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Q1 You initially trained as a doctor, specialising in adult medicine, before transitioning to clinical genetics. What sparked that change, and what has kept your passion for genomics alive throughout your career since then?

I was initially focused on internal medicine, and in the UK, most individuals who focus on internal medicine then specialise in a particular area, like cardiology or gastroenterology. I became aware that there was a specialty around clinical genetics, and I was interested in that because I liked the breadth of the subject. It essentially involves caring for individuals and families across all stages of the life cycle, from before birth with prenatal investigations and advice, right through childhood, adulthood, and the end of life. I was aware that there was significant expertise in clinical genetics in Manchester, where I was based, and we had a very strong clinical department. I also knew that there would be increasing opportunities around research and technological developments. That's what drew me in.

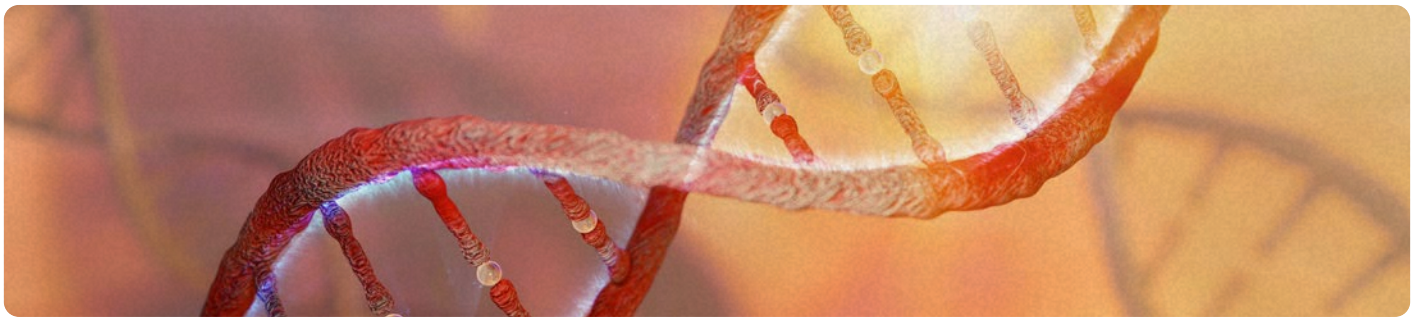
I think the thing that's kept my interest is the fact that there has been so much change, including the opportunity to use new technologies, especially around the diagnosis of rare conditions; the increasing ability to use information to inform treatment and the development of new treatments; and a greater understanding of the contribution of genetics to our health. It's a privilege to work with so many clever people, and I really have enjoyed the relationship between clinicians and researchers, but also the patients and their families. Their voices have really driven a lot of the work that's happened within the genomic medicine space.

Over the last 15 years or so, my group has discovered over 25 different genes that are the causes of several rare conditions

Q2 After your medical training, you spent 2 years in Toronto, Canada, studying the genetic basis of rheumatoid arthritis and inflammatory bowel disease. Was returning to the University of Manchester, UK, always the plan for you? If so, what led you back?

It wasn't necessarily the plan, certainly during my clinical training and my subsequent PhD. My PhD was based on work around arthritis, and it very much focused on molecular biology, as well as the function of genes and how they might interact with each other. A lot of the work that I did in Toronto was more focused on understanding classical genetic studies, and there was a change in the technology just around that time that suddenly allowed you to undertake the genotyping of lots of different genetic variants. Large-scale genomic studies became possible, and people began to explore the genetic contribution to more common diseases like inflammatory bowel disease, asthma, and arthritis.

I was really interested in that, but in terms of returning to Manchester, there were a few drivers. One was a really strong relationship with the hospital where I'm based, and the



university that I'm employed by. I was working in a very strong clinical department that had good relationships and worked very closely with the university in a seamless way. They allowed us to ask questions in the clinic and perform tests and investigations that were appropriate for families with particular conditions. Then, if we couldn't explain their health problems or provide them with the information required to make the right choices or to help with their clinical care, we could take that information into a university setting and do some research. Manchester had an infrastructure that allowed me to explore some of those questions, and over the last 15 years or so, my group has discovered over 25 different genes that are the causes of several rare conditions. That's only possible because I have such a strong clinical team working alongside me. I've also got some outstanding clinical academic colleagues who have undertaken work in related fields, and, as a group, we've probably discovered or contributed to the discovery of >200 conditions, working in collaboration with researchers all around the world. Additionally, my boss at the time, Dian Donnai, University of Manchester, UK, had a real understanding of how genetics could contribute to healthcare and how collaboration across different international groups was going to be important. That led me to a number of roles with the European Society of Human Genetics (ESHG).

Q3 You've led significant work in pharmacogenetics and rare disease research while remaining active in clinical care. How do these areas of your work influence each other, and what are the main benefits?

I think I'm very privileged and lucky to have had so much variety in my career to date. I like doing different things. I find it stimulating, and I like working with different people. The drivers behind rare disease research really came from the strength of our clinical department and the colleagues I was working with, who were seeing families with rare conditions. These colleagues were either identifying conditions that had not been previously described or identifying conditions where genetic testing wasn't able to determine the genetic change responsible for the condition. Starting with clinical data and access to clinical materials allowed us to start using next generation sequencing, so we were one of the first centres in the UK to undertake exome sequencing and discover the causes of a number of conditions. For a number of these conditions, we've gone on to look at the function of those genes, and for some, we're now at the stage of developing new therapies. That has been really exciting. There are a number of colleagues working alongside me who are driving that work in rare conditions, looking at it in different ways and using different approaches. With my colleague Siddharth Banka, Manchester Centre for Genomic Medicine, UK, we've been able to establish the Manchester Rare Conditions Centre, UK, which brings together research expertise, clinical service developments, and education and training programmes.

In terms of pharmacogenetics, my driver was somewhat different. It was partly a sense that genetics, to some degree, has been seen as an area that is only relevant to a very small number of people. I've always felt that that wasn't right, and that genetic information was probably going to be more relevant to a much greater group of people. A real, clear example of this is when people take medications and either have an adverse drug reaction or don't respond to their medication at all. The concept of pharmacogenetics had been developing, and I was really interested in some of the work that had been done and the strong evidence that had amassed. What I couldn't understand was why that hadn't moved into routine clinical practice, what the barriers were, and why we weren't using that information on a daily basis. That's where the main focus has been for me, my colleague John McDermott, Manchester Centre for Genomic Medicine, UK and our team; it isn't so much on the discovery of new genes that are relevant to drug response, but much more on taking the information that we've known for

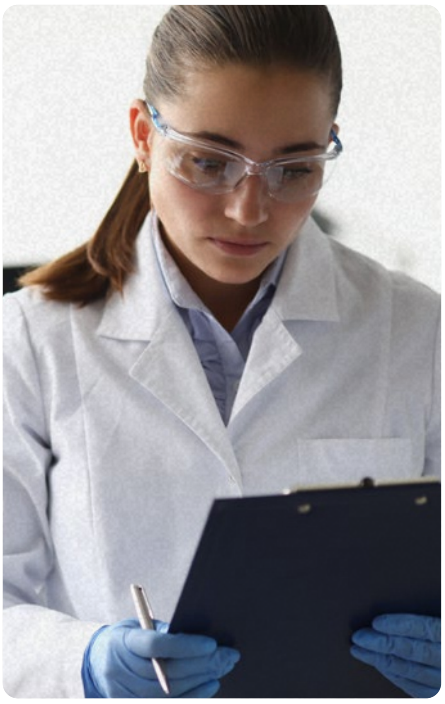
years and making sure that we use it for patients. It's allowed me to get involved in work on both ends of the spectrum: discovery and clinical implementation.

Q4 One of your most high-profile projects is the PALOH study. Could you describe the work that went into it and how it has benefited patients?

The PALOH study builds on the point I made about genetic information and data being available to the world for a long time without having been implemented in clinical practice. Back in 1993, it was discovered that a change in a gene predisposes individuals to severe hearing loss if they're exposed to a certain type of antibiotic called gentamicin (an aminoglycoside). So we've known that for 30 years. If you know that you're going to use that type of drug in a patient with a condition like cystic fibrosis or a predisposition to chest infections, then you can do a genetic test in the lab. Once you have the results, you can decide to give them gentamicin or an alternative depending on whether they carry the change in the *RNR1* gene.

However, I was very conscious that there was a group of patients, specifically newborn babies, for whom the genetic information just wasn't going to be available in a timely way. When newborns are admitted to a neonatal unit, the vast majority of them are given penicillin and gentamicin to protect them against infection (sepsis), and you need to start those antibiotics within an hour. If you send a blood sample off to the lab and get a result 3 or 4 days later, you just can't use that information in a meaningful way. I was aware of a small company in Manchester, UK, called Genedrive, which had been working on a point-of-care technology. I met with them and explored the possibility of developing an assay together, where we could use a cheek swab from a baby, the results could be available quickly, and the correct antibiotics could be given.

The first step was to get a small grant from a hearing loss charity called the Royal National Institute for the Deaf (RNID), Peterborough, UK, in order to develop the prototype assay. We tested that in the lab, and it worked really well: we could generate a test from a sample in about 30 minutes. Then we moved on to a larger grant from the National Institute for Health and Care Research (NIHR) because we needed to see if it could be done in a neonatal unit. Could we generate a genetic test that could be done at the bedside in 30 minutes in the middle of the night, when people are rushing around, and so many other things need to be done? The nurses doing the test are not genetics experts, so the test needed to be done in a way that was robust, didn't require a lot of training, and was cost-effective. We did that test study in the UK (Manchester and Liverpool) a few years ago, and we tested 750 babies. We showed that three of them carried the genetic change, and we gave them a different antibiotic. In addition, we were able to show that using the test did not delay those babies getting antibiotics. This has now undergone a National Institute for Health and Care Excellence (NICE) appraisal, which shows that it is cost-effective. NICE is the UK organisation that decides if something like this should be rolled out on a large scale. What they've said to us is that they want a bit of extra evidence to show that this type of testing can also be done in small units that might not have all the facilities available to a large centre. Therefore,



we're now running a study called PALOH-UK at multiple sites across the UK, including Scotland, Wales, Northern Ireland, and other parts of England. We hope to have all the results from that next year. We believe that if this test is implemented at scale around the world, in 1 year, you could theoretically prevent 14,000 babies from going deaf out of the 7 million a year that are given gentamicin. It's a very nice example of taking information that is known and working out how you can use it in a clinical setting without needing to use laboratory-based testing or setting up multiple new processes.

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Q5 The study has been described as 'transformational'. From your perspective, what have been the key learnings from PALOH, and the work that has happened since, that can be used to implement genomics into everyday NHS care?

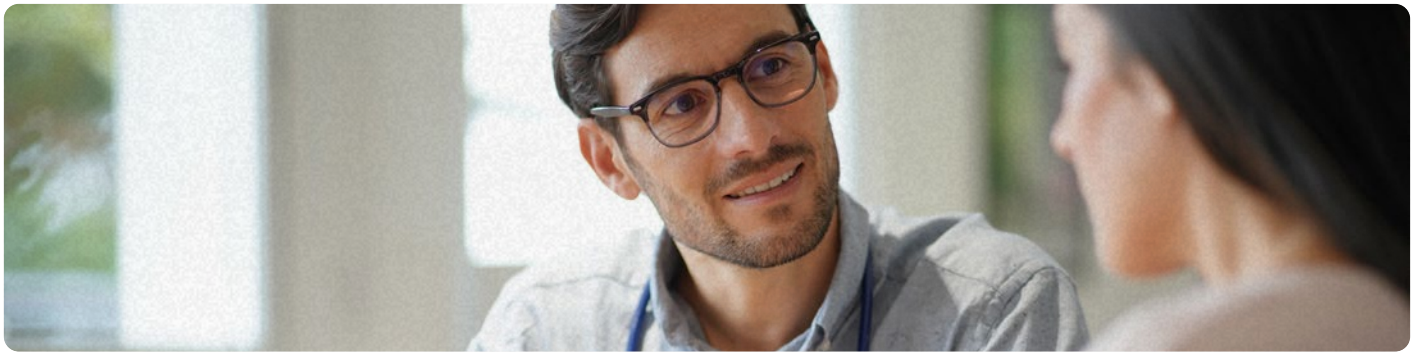
One of the most positive experiences I had regarding the PALOH study was working with our other stakeholders and patient groups to really understand whether this new approach of testing newborn babies was going to be appropriate. It is a very stressful and difficult time for families when a newborn baby is unwell and needs special treatment, and our parent group helped us enormously. We worked together to make sure that the information we were providing and how we were approaching the study were done in a sensitive and appropriate way. Working with colleagues, especially the nursing teams and the neonatology groups, was also fantastic. They were all really enthusiastic. They knew that this was an issue for them and the babies they were looking after, and so they were incredibly engaged in working with us to find solutions.

Another really positive thing was that the eleventh baby that was tested had the genetic change, and the word spread through the whole unit like wildfire: they'd saved this baby's hearing. It meant that all the nurses were really keen to do the test, and we missed very, very few babies. Now it's integrated as part of the routine clinical pathway. Understanding when exactly we needed to do the testing, speaking to the experts in neonatal care, speaking to the parents, and understanding some of the practical issues were all really helpful, and this experience has informed all of our work.

We've gone on to do other studies now on different types of genetic tests in acute settings where you need a rapid result, and we've taken the same approach. You design the study with the clinicians and the patient groups, and then you listen to what it is that they need and want, as well as what doesn't disrupt the important pathways that they have set in place. You don't come in and say, "Here's our new solution." You say, "How can I work with you to make sure that our solution fits into your pathway and what you're doing?" so that it becomes part of their routine care.

Understanding the needs and the challenges for a commercial company, how they operate, how you work in partnership, and what support you as a clinical academic can provide has also been really interesting. This has led to us working with a number of other companies to provide input as they start to develop their own products. As a result, we have a large programme called DEVOTE funded by Innovate UK, Swindon, UK, where we work with a number of different companies, giving them advice, support, or information to help them develop their particular genetic solution.

Another key learning is that, in acute settings, it's very difficult to get patients' permission to carry out a genetic test, especially when working with newborn babies, who cannot give consent. PALOH was the first time anywhere, as far as we're aware, that a genetic test was undertaken without explicit consent. We'd sought the advice of lawyers, ethicists, and the parent groups to make sure that they could understand why we felt it was so important to do the test before filling out consent forms, because we needed that information quickly to make the right decisions for the baby. There was a lot to learn in that respect.



Q6 Are you involved in any other exciting projects at the moment? What results are you expecting from them, and what benefits might patients see down the line?

There are always a lot of plates spinning. I've mentioned some of our work around the acute setting and point-of-care testing, but we're also leading a large programme as part of the NHS Network of Excellence in pharmacogenomics. This involves working in primary care with general practitioners (GP). Around 90% of all drugs in the UK are prescribed by GPs, and a lot of those are common drugs like antidepressants, painkillers, statins, reflux medicines, etc, and we know that how people respond to a number of these drugs can be based on their genetic profile. Thus, we have been undertaking an implementation project called PROGRESS, which involves working with 20 GP practices across England. An individual who sees their GP at any of those practices and needs to start on a medicine will be asked if they would like to participate in the study. They provide a saliva sample, which is sent to our laboratory, and within a week, the result goes back to the GP. When the GP wants to prescribe the medicine, the information pops up in the patient's electronic record to give them some guidance, and that then leads to the individuals either receiving the medication that the doctor had initially thought or a different medicine entirely. So far, with an interim analysis, we can see that in about a quarter of individuals, either their dose or the actual medicine is changed based on their genetic results. If the individual goes back to their GP a few weeks or a few months later and they need a different medicine for a different health problem, that genetic information is still available in their records, so they don't need another test; it's immediately available to their GP to inform the prescription of the next drug they might need. That study is going to finish at the end of the year, and we hope to have all the data from that in early 2026. We think that this will inform plans to undertake pharmacogenetic testing as a routine part of care within the NHS, and then it will just be a question of how we scale it up and roll it out across the country. My expectation is that the data will strongly show that this is of real benefit to patients.

Q7 During your time as President of the ESHG, what impact have you seen the Society make, particularly in terms of improving care across Europe? Are there any exciting plans on the horizon?

I think that the ESHG is a really fantastic organisation. It's been a wonderful experience for me to be part of that group and to have worked with such impressive individuals. I think that the Society has achieved a lot over the last several years through the quality of work that its members are undertaking across Europe, as well as their willingness to share that experience, supporting the training and education of young members, helping them to look beyond the boundaries of the Society, and helping other groups and individuals understand the role of genetics in human health.

We have an Annual Conference, which happens in different cities around Europe. The data that is presented there is absolutely at the cutting edge of science. It's truly remarkable, and we're able to attract some of the top scientists and clinicians in the world to present their data at that meeting. Last year, we had a Nobel Prize winner presenting her work on mRNA vaccines and her work on COVID-19, which was fantastic and really inspiring for a lot of the younger attendees to hear about.

We also have an education group that is looking to explore the resources required by our members and other people to help those who can't attend the conference. How do you make resources available to people in a way that is accessible and cheap, but is of high quality? We've been working on developing apps, and we've introduced some fellowship schemes so that young investigators, clinicians, and scientists can visit different centres and gain experience. We also have a number of web

resources, and we set up a webinar series this year to have some of our top scientists and clinicians speak each month about some of their work.

We then have a policy and ethics group that considers some of the impact that genomics is having at a societal level. Considering the various challenges faced in different countries across Europe, trying to support colleagues in other parts of the world where genetics and research are not looked upon favourably or are not getting the support that they should be.

ESHG has become a very outward-facing group, and any society like that is only as good as the people who are prepared to put in the effort and really commit to making what they do better and more inclusive. We've been supported brilliantly by the Vienna Medical Academy, for over 20 years, and they organise all the elements of our group, providing that institutional memory that ensures we can learn from what's happened before and build upon the positives moving forward.

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Q8 As genomics is a rapidly evolving field, have you encountered hesitation or misunderstanding from healthcare professionals or the public? How do you approach these challenges and help others see the value of genomics in care?

I think it's really interesting, and it's challenging to understand what about genomics makes some people concerned. We've done a lot of work looking at that. You can have the best technology in the world, and you may think you've got the greatest ideas, but if you can't bring your colleagues and the public with you, then there is little point in doing some of this work. We've tried, particularly in the context of rare diseases and pharmacogenetics, to take different approaches, but we very much use a partnership approach by exploring the attitudes and the concerns of our clinical colleagues to pharmacogenetics. We've undertaken studies like discrete choice experiments, where we look for people's preferences regarding the aspects of a service they think are the most important. Is it how quickly you get the result? Is it how you take the sample? Is it the format that the result comes in? You can ask those questions in different ways, and that gives you a sense of the most important elements as you're developing and delivering a service.

There are other methods, such as through focus groups, interviews, asking key opinion leaders, and going out and canvassing opinions as much as you can, to ensure that you're listening to the concerns of the public and professionals, and if appropriate, to reassure them. It can help if you might not have explained something properly or if there might be something that you hadn't considered before, where you need to go back and look at in a different way. I think that's very important for people who may have not been treated well by governments or healthcare systems in the past, and who feel quite anxious and concerned about how this new data could be used against them. It's about ensuring that the safety of the data is in place and that it's used appropriately for their benefit.

At the beginning, when you're thinking about your programme of work, you're having those conversations, and you're designing the approach that you're taking as a partnership. We found that that has worked very well, but you can't just do that once. You've got to keep going back and making sure that what you're doing is appropriate and that you're measuring outcomes from your intervention. So, if you're using a new type of test or a new type of treatment, you need to demonstrate that it has had meaningful benefits for patients and for society.

Q9 If time and funding were not obstacles, what do you believe the full potential of pharmacogenomics could be? How far could it go in transforming the way we deliver care?

I think there are several important changes that are going to happen over the next few years. I think that we're going to see a significant change in the way that hospitals, universities, and industry all work together in this space. For instance, in the past, individuals who worked in an academic setting and then moved to a commercial setting didn't move very freely between the two spaces, and that's changing now.

Some of my colleagues and I have set up a small company called FAVA, Manchester, UK, with which we're trying to address some of the challenges that are not necessarily about generating genetic information, but about ensuring that it's available at the point of clinical need. Generating genetic information is only useful if you can ensure that people are acting upon that information to change their medication and looking at what the downstream effects of that are. In the past, we stopped too early in our evaluation: we created a solution and then didn't see if that solution really enhanced the care in the way we hoped and expected. With this change in the way of thinking, we won't be able to eradicate all adverse drug reactions, and not every drug given to every patient is going to be effective, but we can turn the dial and shift the balance. We can make sure that people feel more confident, that when they're prescribed a medicine, it's much less likely to cause an adverse event, especially if it's one that we know has a genetic component to it.

The other thing to say about pharmacogenetics is that it's only one element of good medicine use. Making sure that a person is on the right dose, that you've made the right diagnosis, that they're not on the wrong combination of medicines, and that they are still taking their medicine is all part of the package that will ensure the best outcome possible. However, I think the biggest change that we're going to see over the coming years is patients feeling that they want to take ownership of their own information and control of their own healthcare. We saw a big shift during the COVID-19 pandemic, where people became more accustomed to using apps, testing themselves, feeling that they understood more about their own healthcare, and doing that in partnership with healthcare professionals, rather than a more transactional relationship, which may have been the case in the past. I think that relationship is probably going to be the biggest difference that we're going to see.