved with because I can see that future.

I want there to be a healthcare system. I really want to help children stay healthy and really live their best lives. That's what's so exciting for me.

**Vivienne:** Well thank you, David. We're going to have to wrap it up there, I'm afraid. You'll find that condition list, in full, on our Genomics England website. If you'd like to hear more about all things genomic then you can subscribe to the G Word on your favourite podcast app. And if you're new to our podcast do check out our back catalogue because there's a fantastic library of fascinating genomic listening available to you.

I've been your host, Vivian Parry. This podcast was edited by Mark Kendrick at Ventoux Digital and produced by Naimah Callachand. Very good to have had you with us. Bye for now.