Strength In numbers

Ahmed, S.F.

Prof. S.F. Ahmed

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Universiteit Leiden

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Strength In Numbers

Inaugural lecture given by

Prof. S.F. Ahmed

on the acceptance of his position as professor of

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Universiteit
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To my Rector Magnificus and Professor Hoggendoorn, Dean of Leiden University Medical Center and esteemed guests. It is with great honour and privilege that I stand here before you in this great hall, delivering this long overdue inaugural lecture to my dear colleagues, friends and family. It really feels like a very special occasion with so many people gathered in this room to listen to this lecture.

What is a rare health condition?

Rare diseases or, as I prefer to call them, rare conditions are those health conditions that affect fewer than 1 in 2,000 people in the general population and as a clinician in the field of children's health as well as endocrinology, the medical field of hormones, the majority of my working life has been actually spent looking after people with conditions that are rare. In general, over 75% of people present with rare conditions during childhood and although it is often reported that a third of these children will not survive their 5th birthday, in endocrinology, almost all will survive into adulthood but will have long-term chronic morbidity which will require careful and expert management. While at one level, a prevalence of 1 in 2,000 sounds as if there are not many people out there with these conditions, there are actually over 8,000 distinct rare conditions and these probably affect about 8-9% of the population which amounts to about 50 million people in Europe. I actually think this is a gross underestimate. In a recent mapping exercise that we have been performing as part of the EuRRECa project, we have created a list of over 500 distinct rare conditions in endocrinology and its allied fields alone.

My early experience of rare conditions

My own focus on rare conditions started in the early 90s when I was asked by my supervisors in Edinburgh, Chris Kelnar, David Bonthron and the late David Barr to perform a phenotypic and genetic analysis of a group of families with pseudohypoparathyroidism, a condition that is reported to have a prevalence of about 1 in 100,000. There are several issues about pseudohypoparathyroidism (PHP) that apply to almost all rare conditions that I have been exposed to. The first important lesson I learnt in this piece of research was the burden on the patient and I believe that one of the most important ways of learning this is by meeting a patient in their own surroundings rather than in a hospital. I visited a patient who had been very severely affected by PHP at his home. Not only were his features almost unique amongst the cases of PHP I had encountered but he was also affected to such an extent that he was severely disabled. Yet despite all this, he was very pleased to see me and to share his experience as he felt that it was important for the world to learn from him. He had always been told by his doctors that he was a unique case and the sense of isolation he had is something many people with rare conditions still experience. There are many other important lessons that I learnt from this piece of work and which have been recurrent themes and became the cornerstones and the basis of my subsequent pursuits. These include the variable and evolving phenotype, the long-term morbidity and the wide-spread distribution of cases over a large geographical area. It was also quickly apparent to me that research and scientific expertise did not necessarily have to co-locate at one centre and to achieve research excellence, researchers and clinicians needed to work across geographical boundaries as a team with a common vision. In the 90's when I was working in this field, there were at least another two research groups who were studying the genetics of PHP. At the time, I found this competition exciting but looking back at it, this competitive approach with a lack of collaboration and complementarity had a limiting effect on my research and to this date this approach has continued to hinder rare disease research. Another issue to highlight in those early years was the need for the collection of standardised data. I am certain that the handful of clinicians who looked after a dozen or so cases in total would have benefited from some guidance on some standardised collection of clinical data. It was clear to me

that the management was very variable but it was so difficult to assess efficacy as the data these clinicians collected were patchy and not uniform across these centres.

Data And Its Use In Routine Health Care

Three decades later, I like to think that as a community we are much clearer on understanding the value of collecting and comparing standardised data as part of routine health care delivery. Infact, I believe that over this time, our relationship to data has changed and it will continue to change. Let me explain this a little bit more.

In the field of health and health care, it is no exaggeration to say that we are immersed in data, some might even say that we are drowning in it. While I stand here and deliver this lecture, Apple is collecting real world data on several personal health related parameters related to me. Data generated by people or patients through wearable sensors and websites are just one form of real world data. Electronic health records, administrative, reimbursement and claims data, public health surveys, population registries and patient registries are some of the other tools for collecting these data and many of these have existed for several years. The real world evidence that can now be derived from these real world data are becoming increasingly important for understanding and improving our management of a wide range of health conditions. Although evidence derived from observational data has often been considered as low-quality as the study design is uncontrolled, increasingly innovative methods of analysing real world data are allowing the evaluation of causal inference through the study of what one can call real world natural experiments where the exposure of interest may occur by processes similar to a randomized trial. While real world evidence is unlikely to ever replace the traditional RCT, it is generally agreed that the broader generalizability of the evidence gathered from real world data can provide insights to the effectiveness and safety of an intervention that is employed in the real world rather than within the confines of a controlled trial.

DSD – A Case Study In Data Collection

The power of real world data as it is called nowadays in the field of rare conditions dawned on me when I was working in Cambridge about 25 years ago where I was exposed to another rare condition, androgen insensitivity syndrome (AIS), which is one of several conditions that are often referred to as differences or disorders of sex development or DSD for short. AIS has a reported prevalence of about 1:50,000 to 1:100,000 people. For several years, the lab led by Professor Iuean Hughes had received samples for analysing the genetics of AIS and these samples had been accompanied with standardised clinical information. An average paediatric endocrinologist will probably come across a handful of cases of AIS in their working life but Ieuan Hughes was encountering a couple of new cases every month, albeit they were virtual cases and by analysing the data on approximately 300 cases we could start seeing patterns which had never been described before. While I was working in Cambridge, I also took the opportunity to enhance my clinical experience by participating at Dr Richard Stanhope's clinics at the Great Ormond Street Hospital in London. At GOS, I also attended a special DSD clinic that was held once a month and this is the clinic where I first experienced the power of multidisciplinary care. Conditions such as DSD require the input of several experts including endocrinologists, surgeons, psychologists, geneticists, biochemists, and gynaecologists and at this clinic the patient as well as the clinicans could avail all of these simultaneously.

To give you an example of how I have used real world data over the last two decades to improve our knowledge of rare conditions, I would like to share my experience of conditions of sex development as a case study. Having experienced what could be achieved by delivering MDT care at a specialist clinic in London and having appreciated the power of large cohorts in Cambridge, I was determined to put all this together into a package on moving back to Scotland in 2000. So, soon after moving back, I started to develop a clinical and research

network for DSD. In Scotland, every person is assigned a unique identifier at birth and this has provided the country with the ability to link health care data from a wide range of sources. Following a relatively painless application process, I was not only able to link data from hospital activity data, maternal and neonatal records and obtain detailed information on epidemiology but I was also able to obtain information on the clinicians who were managing these patients and this was the first step towards the development of one of the first managed clinical networks (MCN) in Scotland.

Networks & Registries

The concept of managed clinical networks had arisen out of a review of the National Health Service in 1998. The idea behind the network was to shift emphasis away from buildings and organisations and on to patients and services. In Scotland, the NHS defined a MCN as 'linked groups of health professionals and organisations from primary, secondary and tertiary care, working in a co-ordinated manner, unconstrained by existing professional and Health Board boundaries, to ensure equitable provision of high quality clinically effective services.' The Scottish Genital Anomaly Network was formed in 2004 and later changed its name to Scottish DSD Network after the DSD term was coined in 2006.

Whilst the linked registry was helpful for purpose of collecting epidemiological data and making a case for the clinical service, it could not provide more detailed information about the cases themselves and this gap formed the basis of several more targeted developments including a Scottish DSD Registry in the 2000s for the DSD managed clinical network. However, given that we are talking very rare conditions and Scotland has a population of about 5 million, a Scottish Registry had limited value. For instance, we tried to use the linked data for understanding temporal trends and we could not see any clear trends. These kinds of activities are a lot more informative when countries pool their resources together as illustrated by the activities of EUROCAT, the European network of population-based registries for the epidemiological surveillance of congenital anomalies. When data from several countries are pooled together under the EUROCAT umbrella, there is an observable increase in the birth prevalence of atypical genitalia.

However, data related activities can be very powerful and effective in even small populations. In Scotland our focus has now settled on a programme called the Scottish Audit of Atypical Genitalia, a nationwide e-surveillance programme which is led by Dr Martina Rodie and which has now been active for almost 10 years and which aims to assess the initial care of all infants who are born with atypical genitalia in Scotland. Usually, the expert is the third or fourth health care professional that the parents meet in such a case and the first impression often does remain the last impression. Thus addressing the care pathway right at the beginning is critical. This e-surveillance programme that is coordinated by Dr Rodie is performed in collaboration with two managed clinical networks, the Scottish DSD network and the Scottish Paediatric Endocrine Group, as well as the regional cytogenetic labs who provide us data which can act as an alternative source of verification, an important aspect of surveillance activities. By targeting service delivery at the initial point of presentation, we can also assess care against standards that we have identified as important in previous studies as well as amongst experts.

Crossing Borders

At the time, the Scottish DSD Registry was developed, there was a strong willingness amongst several international experts to consider collaboration and sharing of experiences and this was illustrated by the DSD consensus meeting in 2005. I don't think this was just because a group of experts were keen to work together but it was also to do with gathering discontent amongst patients. The late 1990 and early 2000s was

also the time when the spotlight of the state had been cast on unsupported clinical activities in the field of rare conditions such as paediatric heart surgery. Patients, professionals as well as the state were all in favour of greater sharing of information and the concept of collection, analysis and comparison of data across boundaries was a half open door by 2005. Several experts in the field of DSD had personal experience of local databases but an online web-based database was relatively unheard of in the field of rare conditions in the 2000s.

This was the beginning of a fruitful partnership with a number of people who have become close friends and in this vein I have to thank Olaf Hiort from Luebeck who is in the audience here. In addition to Olaf and Ieuan Hughes, I was also lucky to have Sten Drop from Rotterdam and Silvano Bertelloni from Pisa with technical support from Richard Sinnott in Glasgow. Our European project started off with pump priming from the European Society for Paediatric Endocrinology and was followed by funding from EUFP7. We quickly realised that the gap we had identified extended beyond the borders of Europe and when the EuroDSD project was coming to an end, we sought funding from the MRC in the UK and changed its name to the I-DSD Registry. I clearly remember meeting at the MRC's office in London in 2011 and being told in no uncertain terms that when the funding finishes, that I should not come back to them as by then the project should be able to sustain itself. A decade later, the I-DSD Registry has around 150 centres in over 50 countries across all inhabitable continents and it sustains itself through a number of different activities including investigator fees, research grants, symposia and unrestricted education and research grants from industry. It has a strong research ethos with the majority of projects being led by a core group of partners in Europe. I think that 'sink or swim' discussion that occurred with the MRC was very important in 2011 as it gave us a clear indication of what we needed to do for the future. It has also allowed us not to put all our eggs in one basket and not be dependent on one single source of funding. Another lesson that was learnt in this project was that once a platform and a governance structure has developed then it can be applied to a number of conditions rather than just a narrow group of conditions. We have applied this economy of scale concept to the I-DSD project which now has mirror registries for allied conditions including Congenital Adrenal Hyperplasia and Turner Syndrome. However, as the user base expands, I appreciate that there is a danger of a disconnect with the stakeholders and of course there are additional demands on project management which are very well known to Jillian Bryce, my long suffering senior project manager.

While developing the I-DSD platform for data collection, we have also continued to engage with our stakeholders and I could broadly divide these into patients, health care personnel, researchers and the pharmaceutical industry. Not only has I-DSD sought patient representation in its management strructures, with the help of an EU Cost Action, DSDnet, which was led by my friend Olaf Hiort, we consulted patients through a workshop and through the international I-DSD meetings we invited patients to become active participants. These forums also allowed us to understand the research priorities of patients. Similar exercises have also been directed at health care personnel who are also critical gate-keepers for recruitment and supply of data. I have always felt that for maximum buy-in the research that is performed needs to be of relevance to these health care staff as well as the patients. I am hoping that the clear understanding that we have developed of what drives these two groups of stakeholders shall be helpful in directing the activities of the researchers in the future. Until quite recently, there was scarce therapeutic development in the field of DSD and its allied fields such as CAH. However, over the last 5 years, advances in steroid replacement at a pharmaceutical as well as a cellular level has opened up the prospects of several novel therapies. The I-DSD project has built links with several companies that have an interest in therapeutic development and not only has this allowed the project to sustain itself with a clear focus on patient benefit, but

it has also allowed the registry to develop higher standards on data quality.

Lessons Learnt from DSD

There are several other lessons that I have learnt from I-DSD but for the purpose of this lecture, one important point is that in addition to supporting several forms of clinical research, disease registries can deliver on improvements in the quality of clinical care and can be very patient focussed. As an example of this, I would like to share with you a recent exercise that was launched by Salma Ali, a PhD student in the team. In her work she had been looking at routinely reported data on adverse events in CAH. This is a condition where due to a lack of adequate adrenal function, in times of stress, patients do not produce enough cortisol and can become quite unwell and may need hospitalisation. There are other effects of this condition as well as its treatment, and while opinion varies as to the importance of these to patients and how they should be assessed, there is general agreement amongst everybody that an adrenal crisis or the need for hospitalisation or the need to give extra steroids to prevent hospitalisation are adverse events we should try to avoid. So when Salma looked at these data across several centres across the world not only did she start seeing trends but she could also define a benchmark around which there was inter-centre variation. Although we had not set out to perform this work with a view to quality improvement, when the manuscript was being circulated amongst contributing centres, several coauthors were keen to know the performance of their own centre in comparison to the benchmark. This informed approach by the collaborators was a clear indicator that the community was mature enough to tackle quality improvement and it led us to the development of centre specific reports which these centres can use locally. I am very proud of this work as it shows that exercises of clinical audit and care quality improvement are highly likely to be accepted by the user community when they are suggested by the community itself rather than being imposed externally on the community. With this positive experience, the I-DSD project has now developed a specific committee for care quality.

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And it's the assessment of quality of care that brings me on to why I am here in Leiden.

As you know very well, if an idea is good it is highly likely that there are at least a dozen people thinking of the same idea. I am certain that Archimedes was not the only person who observed and described volume displacement. Perhaps he was the best at publicity and dissemination! I say that as while I was working on registries around 2015, there were over 800 national or international registries for rare conditions in Europe. What was also clear was that there was a fair amount of duplication in the conditions that were covered by some registries. Projects such as RD-Connect and Orphanet were expressly funded by the EU to create registries of registries but our own work has shown that these registries did not capture several disease registries. On the other hand many expert centres were not aware of existing registries or did not participate despite knowing about them. Possible reasons include concerns about the quality of the registry, its objectives, its governance or just the physical hurdles of data entry. These kinds of issues can have a major bearing on long-term sustainability and at this point I have to mention the visionary work which Domenica Taruscio has been undertaking in Rome in the development of an annual school for rare disease registries. This is a unique educational event that promotes good practice in the field of registries and it is activities like these which make Europe stand out as a beacon in the field of rare conditions.

In the five years leading up to 2015, the EU was becoming very focussed on improving the care of people with rare conditions and was keen to do this through the creation of

reference networks. To me this idea sounded very similar to what had already occurred in Scotland and when the European Reference Networks were being formed in 2016, it was clear that they would need registries. Endo-ERN led by Alberto Pereira in Leiden at that time, posed a particularly big challenge as it was the most ambitious in its coverage. At the outset, it consisted of over 70 centres in almost 20 countries who encountered a very wide range of endocrine conditions. To me this was a nice challenge as it allowed us to design a platform that could cover a small amount of information about several conditions. This task was made easier by the development of a core set of data fields that were endorsed by the EU. The European Registries for Rare Endocrine Conditions (EuRRECa) was launched in 2018 and consists of two registries, an e-surveillance registry which is a very light touch registry that collects no personally identifiable information and a core registry which has the functionality to create more detailed modules for any endocrine condition. In fact, the versatility of these platforms is so high that in 2020, Natasha Appleman-Dikjstra, also from Leiden was able to use these platforms to create EuRR-Bone, a registry for rare bone and mineral conditions. Actually, the platforms that have been developed can be applied to any health care condition that we can think of. Since its launch in 2018, the e-REC platform is now being used in over 40 centres in 20 countries and its spread is a testament to its simple yet effective design. The Core Registry was launched in mid 2019 and despite the fact that we have had limited opportunity to publicise it and sing its virtues it is already being used in 10 countries. When Endo-ERN like all other ERNs was created, it relied on health care providers expressing an interest in joining the network and their level of expertise and potential for active involvement was judged on their stated level of activity. As these ERNs enter their second 5 year cycle, I believe that the data that have been collected through EuRRECa will not only provide hard evidence of activity but will also identify a core group of centres within the ERNs that are keen to participate in collaborative activities.

Challenges

I think there are still several challenges in the field of registries for rare conditions. First of all, I mentioned earlier that these registries can be very patient focussed. And indeed when I have discussed this at dedicated workshops with what I call, expert patients and clinicians, we all agree, that patient involvement in registries is very important. In the EuRRECa project, we have developed a platform that allows patients to report their own outcomes. However, what we have seen with the EuRREca project, and it is early days, is that the patient I see day to day in the clinic or the busy clinician in a standard hospital setting is less interested in the routine collection of patient reported outcomes than the experts at a workshop. So, we need to explore the involvement of the ordinary patient and clinician a little bit more and this will be especially challenging when we are thinking of the whole of Europe rather than a single centre, city or even a country or a specific patient group. Related to this is the concept of clinical outcomes and quality improvement. Whilst it is easy to measure a service by quantifying caseload, it is a lot more complex to measure the quality of the service delivered by clinical outcomes. This can be achieved by collecting generic health related quality of life outcomes. However, many patients and health care providers feel that there is a need for condition specific outcomes and there is little agreement in this area for the wide range of conditions encountered. Even if these challenges are automated, the cycle of quality improvement is a very laborious, albeit rewarding activity. When thinking of the health care professionals who have to recruit patients and enter data, I do feel they need guidance and direction regarding recruiting and what data to enter as well as how often. I don't think it is as simple as saying detailed information should be entered on all rare endocrine conditions or all forms of rare endocrine conditions every 6 months. There needs to be a clear rationale for these actions and there will need to be a selection of a small number of conditions and it is highly likely that there will be some losers and winners in this selection process. Another challenge is around data flow. We need to

think of systems where the burden on the clinician or the patient can be minimised and where data can also be shared with other certified and approved users. I believe that some of this can be addressed at a system level. When the EC's Expert Group on Rare Diseases outlined the criteria for an expert centre, its recommendations included that an expert or reference centre should be able to participate in regular audit exercises; however, this depends on having local resources and unfortunately most expert centres do not think through this very carefully. Infact, a data manager is rarely considered to be a vital part of the multidiciplinary team but may actually be the most important member if we want the expert service to thrive. Another system level change that needs to happen is related to the ability for data linkage. Going back to my experience in Scotland, the universal identifier has been very beneficial for data linkage and this was not something that was just created for people with rare conditions. However, the ability to link data for rare conditions will require crossing borders. I have my fingers crossed that the current direction that the EU is taking with the European Health Data Space will make the provision of a unique health identifier number to all its citizens a reality and as this happens this will reap huge dividends in the future.

Having arrived at the end of my discourse, in the first place I would like to express my thanks to the general board of the Leiden University for having appointed me to this chair. To create a post of a Professor of Endocrine Registries is truly far sighted and sets a precedent which will allow the University to stay at the forefront in this field for years to come. Furthermore, I would like to thank all who have devoted themselves to my appointment. Amongst these, I would like to particularly thank here Professor Hogendoorn, Dean of LUMC and the members of the Department of Medicine at LUMC, in particular Ton Rabelink, Olaf Dekkers, Natasha Appelman-Dijkstra and Nienke Biermasz for the enthusiasm with which they welcomed me and the pleasant and stimulating cooperation I have experienced over the last few years. Professor Dekkers, Olaf, has not only shared his office with me in LUMC but has also continued to maintain my scepticisim in almost everything scientific. Professor Biermasz, Nienke, has reinforced my views that clinical academics are primarily there to devise novel methods of improving the care of patients and evaluate the effectiveness of existing therapies and interventions. And then, Dr Appelman-Dijkstra, Natasha. It has been an absolute pleasure working with you; I feel that there is a level of sixth sense going on between us. Last but not least within this family of distinguished professors, I would like to add Professor Pereira, Alberto the synergies and complementarity that we have shown in our achievements over the last seven years and which are envied by many across the world could not have been achieved without the joint common vision that we have had in the field of rare conditions. A special word of thanks also goes to the Office for Rare Conditions Registries support team in Glasgow led by Jillian Bryce and the new Registries support team at LUMC led by Tess de Rooij and Ana Priego.

I would also like to thank a number of people personally who have greatly influenced my development over the years. As you know this is not the first chair I have ever held. I was conferred a personal chair of developmental endocrinology in 2009 at the University of Glasgow and this was followed by the award of the Samson Gemmell Chair of Child Health at the University of Glasgow, the oldest chair of paediatrics in the United Kingdom. I would like to thank several people including the late paediatric surgeon William Bissett in Edinburgh and Cliff Roberton in Cambridge who attracted me to the field of paediatrics. Whilst there several others along the way who have injected the bug of research and academic endeavour, I would particularly like to thank Professor Chris Kelnar in Edinburgh, Professor Raj Thakker, formerly in London and now in Oxford and Professor Ieuan Hughes in Cambridge.

In a letter to Robert Hooke in 1675, Isaac Newton stated that 'If I have seen further, it is by standing on the shoulders of giants'.

Actually, I think Newton probably borrowed this metaphor from Bernard of Chartres! There are several other clinicians and academics who have been instrumental in my success, too numerous to mention and many of whom are in the room today and I think you know who you are!

Last, but not least, I would like to thank my wife, my partner for 35 years, Shazia; behind everything a man does, there is a woman, a mother, a sister, a daughter or a wife and this is so true in my case.

I have spoken.

Prof. S.F. Ahmed

Professor Faisal Ahmed graduated from the University of Edinburgh in 1987 and received the bulk of his training in Edinburgh and Cambridge. In 2000, he was appointed as a consultant in paediatric endocrinology at the Royal Hospital for Sick Children, Yorkhill, Glasgow and after holding the Leonard Gow Lectureship in Child Health for a few years, he was appointed to the Samson Gemmell Chair of Child Health at the University of Glasgow in 2012. Since 2019, he has also held an appointment at the University of Leiden as Professor of Endocrine Registries. In Glasgow, he founded the Developmental Endocrinology Research Group and the Office for Rare Conditions and has published over 300 communications with a particular focus on improving the health of people with rare endocrine conditions, and especially those with conditions affecting sex development. For his contributions to the field of paediatric endocrinology, he was awarded the European Society for Paediatric Endocrinology Research Award in 2021.

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