**The G word transcript**

**Can whole genome sequencing support provision of tailored care for patients with cancer?**

**Naimah: Welcome to the G Word. What does it mean if we can test for inherited genes?**

Nirupa: It can influence how their cancer is treated. So it means that there may be certain types of therapy that are available if they have a specific inherited cancer gene, number one. It also can impact in terms of preventing further or other cancers related to those genes, and it may impact the type of surgery they have, and also the type of overall cancer treatment. And then finally, if they have got an inherited cancer, then, as I mentioned before, it may impact in terms of testing and screening for their family members.

**Naimah: I'm your host Naimah: Callachand. Today, I'm delighted to be joined by Dr Nirupa Murugaesu, who's a consultant in medical oncology at Guy's and St Thomas' NHS Foundation Trust, and the principal clinician for cancer genomics and clinical studies here at Genomics England. And Professor Sir Mark Caufield, who's a Professor of Clinical Pharmacology at Queen Mary University of London, and who previously served as chief scientist for Genomics England and was instrumental in the delivery of the 100,000 genomes project. Today, Mark and Nirupa are going to discuss key findings from a recent paper that's just been published in Nature. If you enjoy today's podcast, we'd really love your support. Please like, share and rate us on wherever you listen to your podcasts. Now, let's get into the interview. So first of all, Mark, I wondered if you could give me a bit of background on the 100,000 genomes project?**

Mark: So the 100,000 genomes project started in July 2013 following an announcement by the then prime minister, David Cameron, that the UK would be the first health system in the world to sequence 100,000 whole genomes, which is as much as you and I can read of the genetic code. In the case of cancer, which we focused on here, in cancer we were sequencing sections of the tumour and comparing them to DNA inherited from your mum and dad, and that comparison allows us to work out what is driving the cancer, what may be affecting its potential for treatment and how we might choose treatments for patients. So this is a real opportunity to create precision cancer care.

**Naimah: And Nirupa, can you tell me what the 100,000 genomes project meant for these patients with cancer?**

Nirupa: I think, firstly, we're very grateful for all of the participants in the programme, because what it's allowed us to do is to look at the data as a whole, and having all of that sequencing data alongside clinical information has been incredibly valuable, it has also developed the infrastructure for testing. And really I think for patients with cancer, they participated in this programme as a research project, and unusually for a research project these results were returned back to treating clinicians to clinical teams, if there may have been a result that would impact or change their management. But I think, importantly, what it enabled is the implementation of standardised cancer testing in the NHS, and really enabling that for a wider range of patients, not just those that participated in the project. And because of patients participating, this then allowed all of the data to be stored in a single place, and this has been incredibly valuable for clinical academics and researchers.

**Naimah: And can I ask what specific types of cancer that were looked at in 100,000 genomes project?**

Nirupa: Again, the project was set up such that we allowed a number of different types of cancers to be sequenced and, therefore, very permissible, because we also wanted to ensure that some of the less common and rarer cancers were also sequenced and, as you would expect, more of the common cancers as well. In addition, I think the opportunity to sequence paediatric cancers, as well as haematological malignancies, or blood cancers, was also key as part of the cancer programme. Here, we focus on the solid cancers, but obviously there was a much wider range of cancers that were sequenced.

**Naimah: And next, can we move on to talk about the findings of the study?**

Nirupa: I think, firstly, by undertaking sort of a pan-cancer analysis, it really gave us an overview of the number of target and genes that were found to be actionable. And what I mean by that is that they have a, well, clinically relevant, and we can see that in certain cancer types, such as in brain cancers, in colon cancers, lung cancers, there were within the genome sequence more than 50% of these cancers had something that was what we would call actionable. So there was a mutation in a gene for which this would influence treatment. And as we started to look more across the entire cohort of patients, you can really get an idea of the fact that the more that we sequence, and the more comprehensive the testing is, the number of different types of mutations that we were able to discover.

**Naimah: And when you mentioned that these findings were actionable, what does that mean?**

Nirupa: So what that means is that has an impact in how the patient will be managed and treated. It may influence, firstly, the type of surgery they have, it may influence the type of cancer treatment that they receive. And all of this, I suppose, comes back to the point that Mark mentioned, of precision oncology, so we more precisely treat patients based on their individual cancers.

**Naimah: And could you give me some examples of maybe some of these genes that were found in the study that were actionable?**

R1 Yes, so the types of genes also matter, or the type of mutations. So some of them were in known cancer genes, and if you have, for example, a mutation in lung cancer, in a gene called the EGFR gene, we know that there are cancer therapies that can be provided that target specifically this mutation. So that's one example, and this is quite well characterised and understood in oncology care. But what we were also able to do with whole genome sequencing, is identify different types of mutations that are harder to characterise routinely. And these are often included things that we call pan-genomic markers, where we can see what the mutational landscape is of the cancer, the different patterns of mutations can be gleaned from this, and often this can then give you an idea of the underlying biology of the cancer. But importantly, in certain types of cancers, such as high grade serious ovarian cancer, it highlights which patients may have a particular marker that means they may or may not benefit from a particular type of therapy. So in this particular case, the class of therapy is called PARP inhibitors.

**Naimah: And how did the study compare to other similar stuff studies in the genomics area?**

Nirupa: That's a really good question, and I think we looked at this from other large sequencing endeavours, such as the ICGC, TCGA, so these are big studies where have been whole genomes sequencing. Also within the Hartwig Institute in the Netherlands, they've also undertaken whole genome sequencing for cancer patients. And what we were able to identify is that the patterns of mutations were as expected, we found, you know, a lot of similarities. I think the difference, the main difference is not just identifying the type of mutations across the different cancers. But the fact that we were then able to look at the longitudinal outcome, and correlate some of these genomic markers with outcomes related to both therapies, as well as survival impact of having certain mutations in terms of prognosis.

**Naimah: Mark, do you have something you'd like to add there as well?**

Mark: Yeah. So one of the things that we did in the 100,000 genomes project, was to evaluate the best way of measuring the whole of your or my genetic code. And we discovered that very early on that if you expose the tumour to a preservative, which is called formalin which keeps the tumour preserved, that actually you could get quite a number of misleading findings. And so to address that, the distinctiveness from former programmes, such as Nirupa mentioned, like the Cancer Genome Atlas, is that all of the tumours that we studied in this paper were actually produced under fresh tissue conditions, and have not been exposed to a preservative. And that means that what we have is a really accurate reflection of the variation within the tumours. And the other thing about this particular resource is it's the biggest resource. We were able to look at 13,000 people with solid tumours, but we also had blood cancers and other cancers which also feature of this paper.

And a further remarkable thing about this is early on, Nirupa and the team and I decided that we would longitudinally life-course follow the patients and by accruing data from multiple sources in the health system. So, every attendance at the hospital, what chemotherapy was had, we've been able in this paper to recapitulate signatures that clearly show that certain mutations are harmful. And many of the findings that we've made are absolutely, if you look at the survival of patients particularly, you can see almost identical patterns to those in clinical trials. What this means is that by the really rich data set which is now many billions of clinical data points on these patients, we can actually look for long-term signals of benefit and harm that perhaps would not be detected by a clinical trial that might last for six months or a year. So this is a really valuable resource, and the really great thing is we can use what's called real-world data, which is where we take routine health data, and we can recapitulate the findings from tightly controlled clinical trials. And I think that's quite an important finding.

**Naimah: That kind of brings me onto the next question, Mark, where I want to talk about the value and benefit of genomics sequencing for cancer patients. I wondered if you could expand?**

Mark: Well, what we know from one of the genomics medicine centres which were regional hubs, is that they use the information that we return, that Nirupa outlined earlier in a report, for 25% of their patients. Which means that they concluded having evaluated that as the clinical team locally, that there was something the patients could benefit from. Now, what we think is this makes the case for certain cancers being part of the national genomics test directory whole genome sequencing, but it's still the case that the majority of testing for cancer is now very large focused panels that are focused on specific gene features. But in some measure, this work is also able to reassure us that those gene features are the right ones to focus on, so this work has been very useful in that respect, even where the NHS today cannot make the financial or clinical case for using whole genomes in specific cancers. So I think the programme's made a massive difference.

The biggest thing it's done for patients, which Nirupa was very actively involved in, is it's allowed us to create a national genomics test directory. So when we started this, cancer genomic testing was completely random and would vary from one postcode to another, one hospital to another. And what Nirupa and the cancer team created is a national cancer genomic test directory, which now means that standard of care, that's the basis for reimbursement, and it's available across the landscape of 56 million people. And given that one in two of us will have cancer, this is a massive advance.

**Naimah: Yeah, you've really highlighted the impact of having access to such a large database. And I just wanted to ask as well, what are the challenges associated with implementing routine whole genome sequencing into clinical care?**

Nirupa: I think as with all of these things when implementing something new within a healthcare system, it requires a level of education, upskilling and also, as Mark has touched on, how we handle the tumour tissue, so that it's handled in a genomic-friendly way to enable the best results if you like, because we want to ensure that their DNA is not damaged so that we can get accurate read-outs on the results. So there are challenges and there is also cost implications in weighing up the pros and cons. And I think what we were able to show, and by undertaking this sort of pan-cancer analysis, is where there are those cancer type where there is a real need for whole genome sequencing, or where it can be justified, because there are a number of different types of mutations both within the tumour. And also from a blood sample that is also taken, so this is your constitutional DNA, so this is if there is a risk of an inherited cancer. So we are able to pull together all of this information, and obviously that's important, not just for the patient, and their management, but also for family members. So I think really what this shows is that where you have to identify many of these different types of mutations, whole genome sequencing enables that through a single test.

**Naimah: Mark, would you like to add something else there?**

Mark: One thing I think which Nirupa's very much part of, is the distinctiveness of the Genomics England approach has been to involve the NHS at every stage. Now, what that means is we estimate that at the peak of the 100,000 genomes project, 5,000 frontline NHS staff touched the project at some point in their working week. What that does mean is that Nirupa and the cancer team could realign the cancer tissue handling pathways. But it also meant that we were able to upskill the frontline workforce, such that at the end of the programme, when we produced a genomic test directory, they were really up for it because they did not want all the hard work they'd put in to stop. And so what we've done is produce the national test directory within five years of starting, that wasn't a deliverable for the project, but it was nonetheless obvious to all of us working in it, including NHS England, that there needed to be service transformation, and we've managed to effect it.

Now, if you look at other settings where perhaps Nirupa and I might have a research team, we might do it some distance from the health system, it would be in the health system, but not with the health system, then it takes between nine and 16 years to get these things into clinical practice. And that was achieved here in five years. So there is a lesson from this, the cancer programme particularly, because the cancer programme testing was very limited when we started, but you can take an entire workforce on a journey and leave them with the legacy of an entirely transformed system for patients. And thankfully because we got, Nirupa and I, the NHS to agree to reimburse for the testing directory being used, we have eliminated a lot of randomness that was in the system previously. So it's quite an important advance in that respect, and it really does show in the beautiful work that Nirupa was describing exactly how you can use this information to change an entire system. And the NHS is not the easiest system to change in the world.

**Naimah: Nirupa, you mentioned the findings show that there was potentially inherited genes. Can you tell me what does that really mean for patients, if we're able to diagnose these inherited genes sooner in life?**

Nirupa: It can influence how their cancer is treated, so it means that there may be certain types of therapy that are available if they have a specific inherited cancer gene, number one. It also, can impact in terms of preventing further or other cancers related to those genes, and it may impact the type of surgery they have, and also the type of overall cancer treatment. And then, finally, if they have got an inherited cancer, then, as I mentioned before, it may impact in terms of testing and screening for their family members. And that's really key as well, because this means that their cancer can be diagnosed, if they do develop a cancer, because they're being monitored, because it's much more targeted, their approach in terms of screening for a particular type of cancer, they can potentially have their cancer treated much earlier. Or even better, before it becomes what we call an invasive cancer but at the pre-cancerous stage. So this has huge implications, and what we're finding actually with more and more testing – and this is not just... our study was consistent with other studies that have been published – is that when you undertake more routine testing, then you are able to identify this. It is not common amongst the population, but in those patients where it is relevant, it really can impact their care.

**Naimah: Mark, do you have something to add there?**

Mark: Well, I think Nirupa's just highlighted a really important point. So to bring that into a little bit more ways of which people listening to this can relate to it, we have a family where there was a women who had no family history of breast cancer, she developed breast cancer, and in the tumour we found that she had a BRCA 2 mutation. We also found that she'd probably acquired that or inherited it, we don't know. That for her meant that she could enter the Olympia trial, which was running at the time, which Nirupa alluded to earlier, was a study of PARP inhibitors. But without that genetic makeup she'd never have got into that trial, and she probably wouldn't have been tested for BRCA at that time in the NHS because she had no family history, I think that's probably right, Nirupa.

And then there was a family-wide consequence for that, because she had a brother and son, and she also had a daughter, and the daughter was under 30 at the time and underwent BRCA testing and was BRCA 2 positive. But she has the opportunity now to enter intensive breast screening from the age of 30, and that's what's happened. And her brother, and this is the lady who had the breast cancer, her brother and her son may be at risk of prostate cancer, so they can consider testing. So Nirupa makes a really important point, that when people have inherited a previous disposition to cancer, that can have a family-wide impact. And one test in one family member can open the doors to opportunity for others to understand their risk and to be screened more actively and intensively, hopefully with meaning that if they do develop cancer it will be detected very early, or maybe we can just prevent it altogether.

**Naimah: Thanks, Mark, a really good example of the impact that this testing has had. I just wanted to touch back on your point, Mark, that you'd made about real-world data. And I wondered actually, Nirupa, if you could kind of explain to me why it's important to link real-world data to the genomic data?**

Nirupa: Yeah. So I think the work we've done here really does emphasise this, because when we refer to real-world data, we're talking about different types of healthcare data across the population. And we had the opportunity to link the genomic data to a number of key data sets that are curated by the cancer registry, the national cancer registry database. And this includes things like all of the population base systemic anti-cancer therapy, so we know that for each of the participants the type of cancer therapy they receive, and also, as Mark has mentioned previously, the hospital episode. So when patients needed to be... we can see their data in terms of admissions, investigations, and so on. And these are really valuable data points, because you get an indication of when patients may have had to then have further testing, or if there is a risk of recurrence and importantly survival data, because a lot of this has been, in terms of a lot of the cancer genes have been well characterised and tested.

But what we were able to do here at a pan-cancer level on a large cohort of patients over a period of time, is to look at if you had a particular mutation, what is the impact of that in terms of outcome for a particular cancer type, and even more broadly, on a pan-cancer level? And actually, as this type of data accumulates, I think the real value, and if you've got a larger number, you know, what is the value for patients who've participated in this programme going forwards, is that as that data accumulates and the numbers go up, we are able to then ask more detailed questions. What is the impact of a particular type of mutation, or a particular type of variant within a gene? And, importantly, what happens when you get a different sequence or a combination of genes? And how does that impact? And this, I feel, is the way that we are going to move more towards precision oncology, because we are beginning to understand the cancer in more detail, how it is going to behave, and then try and tailor therapies accordingly.

**Naimah: And Nirupa, I wondered if you could tell me as well if the findings from this study have benefited directly those patients that were involved in the 100,000 genome project?**

Nirupa: It has benefited some of the patients because, as Mark has mentioned, there are findings that we weren't expecting in terms of potentially inherited cancers and, therefore, this has had implications. The way that the project was set up from the outset, is that we were obtaining tumour samples from patients who had not received any previous cancer therapy. And what this meant is that this was predominantly in patients, so they were treatment naïve with early stage disease that were having surgery to treat their cancers. And as such, what we know is that fortunately most of those patients did not require further therapy, because their cancers were treated successfully with surgery. But what it did tell us, and what it's really highlighted, is the number of important genes that were identified. And so whilst it may not have impacted patients directly, it's enabled us to study the biology of the different types of cancers, how they behave, along with the longitudinal clinical data.

But what it is doing now, is through the national test directory through the genomic medicine service, is enabling testing for patients that unfortunately now have more advanced cancers, but where these genomic findings are more likely to impact directly in terms of therapy. So, for instance, as we've mentioned, the ability to have whole genome sequencing for patients with high grade serious ovarian cancers, means that this will impact the type of treatment they have. And this also was the tumour type where we found the highest number of patients with BRCA mutations, so we have a potential inherited risk of a cancer as well. So now what we have learnt and the infrastructure that we have developed has enabled this to have a real impact, not just for patients in the project now, but wider within the NHS.

**Naimah: Mark, would you like to add something else there?**

Mark: I think Nirupa's encapsulated it very well. There were a range of benefits, so I mentioned earlier that in one centre 25% we have evidence got a benefit for their treatment for their cancer in some way shape or form. So an example to what there might be is that some people got a medicine they wouldn't have received from routine care, and that might have been licensed for the treatment of that tumour, but it wouldn't have been the first line treatment choice. Some people got medicines that they wouldn't have got because we don't normally associate using that medicine with that cancer, but they had a signature that showed that they were very likely to benefit. Quite high numbers got an opportunity to get into a clinical trial, which is really important because if you look, over 50% of global oncology trials now have some kind of biomarker or diagnostic, or something like this alongside, what better than to have a comprehensive inventory of the variants and the cancer, and to be able over time to use that library to understand better the treatment course of that patient. And that's what I think a whole genome adds, rather than the single, look at a single part of the genetic makeup.

And then finally, some had lots of mutations, really high rates of mutations, and maybe they should receive specific advance therapies, like immunotherapies. Or alternatively, they had a feature in their genetic makeup which it looks like they inherited, as Nirupa absolutely correctly said earlier, these people need to be followed-up and they need more intensive screening, because this is how you detect cancer at an earlier stage. And the final way people benefited is we could detect genetic changes in their DNA that meant that if they were exposed to certain medicines, they were likely to suffer harm. And there's a particular, two medicines, 5-fluorouracil capecitabine, where possibly about 5% of people will need either a reduced dose or a completely different medicine, because it will be very harmful. And so this is about getting the right medicine to the right patient first time, and getting the right outcome for that patient downstream.

And I think, you know, Nirupa's encapsulated it perfectly, there's a whole range of benefits that the patients can accrue from this. And I think we should probably, Nirupa, say that people were quite cynical when we started, about what it would be that you would get over and above, for example, the cancer genome map that's at the international cancer genome consortium. And, you know, I'd had leading cancer scientists in Britain say, "Oh well, we've discovered it all, there's nothing to find here." And I think what this paper shows is that's not entirely true.

Nirupa: I would agree with that Mark, but I would also probably add that it highlights the value of having a large data set alongside that clinical information. And what we were also able to do, is whilst we very much talked about what were the gene targets that had a direct impact or genomic markers that impact care now, for which there is an approved therapy. What we've also been able to do through this analysis, is actually highlight the number of mutations that have been identified for which there is a licence therapy in another cancer type, but not in that particular cancer type. And what that means, is that specially now, as we have more and more biomarker-driven therapies, I mean, if we look at that compared to when the project started and now, that has increased dramatically. And what that means is then there are sort of licensed medications that actually can be used in non-licensed indications via a clinical trial, via these very, you know, these basket studies which are across cancer types and are actually based on different types of molecular markers. And really, we're able to show this at a pan-cancer level across the 13,000 tumours through the results from whole genome sequencing.

**Naimah: You've both kind of touched on this throughout and, you know, we've talked about the development of personalised medicine. And where do you see the future of cancer treatment in the next five years? Maybe, Nirupa, we can go to you first?**

Nirupa: That's a very good question. I think and what I hope is that with more comprehensive and equitable and standardised testing for patients, especially within the NHS, that this will enable more personalised and targeted therapy alongside, you know, systemic chemotherapy. And as well as that, better selection of patients that are likely to benefit from the newer immunotherapies. And also where sequencing is very exciting, is that once we begin to understand more about the individual tumours, you know, going forwards there are a number of cancer vaccine trials, and the aim of those are to have specific vaccines that are going to target an individual's tumour. So I think in the next five years, this is I think a very exciting space, I hope so, because we need to keep doing more in the space for our patients to try and improve therapy and precision oncology for them.

**Naimah: And Mark, do you have anything to add to that point?**

Mark: I think Nirupa's right, that there are new therapy extractions coming on, vaccination's one way. But I think that what will become clear is whether we can use any molecular mechanisms for early detection of cancer. The battleground here is that we all too often detect cancer late, when it's already outside of the organ it originated in and may be spread in other parts of the body. It's very hard to effect a cure, almost impossible in that setting. But what if we could detect cancer earlier? And then what if we could place a whole genome or detailed molecular characterisation alongside that? And then, as Nirupa suggested, give someone a vaccine tailored to their tumour that would eliminate it. The real problem is all too often we detect cancer late, so maybe some of these new molecular diagnostics, such as cell-free tumour DNA will usher in an era of early detection.

And one of the things, and particularly before we did this project but also up until the beginning of the last decade, there were very few good biomarkers of cancer that were usable in the health system. So we have for the first time opened the vista of having early detection, if we combine early detection with detailed molecular characterisation, possibly a whole genome, possibly another test, then I think we really can usher in the era of precision medicine. And so I think Nirupa's absolutely right, there will be new treatments, there always will be, but what we have to do is to get detection at an earlier stage.

**Naimah: We'll wrap up there. Thank you to our guests, Dr Nirupa Murugaesu and Professor Sir Mark Caulfield for joining me today. If you'd like to hear more about this, please subscribe to the G Word on your favourite podcast app. Thank you for listening.**