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The Promise and Reality of Precision Medicine in Northern Ireland

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Professor McMullin:

Good evening, welcome everyone. My name's Mary Frances McMullin. I'm President of the Ulster Medical Society, and I'm delighted that we're here tonight for the Colonel Desmond Whyte Memorial Lecture, which happens every year as part of the Ulster Medical Society programme in Altnagelvin, specifically as far as I can gather, set up for that purpose. So Colonel Whyte, I found out about, is a very interesting person, and I'm sure there's many people in the room knew him. My colleague, who worked here over many years, Robert Cuthbert, informs me that he was Mr Altnagelvin right from the beginning. However, when you look up about him, he actually had an extremely interesting war record. He was in the Second Chindit Expedition in 1944, he got the DSO, but everything I read said he really should have the VC, but he didn't care. He then trained as a radiologist, and came here in 1957, he was here in the hospital from the beginning. He was very active, many, many people, when we were talking tonight, remember being taught radiology by him.

It's also very interesting, because I'd heard of this guy before, because I know his haematological diagnosis, which he did not die of but died with, the year before the wonder cure for that disease appeared, and he's always quoted as somebody who lived for many, many years with the disease, without having to wait for the wonder cure, and it didn't do him any harm, so it's quite interesting, coming back. However, this is the Desmond Whyte Memorial Lecture, and I'm delighted tonight to have Professor Manuel Salto-Tellez, who has agreed to give this lecture. Now, Professor Tellez is the chair of molecular pathology in Queen's University, Belfast, I think probably for the last eight years, and also a consultant pathologist and leads Queen's Precisions Medicine Centre of Excellence. He actually trained in Spain, Germany and the Netherlands, and then in histopathology in the UK and molecular pathology in the US. He worked in Singapore for many years, and then luckily came to Queen's, and he's now a leading light in molecular pathology, obviously in Queen's, but much wider than that, with the college and in general his many publications, and over 275 publications and a large grant income. So the theme I've had for this year was diagnostics in the future, and trying to look to see where things are going with diagnostics, which I think is, if you make the diagnosis, then you go on in that in medicine, and that's why I wanted to ask Professor Tellez, and he luckily agreed immediately, and he's going to talk about the promise and reality of precision medicine in Northern Ireland, so Manuel, thank you very much.

Professor Salto-Tellez:

Thank you so much for the kind invitation and the kind introduction. My task today is to pontificate about personalized medicine, and as you, or some of you know me, know very well that pontificating is the passion of my life, so I really like it, so hopefully this will be relatively easy.

My task is personalized medicine, and I'm going to try to do this in four bits: tell you a little bit of what I think are the global challenges today that we have in medicine, which also affects to Northern Ireland, tell you a little bit about the programme that we developed over the last couple of years, tell you where I think things are going in this space, and then hopefully we will try to read what the future may bring us.

Before that though, I would like to really congratulate Mary Frances for this programme. If you exclude my lecture, this is probably the best programme that we have seen in personalized medicine in Northern Ireland that I can remember. The fact that people of this calibre have agreed to come within the space of one year and talk says very much about the person that has organized this programme, so really, congratulations—it's a very special programme.

So global challenges: when I was a medical student I really wanted to live exciting times, and that was what I was hoping for. When you start working across the world, you realize that interesting times may mean different things for different people. Sometimes it's a positive, sometimes it's a negative. Positive or negative, I think there is no question that we are living in very interesting times. We know, for instance, and the Bengoa report and other reports have reminded us in Northern Ireland, that it's going to be very difficult to sustain practising medicine the way we are doing it today, and that we may have to revisit the way we organize ourselves. We have a very clear distinction of what is research and what is diagnostics, and yet that distinction is getting more and more blurred as we move forward. For instance, the oncologists in the audience now, the number and the quality of the patients that you put in clinical trials, is not only a research activity, it's also in many ways a measure of quality of healthcare. At the same time, we know that if you are delivering molecular diagnostics in a laboratory that is also involved in research and development, you probably have earlier access to technology, a clear access to know-how, and probably your end product is going to be better.

You know, we have a lot of hope in translational research. We think that linking basic discoveries with clinical applications is the gold standard, and yet we

have to say that we are doing translational medicine in general very badly. For every hundred papers that are out there claiming that there is a finding that is translatable into clinical applicability, less than 1% make their way into a developed application, and together with my colleague, Richard Kennedy, we try to understand why we came with these filters of reality. If you take into account those biomarkers that we don't know much to start with, those that were developed with technology that was sub-optimal, those that were developed in the studies that were not designed properly from a clinical point of view, or those that were validated and developed in an assay in a sub-optimal way, that you can really explain why we have this attrition rate, which is not small. We have a conundrum, as you know, in drug development. You don't have to go to developing countries. We know that the cost of providing a drug that is ready to use for patients is extraordinary, and is because of the way we organize our clinical trials, and there is a very clear need to try to revisit how we do this in a way to make all these processes more manageable, at the same time maintaining the quality of what we do. We have a lot of hope in personalized medicine, and to be fair, it's working. There are patients that are living longer lives, are living better lives, because of personalized medicine. The problem that we have is that, with the current paradigms, many of these patients come back with disease, with disease that is molecularly very aggressive, and is more difficult to treat, and what we are doing is essentially buying months, perhaps one or two years of life, to these patients. And in fact, the other issue is that, imagine that you live in the best-possible scenario, in a hospital that has all molecular tests and has access to all potential clinical trials available for those patients. It's likely that there is still the vast majority of your patients will not enjoy personalized medicine, because we still don't have the drug for those targets. Now, you can compare that with the new kid on the block, immune checkpoint therapy, but for some cases, in some diseases and some patients, we are seeing long sustainable survivals that we've never seen before, outside the haematology field, of course, but then we know that this is happening only in a percentage of patients, and we still don't know why. Then we have another problem: the UK is arguably the largest producer of research, high-quality research in the world, it's second-to-none in other parts of the world, and yet, when we look at the venture capital that is behind those ideas, to make them available into potential patient use, we know that we are not very well there, and that we need to change that, and we need to change that practice. So all these were in our minds when, eight years ago, we came to Northern Ireland to develop a molecular pathology programme. How can we address all this, and how we can we do this from a small place in the periphery of Europe, in the periphery of the UK, in the periphery of the periphery? We thought that probably the best way would be to have a model that would challenge some of these questions, and that's where we came with a very specific, a precision medicine programme for molecular pathology programmes. The word here was integration—there are going to be many parts of the world that are going to tell you that they have a very good biobank, that they do wonderful immunohistochemistry, that they're great in molecular studies, that they are very good in the histopathology or in bioinformatics, but a place under a single roof, where you can develop these with the quality that we know and is appropriate for clinical patients, but also being used for research, that didn't exist, and that was our task. If I tell you that there are people in my university that still don't understand this concept, don't be surprised—it's not easy, just like some people in the trust think that, why are we doing tests in what is perceived as a research laboratory? Well, I can assure you it's the Belfast Trust's space. Well, that is what we wanted to do. Eight years down the road, we've developed a programme where we have very interesting molecular diagnostics going on, and I'll tell you a little bit more about how it's going to be developed, because it's the key to personalized medicine in Northern Ireland. We have research programmes in genomics and in digital pathology and artificial intelligence, we have a very strong education programme with a very strong MSE in cancer, we have developed a very strong Northern Ireland biobank. My colleague, Jackie James, underpins much of the research that we do, and we have developed a precision medicine centre of excellence, which I would like to explain to you later on what that means. Overall, we've managed to amalgamate 60 people with significant traction. This is where we are, so we do molecular pathology, we do precision medicine, but what is that really? To be honest, there are as many definitions as people have tried to define this concept, and in fact we use a different definition depending to which grant call we attend, because we want the money! But in any case, there's probably two ways of understanding this. You can define molecular pathology as the interrogation of clinical samples to understand better the nature of those diseases. Those would be translational research, and you know the model of these papers, you've seen them many times. We take clinical samples, well annotated clinical samples, we do morphological studies, we interrogate them from a molecular point of view, we see how our resources correlate with clinical outcomes, and those are our results. This is molecular pathology so widely known that most of these studies are not done by molecular pathologists any more—many of them are done by very good clinicians.

Now, you can think of molecular pathology essentially as an application of those disease mechanisms for diagnosing, prognostication or treatment of diseases. Then, we are talking about molecular diagnostics, and as you know, many areas of medicine are already fully embedded in molecular diagnostics. Virology is probably 100% molecular; haematology very much the same; genetics, I don't have to tell you. What I am talking about today is probably the application of molecular diagnostics to histopathology or to

cytopathology, that is the area where we are moving. That's why we developed this clinical service, so why a clinical service in precision medicine? Well, let's maybe give you an example. In 2012, I was asked to review the best examples that we had of precision medicine, i.e., of antibodies and the small molecule inhibitors, targeting very specific known genes and pathways, to essentially treat all diseases in new ways. I counted 16. Two years later, in 2014, a colleague of mine did a similar exercise, and the number had gone up to 32, and just last year, when I joined one of the NICE groups to discuss the management of colorectal cancer, I looked at the NICE list, and the list, I didn't bother to count. So obviously this is a model that is here to stay, the model that you have drugs that can specifically target specific molecular pathways, and we know how they are operating. So the molecular diagnostics today is a commissioned molecular diagnostics service for the whole of Northern Ireland. These are the people that are working on it today. We are doing many of the bread-and-butter tests in solid tumours. By hopefully the middle of next year we are going to start developing next-generation sequencing for many our [haematological?] malignancies and solid tumours. In fact, the molecular haemato-oncology service will be amalgamated with these as well, and obviously we are, as Mary Frances kindly told us earlier on, very much in many of the national initiatives. Just to avoid taking you through all those tests, allow me to give you an example. What are we doing, for instance, for lung cancer in Northern Ireland today? So for lung cancer, we do Reflex testing for every non-small cell lung cancer for PDL1 testing. For adenocarcinoma, we add EFGR mutations and ALK. [DROS?] is available on request—we have finished the validation—and also upon request, we can look at EFGR mutations in the peripheral blood. We do EGFR testing. As you know, EGFR is a very prominent member of a very prominent family of transmembrane proteins. We know that many of these mutations confer sensitivity to tyrosine kinase inhibitors. Some of them confer resistance, and in fact, when I try to explain to our students the basis of personalized medicine, probably one of these first trials, the IPAS trials, explain it better than anything else. Patients that are EGFR mutant or wild type, if you give them chemotherapy, they're going to have a similar survival. If you give TKIs to patients that are EGFR mutant, you help them. It's again, as usual, the same curve. We are buying months, years of life, but the patients come back, but see what happens when we gave TKIs to patients that are wild type. Not only we are not helping them, we're making them a disservice. The chemotherapy, the standard of care is better. That is the reason we are doing testing with many of these drugs. So, so far, we have done a significant number over the years, and our numbers, both in quality and delivery, are very much according to national standards. We can do these tests in [cell-free?] DNA. We were one of the first six laboratories in the UK doing this. The idea is that, if you test for EGFR mutations, you can detect molecular recurrence after treatment, and you can also identify those mutations, like the T790M, for which you already have the third line treatment. Interestingly, the use of these tests, the most widely used of these tests, is actually by oncologists when they see that their biopsy was not good enough to do an EGFR testing, because there wasn't enough sample. Then it's easy to get a blood sample, and if the mutation is there, you know that you can treat accordingly. We do ALK testing, so ALK testing and crizotinib is a well-known story. In the US, the drug is associated with a test, but is extremely expensive. In Europe, most of us have a screening tool, mostly immunohistochemistry confirmed by fluorescent in situ hybridization, and in fact our validation showed exactly the advantages of each of these tests, and how they should come together to apply them as a whole, and again our deliverable is very much according to national standards. We were talking about this earlier on—we are doing PDL1 testing. The reason, as you know, is also very clear. For some patients with stage four adenocarcinomas, for instance, we are seeing long sustainable survivals like we've never seen before. The idea here is that the tumour cells are silencing our immune system, and if you block that link between the tumour and the immune cell, the immune cell will be able to have its anti-carcinogenic effect. The stories are probably a little bit more complex than that, but yet PDL1 seems to be the biomarker that, with all its imperfections, is working today in the clinic. In fact, we published early this year what I believe is the largest clinical series on PDL1 testing, our first seven or eight hundred patients, so here we started presenting what is the performance of the test in real life, and interestingly we started exploring something else, that is going to be part of my lecture later on. Can we use digital pathology and artificial intelligence to improve the delivery of personalized medicine? This early study told us that indeed that is possible, and that there is room for that. This lady, the Chief Medical Officer, Sally Davies, has transformed the way molecular diagnostics is going to be practised in England, that is currently being practised in England. The idea is that there's going to be 20-odd genomic medical centres that are going to send all their clinical samples for testing to approximately seven genetic hubs that already have been chosen, by the way, and that molecular information is going to go back to those genomic medical centres to start managing patients. This has been very controversial, because obviously it's putting a long distance between tissue pathology services, genomic services, clinical services. I can tell you that the decision in Northern Ireland has been that the genetic hub is going to be our laboratory, so the commissioners are going to spend £10 million over the next five years to make sure that all the patients that need testing in cancer and in rare diseases are going to have it by next generation sequencing, which is an idea that we presented when we started this process eight years ago, and I'm very happy that we are going to have a single virtual molecular pathology service to cater for all the needs,

and the reason is obviously because, through competitive funding, we've been able to create a laboratory with the capacity to be able to do that from a technical point of view. So this will be the first panel, the solid tumour panel, that we will be using for this purpose. So this has been designed so that all the mutations, all the translocations, all the copy number evaluations, that you need to treat solid tumours across the board, for which there is already NICE-approved drugs, can be tested in one single test. Here you have the ideal paradigm of all the mutations that you should test in lung cancer, and I can tell you that all of them are present in this case, and the same, we could say, with malignant melanoma, with colorectal cancer, with gastric cancer, with breast cancer, endometrial cancer, etcetera. The reason this is happening is because I think the laboratory has shown that there is good quality behind. For instance, we joined one study in lung cancer as well, that is supposed to analyse cases from the whole of the UK to understand much better what is the molecular basis and the cancer evolution of this specific cancer type. For that, we've been receiving samples from many parts of Northern Ireland, and what we are told about the quality of the work that we have done is that it's certainly above the average of what has come through the UK, so there is a good quality in the service. Where are we going with this? Well, one of the good things of having been in the business for more than 20 years is that you begin to have a bit of a historical perspective, and it's very clear that, since pathology became a clinical discipline at the middle of last century probably, there's probably been three main revolutions in pathology. One came with the application of immunohistochemistry, so this was a tool that pathologists loved. We started throwing antibodies at everything. The taxonomy of many of our cancer types was totally transformed by this analysis, and pathologists did very well, so the idea that we could have a tool that will tell us about the intensity of a protein, subcellular localization, lineage specificity, that transformed in many ways the way we started looking at cancer.

The second one has come with the genomic revolution, a little bit later than the discovery of the helix. Very important is helping many of our patients, we are changing complex pathology taxonomies where pathologists pontificate about, if that cell means one thing or another, when often there wasn't any clinical relevance with those sub-classifications, into classifications that are potentially more meaningful from a clinical point of view. The problem, as I tried to tell you earlier on, is that this is helping some of our patients very modestly, and it's not helping many of our patients at all. We need new tools. We need new tools that are going to help us to help our patient better. How do we do this?—well, I think that in a few years down the road, when we look back at these years, probably we are going to recognize a third revolution, which is the one that is coming with digital pathology and with artificial intelligence. The promise of artificial intelligence is phenomenal. If you open a medical journal today, you will be told that you can analyse genomics with artificial intelligence and make significantly more sense of it, that you can analyse radiological images and pathological images, and get information that you never could before, that you can actually look at clinical records from patients, and start having decisions that could be more accurate than the subjective decisions of the oncologists, that you can actually take all this information to the web, and start getting information about individual patients that is close to epidemiological information, and can help you with the patient much better, or that you can take all that information and put it in a big population data, and tell you significantly more information about that patient, that is going to tell you how to treat the patient better. All this is obviously a promise, but it's a promise that is becoming a must, and how much of this we are going to be able to deliver at the end of the day, I think is a very big question, but it's interesting to think that of all these potential uses, the uses associated with pathology are probably the ones, together with radiology, that are more advanced. We know, for instance, today, that if I come to work in my pathology department, and instead of switching on the microscope, I switch on my computer, and I look at the pathology images that have been scanned, instead of looking through the microscope, the clinical result, if I am well trained, is going to be the same. There are already two studies which have proven to FDA that there is no inferiority by doing it that way. We know that this process can help pathology much better. Now, many of you may be associated with these, but let me refresh your memory. What happens when a sample comes to pathology? Usually formally fixed but we embed it, we cut it, we trim it, we produce an H&E, manually or automated. That H&E may or may not be scanned, and in silica or in glass, it's presented to a pathologist, and 50, 60% of the cases, the pathologist is going to say, this is chronic gastritis, this is severe dysplasia, this is cancer. More often than not, we are going to do immunohistochemistry, or in situ hybridization, usually in an automated fashion, that you can scan or not, and that can lead you to a diagnosis. And more often than not these days, in 3,000 cases this year, we are going to take those samples, we are going to do annotations, we are going to strike the nucleic acids, and that is going to lead to small panel testing for diagnosis, or high throughput analysis through bioinformatics curation into a clinical diagnosis. I don't know of any pathway in medicine that is as fragmented as this one. As the biochemist, as the microbiologist, they have seen these pathways. Here we are with every fragment of the piece in a different machine and in a different way. I think that digital pathology can help this process. For instance, what are we seeing now?—this is a more basic version of what I've just presented to you. What do we know that digital pathology can do today? We know that we can apply algorithms created, by the way, in Northern Ireland, that can tell us which area of the tumour to annotate, with results that are comparable to a pathologist

actually going into the system and marking that area.

We know that we can score immunohistochemistry in a way that may be closer to the clinical outcome that the opinion that I may be giving on Monday morning, or on Friday evening, which is likely to be different. We know that, because we know that in the whole development of new drugs, there is a companion diagnostics that you can apply through digital pathology. We know that today, artificial intelligence can detect very specific pathological features. For instance, micrometastasis in lymph nodes, perhaps more accurate than the human eye, and we know, surprise, surprise, that today, that by looking just at an H&E, you can start understanding what is the molecular basis of a disease. We know that with mutations in lung cancer, we do that by microsatellite instability, we know that, for instance, with HER2 in breast cancer. This is beginning to happen, and I'll tell you some of the work that we've done here, just to illustrate that point. What is the elephant in the room when you want to apply a large next-generation sequencing panel? Well, that there is a large attrition rate, and we have many examples in the UK telling us that, telling us that quantity and quality of DNA is essential. We know, and my colleague, David Gonzalez, has shown this very elegantly, that there is a direct relation between the amount of material that you have in your DNA instruction, and the success of your DNA, of your next-generation sequencing. We know, by the way, that pathologists are absolutely useless at indicating how much material there is in a slide. There's been plenty of studies telling us that the variation is significant. We are good at many things, we're not so good at that.

As I mentioned earlier on, we have developed a tool that is able to do this in a consistent manner, and this actually is a bit of a moment of pride, if you want, for Belfast, and I'll tell you why. This is a tool that we developed together with a local company, a spin-off from Queen's called PathXL. The tool was called Tissue Mark, which is one of these tools that did it from conceptualization to commercialization in less than two years. A large company, Philips, liked Tissue Mark, therefore liked PathXL. Philips bought PathXL, Tissue Mark is now one of our star products. Philips has invested three times in the development of the Belfast unit, so much that it's probably one of the highest hubs for digital pathology today in Europe, and this is a tool that is used, for instance, in [?] in some of their schemes, so it seems to work. In fact, if you look at one of those products today, and you ask them, tell me what is the cellularity, this is one of those cases that many of you are looking today from a clinical point of view. This is colorectal cancer, it's stage four, lots of lymphocytes, poorly differentiated, MSI high, the ones that we think could be amenable to anti-PDL1 therapy. This is what the tool is doing today, telling us exactly the vast majority of the tumour cells, and differentiating them from other tumour types. In Belfast, in my laboratory, we developed QuPath—well, I didn't develop it, I created the programme. It was developed by this gentleman, Pete Bankhead, who is probably one of the brightest minds I've ever worked with. He is now a senior lecturer in Edinburgh. Now, QuPath is the most used tool in the world today for digital pathology analysis of tumours, more than 50,000 downloads, more than 200 citations, and I think it's very useful for two reasons: first of all, because we decided to do it open source; in other words, it's free, and people like that, but also because it's actually very accurate in the way we deliver it. For instance, we wanted to know that that tool could tell us clinically meaningful information, so we took a cohort of patients that we've been working on for years now in Northern Ireland, the AP700 colorectal cancer cohort, has been published in other sites before. We started looking at some of these biomarkers, and the clinical relevance of how QuPath was able to identify those biomarkers was very, very clear. So in the last ESMO, because this is so well-known, I was asked to evaluate what has been the impact of QuPath in oncology. Now, at the time, there have been, depending on where you look at, 94 citations, 172, this was September, we are now close to 200 citations, as I mentioned earlier on, and as you can see, it's a tool that is used for diagnostics as much as translational, as much as basic, and it has one of the highest citation indexes today in the field, because it works, because it's a very logical way of analysing results. We applied it to breast cancer again, and even in biomarkers that we know are notoriously difficult, like Ki67 scoring, the results were very, very good. In fact, one of the leads in this field, David Rimm, actually decided to take 150 breast cancers, decided to take Ki67. He used without us knowing about it, two off-the-shelf pretty expensive kits, and QuPath, just downloaded for free, and the performance of QuPath was remarkable. In fact, we are using that now in our lung cancers with a test that is extremely difficult, like PDL1, together with multiplexing, and we think we are on the way of improving the way we are doing this test against a very subjective interpretation.

So this is many of the things that we are doing today, and as you can see, I've broadened the discussion of personalized medicine from DNA-based and RNA-based tests to other tests that I think are also very meaningful. As I mentioned earlier on, we decided to have an integrated programme. We thought that integration was meaningful. The result of that integration is beginning to pay in this area of the programme, it's the precision medicine centre of excellence, so this is an investment of £10 million, mostly from Invest Northern Ireland, that has already brought in a year, £5 million to the local economy.

The way we argued our case was the following. We know, as I mentioned earlier on, that there is a lot of discovery going on in the UK. We know that there is a gap between those discoveries and industry taking those discoveries and making them into a proper diagnostic device, and then we know that, once we have that diagnostic device, we need to show to universal healthcare systems, like the NHS, that those tools are cost-efficient, and they're worth using, so we thought that we could help in both areas, in bridg-

ing the space between discovery and industry, and in the adoption bit of doing those tests in the NHS, and for that, we managed to put up a very interesting team. We were told that we wouldn't be able to recruit the level of talent that was necessary for something like that. I can tell you that the bioinformatics team applied from Manchester. We were not very popular in Manchester for a while, I can tell you that. Mark came from Leeds, Manitia came from the Marsden, like David, Louise came from Cambridge, Liz came from Southampton, Jackie, Dara, Cathal, came from Almac, Beryl and Perry are local talent. It really made a point, and the services now are full-blown. One of the things that we want to do is to try to understand what the future may bring us, and what I have told you are two different types of tests, that are actually running in parallel. We think that these tests should come together, and that the information that we have from tissue hybridization and from genomics should try to help inform patients much better, and this is one of our main activities today. And one more thing which I think is very relevant, something that is very clear in the last eight years, we are operating with five trusts, with four pathology departments, two cancer centres, two universities, with a catchment population of 1.9 million. We shouldn't be fragmented. There should be single programmes, even if they are, which doesn't mean that they need to be in one single place, but we need single programmes. We need every single patient in Northern Ireland helping in developing programmes like this, because I think only then we are going to be able to make the most of what we are doing. This is our building. I show this picture at night, because during the day, I can assure you it's a horrible building, it looks very, very bad. We are essentially on the ground floor and the first floor. These are some of the people that have done some of the studies that I've presented today. These are the [?] collaborations, and the people that pay for our bills. Thank you very much for your attention.

Professor McMullin:

Okay, so thank you very much, Manuel, for an absolutely excellent talk, but just before you leave, there's a little token of the Society's appreciation.

Professor Salto-Tellez

Thank you.