**The G Word Transcript**

**The last 10 years and the next...**

**Vivienne:** Hello, I'm Vivienne Parry, Head of Public Engagement at Genomics England, hosting today's episode of The G Word. We're trying to bring the benefits of genomic medicine to everyone. And that involves accelerating genomic research and also working with the NHS to bring genomics into the heart of healthcare. Genomics is a word that can trigger really strong responses, fear, anger, even. There's a lot of information out there, a lot of myths t0o, and it's not all accessible to non-experts. So we want to talk more about this word, The G Word: genomics. That's what this podcast is about. Welcome to The G Word.

Today, we're celebrating an anniversary. It's 10 years since the 100,000 Genomes Project was announced by Prime Minister David Cameron in the heady days of celebration and optimism that surrounded the 2012 London Olympics. Genomics England was formally set up the following year to deliver this landmark project. I'm joined today by two people who played a critical role in those years to reflect on the past and the future. With me is Jillian Hastings Ward, chair and founding member of the participant panel, representing the interests of Genomics England participants and decisions about how their sequence genomes and health data are used by Genomics England. And by Professor Sir Mark Caulfield, who's Professor of Clinical Pharmacology at the William Harvey Research Institute at Queen Mary University of London (QMUL). He was in charge of the scientific strategy, oversight and delivery of the 100,000 Genomes Project. Hello, to both of you. So, I want to know from both of you, when did you first hear that phrase, the 100,000 Genomes Project? Let's start with you, Mark.

**Mark:** So, I first heard that phrase, Viv, when Dame Sally Davis, the then Chief Medical Officer, telephoned me at about 5:30 on a Friday evening, and asked me whether I would consider being the Chief Scientist. And she said, it's called the 100,000 Genomes Project, and we're forming a company called Genomics England, which will be owned by the Department of Health and Social Care. And so I said, Tell me a little bit more, and she told me that it will be focused on rare disease, cancer and infection. And I said, I will think about it over the weekend, have a chat with my wife, which I did. And on Monday, I accepted.

**Vivienne:** At that point, it should be said that nobody had ever sequenced 100,000 genomes before. So, it was really a bit of an ask.

**Mark:** It was, indeed. It was, most assuredly. There are both upsides and downsides of people never having done something, you can shape the landscape, you're not having to fit into someone else's pathway, or assume that their approach is the right one. But it also is quite nerve racking. So, one of the first things we did, Viv, was to visit the major centres in the UK and in America and across the world, where we had heard that they were doing whole genome sequencing. We discovered that there was no clear consensus on how to do this. And indeed, the pipelines that would be necessary didn't really exist, but that there was a technology that could allow you to sequence genomes at scale. And, in response to David Cameron's announcement, that company, who successfully tendered for the contract for the 100,000 Genomes Project, called Illumina, actually had the technology developed at the scale that was needed. But, of course, then the analysis all the rest of it downstream, that wasn't there.

**Vivienne:** So, the first thing that we should say is that we held a bake-off as I recall, so all these companies all over the world were sent the same genome, and they all came back, as I remember with different answers. And that was quite difficult. And Illumina was the one that had the technology that seemed to be able to deliver. And perhaps we should also say that, at this point in time, if you had a rare condition that was undiagnosed, what happened was that people had to kind of guess where in the genome to look or what gene to look for, and it took a very long time, perhaps two years, and still they might come back with nothing. And the whole genome, why people had started to get excited about the whole genome was because right from the Human Genome Project onwards, people have realised that there was an awful lot of DNA that was doing something, but we weren't sure what, and actually, as we now know, is incredibly important in telling particular genes when to switch on, turn off, do different things at the wrong times, all those kinds of things. So whole genome sequencing was where it was at. And then, what did we do? Just explain, Mark, what we were doing to try and speed this process up, this pipeline, as we called it.

**Mark:** I think the first thing to say, Viv, is that for this to really succeed, we had to anchor it in the National Health Service. So, we work with National Health Service England formed genomic medicine centres, they've now essentially been converted into genomic lab hubs and Genomic Medicine Service alliances, but there were 13 of those of peak. What that meant was, at the height of the project in 2017 and 2018, about 5,000 frontline NHS staff touched the project at some point during their working week. And this is really important because if you want to accelerate something into healthcare, you need the health service to embrace and champion it. And we know from other studies, for example, it can take a clinical trial to be adopted into the health system between nine and sixteen years. We didn't want that in the 100,000 Genomes Project, so we got the NHS involved from the outset. And then we built pipelines, these were initially a bit slow and it took a long time to return results, but gradually, they've improved in their fidelity and output. There's still a work in progress, some 10 years after David Cameron's announcement, though.

**Vivienne:** And were there moments when you thought, this is complete madness, this is never going to work?

**Mark:** There were a number of times where members of the clinical genetics or cancer community would huddle around me at meetings and tell me, You do realise this is completely insane. If you just gave us all the money, we would do this for you but with a much simpler test called exomes and panels. So, I said to them, I can remember one meeting in Liverpool where I was surrounded by quite a number of clinical geneticists who were very adamant that I was in urgent need of help. And I said to them, very simply, I understand where you're coming from. But this is your moment. This is a service which has not had the investment it needs; this is your chance. This is the moment to change this for everyone in the country and to get the equity of access to genomic testing, because it wasn't like that before the 100,000 Genomes Project. And, I said, the other possibility is that I go back to London, and John Chisholm and I, who I worked with on this project, go and see the Prime Minister and tell him that you're not up for it. But if I do that, then the money will go to something else. And there will be no investment in this for some time to come. Because politically, returning to it if we don't succeed, is not going to happen for years. And so, we had an absolute duty to make this work for patients, for the future of the health system, and to get the right service for the right patient, as far as we could through that project. But I did face suggestions that I needed my head examined. And, actually, one other thing, you asked me whether over thought I needed my head examined, there were times in the room I'm sitting in surrounded by the team, and sometimes amongst the participant panel, I might have uttered the words, we just need to hold our nerve here. Because sometimes it was really challenging and very difficult. And when you particularly heard the stories of people affected by rare disease or suffering cancer, it would be very difficult for your heart not to go out to them. And I still hear some of those people speaking to me, usually by dreams these days, but occasionally in person.

**Vivienne:** Jillian, tell me, when did you first hear this phrase 100,000 Genomes Project?

**Jillian:** Well, I first heard the 100,000 Genomes Project mentioned in September 2015. My son, Sam, was about 18 months old at that point, and from about three months of his life onwards, we realised that he had some medical problems and nobody could really tell us what the root of those was. So initially, he presented with a visual problem, which we were able to address quite quickly with the ophthalmology team, but there wasn't any understanding of what had caused that initial trouble. And by the time he was a year old he was given to by the paediatricians to have a developmental delay, which was causing them great concern, because he wasn't meeting any of the standard developmental milestones for a child of his age. So, they ran all the tests that were at that time available in mainstream NHS Care, and they still drew a blank. And, obviously, it wasn't that there was nothing wrong with him, but there was certainly no understanding at the time of what the driver was. So, we were referred to the 100,000 Genomes Project and offered the opportunity to sign up for it as a family to find out whether Mark and his colleagues would be able to tell us what the underlying genetic cause of Sam's issues was. As you've already alluded to, that the pipeline was longer than anyone anticipated initially. It took a couple of years, but we were able to get a result back for him. And thanks to the 100,000 Genomes Project, Sam was the first person diagnosed in the mainstream NHS in England with a GRIN1 genetic disorder. And that's been wonderful for us to know as a family, who else we can find around the world with the same condition, but also, I'm really delighted that GRIN1 genes were added to the gene panels that the teams were using to diagnose more people as a consequence directly of the 100,000 Genomes Project. And that's meant that we've been able to find a lot more since then, who shared the same condition. And, hopefully, in due course, we'll have enough people that we can get more researchers interested and make real progress together.

**Vivienne:** And then we had the great fortune that you joined the participant panel. Just tell me very briefly about that. Because what were your hopes for that in the beginning?

**Jillian:** Blame me? Well, yes, it very early doors, I think we’d left our email address with somebody at St. George's Hospital and we signed up for the 100,000 Genomes Project, and said, Yes, we would be interested in hearing more about the project as it develops. And so, a few months later, an email arrived that said, Hello, we are working with Genomics England who are setting up a participant panel, and they're looking for people who would be interested in joining the panel, and we were to submit a couple of paragraphs of interest and explain what you'd like to bring to the party as it were and what you'd like to get out of it. At that point, I was very clear that although as a family we may never get answers for ourselves, the whole purpose of this project was to learn more about what makes us human, altogether. And that sounded like a really interesting thing to be part of. As I, at that point, still on an extended period of leave from my job in the civil service, because of looking after Sam, and about to leave altogether, I was looking for something else other than childcare to do with my time. And I thought this would be a really interesting way to use the skills I had in a productive way. So, I put my email in and two days later, I got a phone call from you, Viv, saying hello, we'd be interested in talking some more about your drivers and what you'd like to do here. I remember, sort of scrambling to think of something coherent at the time, but then was deleted at the end of the call, when you said, well, first meeting is next Tuesday, can you come please? I was astonished, but really pleased. And so that was that. So, joined a group of other participant representatives who I think have been recruited in similar ways from all over the country around an extremely shiny table in one of Mark's offices there at Queen Mary University of London. And that was the start of our story.

**Vivienne:** And, didn't we luck out getting Jillian Hastings Ward to be involved in our participant panel? Because I set up the participant panel originally. In fact, I was employee number three, it says on my pay slip at Genomics England, and the participant panel has done more than ever I could have expected, it's been completely wonderful. But I wondered, what has been the highlight for each of you over the last 10 years? I mean, there’ve been some low times, as Mark alluded to. But what have been the highlights? Mark, what's a highlight for you?

**Mark:** I think one of the highlights was completing the 100,000 Genomes Project, and then reflecting on what we've done, because between the 7th of February 2018 and the 2nd of December, which was a Sunday, at 2:40am, we sequenced 52,000 whole genomes. And I don't think anyone has done that many in that space of time, before. They may have done it afterwards with big chords. But sequencing that and knowing that we had actually delivered the milestone and calling people up, like the participants panel and assembling the team and saying – who actually thought we were getting them into a room to tell them that their jobs were over – but in fact, actually, it was to say that they'd actually done it and hit the milestone.

**Vivienne:** That was, to interrupt a moment, we had completed the recruitment and we actually sequenced 100,000. But, of course, then, the work began and to try and bring interpretation and analysis to all those who’d submitted their genomes.

**Mark:** And that inevitably took a lot longer. For quite a number of people, they still don't have an answer. But, certainly, even though I’ve left Genomics England now, my team and I won't give up trying to find answers for people, irrespective of how long it takes. But I also think the next most wonderful thing for me was the bringing live of a genomic medicine service, because that wasn't necessarily given to us, as you'll remember, Viv. It wasn't one of the four axioms, which were to do research ethically and transparently to deliver the programme, to involve participants, and to have commercial interactions. It wasn't given to us originally to develop a generic medicine service. But fortunately, the partnership with Jillian and the participant panel, the partnership with the NHS, the partnership with researchers around the world, and the work of everyone, brought together a desire that this should not end. And that achieved something more than any of us could have hoped for.

**Vivienne:** Jillian, what about you, what are the highlights?

**Jillian:** In terms of what the panel has achieved so far, I think one of our highlights has been something that we almost have become so used to now it's almost unremarked upon, but at the beginning was outstanding – that we had the senior leadership of this project coming to talk to us around the same table, and we can throw questions at them, some politer than others, and find out from them more about what was going on and what they were going to be able to deliver for us and the communities that we were there to represent. And that level of collaboration and cross questioning between project leadership in a thing like this, and people whose details actually are stored in that project, seem to be something quite new and something which we feel has been really important and a real key feature of the work that Genomics England has done and continues to do, in having those ongoing conversations on a regular basis, in a spirit of openness and collaboration, rather than necessarily just having a news bulletin downloaded upon us and then leaving again, you know. So, for me, that's the heart of what I'm happiest about so far. But then, I think, on other aspects of this, personally it's been wonderful to be able to go out and meet researchers and clinicians all over the world, actually, thanks to this programme, who are doing amazing things with genomic data. And learning from them about just, you know, getting a hint of what the science is able to do now is mind blowing. As a non-scientist myself, it's just outstanding. But it's really exciting that, over the next 10 years or so, we could still be leaping forward and diagnosing and then hopefully building communities with a whole lot more patients out there. And that's fabulous. I'm sorry, I can go on all afternoon. But I think another of the important ones has been to be part of the Access Review Committee, hearing from the researchers who are applying for permission to come and use the data which is held in the National Genomic Research Library and reading their applications. And just thinking, yes, I know people who have the condition that these guys are interested in and wouldn't this be fantastic, if they can find more answers for them. That's been a real honour and a privilege to be part of.

**Vivienne:** And that's been a key role, hasn't it, of the participant panel, that you have DNA in the data set. So, you have, literally, skin in the game? So, it's your interests that you're considering and those of the other participants when you're interrogating people who want to come and use the data?

**Jillian:** Yes, that's right. And to that end, I'm still keenly aware that, although we've now got a wonderful number of people who've got a result from this programme, there's still more waiting and hoping that one day they'll find an answer through this as well. So, we on the participant panel are driven to keep asking, what more can you do to help them and look for more answers? And that's something which we'll continue to do in perpetuity.

**Vivienne:** So, Mark, at the beginning the 100,000 Genomes Project was just that, a project. But now Genomics England is a different kind of organisation. How is it different now from when it was, then?

**Mark:** The mission given to us was given jointly to NHS England and to Genomics England, there was a shared mission. Now, Genomics England has a number of specific programmes that it’s going to do. One particular one that I'm very delighted that they got funded was one that Jillian and I were involved in structuring on with you, Viv, actually, on a genetic analysis in children group. And this is about examining the role of whole genome sequencing in the newborn period. And asking the question, can we, if we use that instead of our normal heel prick test, which measures nine things, can we find treatable genetic disorders that we could intervene, maybe reduced disability, possibly avoid harm all together? And we found that, by approximately 1 in 190 live births in the UK will be affected. That's about 10 children born every day. And the about 600 conditions or so may have a treatment. Often this is a dietary change, sometimes it's a vitamin, sometimes it's a medicine, and occasionally, it's a transplant. But essentially, there is a possibility to intervene before the child's fifth birthday. So, this programme is being piloted now and in the NHS. Hopefully next year, we'll start to establish a hundred thousand person birth cohort that will allow us to understand the role of genomics in very early life to actually possibly prevent or even just make less prominent, the disability from rare risease, which is profound. And what if we can change that?

**Vivienne:** Back then, there were about a dozen of us squashed in a disused lab at QMUL. Now, Genomics England is coming up to – in fact, may have exceeded now - 500 people and will shortly be moving to a brand new office in Canary Wharf. So, it's expanded enormously. And, now, sequencing 100,000 genomes is commonplace; people are able to do it. And, indeed, very, very quickly, and the technology has come on in leaps and bounds. And, I know, Mark, that you see all of these new technologies and discoveries that are pushing forwards genomics, what do you think we'll be seeing in the next 10 years from genomics?

**Mark:** So, I think we will begin to apply not just the whole genome, but other measurements of other components of our body proteins, metabolites, and using that to get a focus on the bit of the genetic code that is causing a rare disease. So, we’ll unlock more rare disease diagnoses. I think we will employ genomic testing, but probably also other types of tests, other biomarkers, possibly looking at the message that transmits the information from the genome to make the protein that's called RNA. And we may use that alongside the DNA and other measurements to improve cancer care. I think we will move the chain of care earlier in cancer, because using other types of genomic or omic tests, we'll be able to detect cancer earlier and therefore we will be able to intervene, not at a stage when the cancer is unlikely to be cured, or already incurable, but at the stage where it can be cured. So, I would hope that, for one in two of us who will suffer cancer in the future, we will be able to detect it before it's reached outside the organ of origin, and then we may be able to in effect cure.

And I think the other thing I expect is, as we showed in the COVID project, of which you inspired by the way on an email on a Sunday night, asking me, What are you doing about COVID? And from that, your email, we constructed a programme with the *genetics and mortality and critical care* study that has sequenced about 14,000 patients who sadly went to ITU and fourteen and a half thousand people who were exposed to COVID but had mild and asymptomatic infection. And just with the first 7,400, we have detected 23 regions of your and mine genetic code that makes you more susceptible to have severe COVID, and one of those has provided information that encouraged the recovery trial to test baricitinib. In February 2022, they announced the baricitinib reduced mortality and length of stay in ICU over and above other medicines, steroids and tocilizumab. that we were already giving to severely ill people. So, I suspect we will see a broadening of the use of genomics, but we will also see other omics, proteins, RNA, metabolites being measured. I think we will see the gain of opportunity for patients to detect cancer earlier, and maybe even other diseases. And, also, I think the final thing is that now, in some disorders, by actually – for example, in arthritis, taking a biopsy of the joint lining of this joint here – I can actually shine a Doppler field on the lining of the joint, see which bits are inflamed, biopsy that, and then I can look to see what the makeup of that lining is and what the molecular signature is. And I can then choose your treatment for rheumatoid arthritis. So, I think there are many ways that this will expand beyond the original confines. Of course, that's talking about the human. But we saw extraordinary things in COVID with sequencing viruses, too.

**Vivienne:** It's astonishing. And I remember to this day, a bit, when I was a correspondent for the BBC, talking about the first draft of the Human Genome Project and saying, as we all did, of course, that it would be useful in medicine by Tuesday, teatime. It's taken much longer than that, but it is absolutely astonishing. Jillian, what are you hoping for in the future from genetics?

**Jillian:** I think the first thing is that I hope that lots of other families in the future are able to benefit faster from genetic diagnoses. Whole Genome Sequencing does hold the potential for really getting to the heart of what's causing different people's troubles earlier. And that means that families will have less time in that diagnostic odyssey that we've heard so much about, and hopefully be able to access treatments and that community, together, faster than we did. That would be the first hope, really. I know that we're making great strides in that direction already, but there's still more to do there. And I think, secondly, I would really hope that now that we have a way of getting diagnoses faster, that we can build communities of participants and patients affected by the same condition and introduce them more early on to researchers and clinicians who will have an interest in that specific condition, and the skills to go about helping that community answer some of those questions faster. I know there are some excellent patient organisations and support groups out there already trying to work on this. But there's so many thousands of different rare genes out there, it would be great if we can see more effort and more resource put into even more of those teams as we move forward.

I think, also, the collaborative model of working that I think the participant panel have been pushing forward with Genomics England, and recently wrote about in the European Journal of Human Genetics, I just have to get that plug in there. And I think that there's sort of lessons that we have learned so far, about the essential ingredients for success when you're talking about collaborating with patient communities and groups of researchers. And hopefully those things will become commonplace across the genomics landscape and beyond.

**Vivienne:** Well, it's been an extraordinary decade. I've loved every minute of it. I've been passionate about genomics, literally since I was first introduced to DNA as a school child. And I was fascinated by it – and look at where it has got us now. It's just extraordinary. Thank you to both. It's been such a pleasure working with you both over this last decade. And thanks to you, too, for listening to this discussion about The G Word and for joining us on this journey to highlight and debate the implications of genomics as it comes to the mainstream of healthcare and society. Remember to subscribe to The G Word on Apple podcast, Spotify, or wherever you listen. If you have views on these topics, or if you have a suggestion for someone we should interview, then do write to us at podcast@genomicsengland.co.uk. And do remember that if you've enjoyed listening, that giving us a five star review really helps other people find out about the series. And I'd appreciate it very much if you would do that. I've been Vivienne Parry, see you on the next episode of The G Word. Bye for now.