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Q1 When did you realise that you wanted to pursue a career in paediatric and academic nephrology?

I only ever wanted to be a paediatrician, thanks to *ER*'s Doug Ross, and my first job was on the nephrology service in Temple Street in Dublin, Ireland. In that first week, we started a newborn on dialysis, and it seemed almost magical that a child born with no kidney function could survive to live a normal life, thanks to technology and the work of this incredible team. I knew that this was the career for me.

They were an incredibly inspirational team, and I remember nurses in particular, like Sheila Boyle, who impressed me with their dedication, knowledge, and understanding of patients. Two consultants, Atif Awan and Denis Gill, both had a huge impact, as I saw how much they cared for their tiny patients and how our interventions could completely change their outcomes. I was so inspired by Gill, a Professor of Paediatrics in the Royal College of Surgeons Ireland (RCSI), who had a massive impact on the type of doctor I wanted to be. Gill opened my eyes to how teaching, research, and clinical practice could intersect to create a meaningful and satisfying career. I have been driven to uphold these standards every day of my practice since.

Furthermore, paediatrics is fun! Yes, it is serious, and frequently our patients and families find themselves in circumstances that they could never have imagined, but there are always stickers and bubbles, and a child's attitude that is firmly rooted in the now. Children impacted by kidney disease, and in particular kidney failure, have been dealt a very difficult hand in life. Kidney failure impacts every aspect of their emotional, social, and educational development. Unlike many branches of medicine, in paediatrics it is all personal. We have all been children, we all remember the challenges of childhood and adolescence, and it does not take much imagination or empathy to overlay kidney failure onto our own childhoods, and imagine how challenging it could have been.

I want to do everything in my power to enable children with kidney disease and kidney failure to live their best lives. In my opinion, this starts with making an early and accurate diagnosis so that we can start treatment that delays kidney failure; predicting the future for their families to allow them to dream big dreams that include their child's diagnosis; allowing their parents to make informed reproductive decisions in expanding their family; and, where possible, informing the selection of the best possible kidney donor.

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Q2 Alongside your clinical work, you are the Academic Lead for Graduate Research at the University of Melbourne School of Medicine, Victoria, Australia. What does this role entail?

One of my passions is education and nurturing students through their degrees to become independent researchers. As Academic Lead (Graduate Research) in the Melbourne Medical School, I am working to implement strategies and initiatives that enhance the graduate researcher experience, and improve supervisor capability. These initiatives have included a series of communication workshops and career events, as well as a monthly graduate researcher newsletter focused on promoting opportunities for collaboration and skills development.

Q3 What drove your interest in renal genetics, and how did you come to set up the renal genetics service at The Royal Children's Hospital in Melbourne in 2016?

I am an endlessly curious person, and this drove my interest in renal genetics. More than anything, I want to understand why my patients have kidney disease, and I believe that this understanding leads to better outcomes. At Melbourne Children's there is a lot of support for people with ideas and the ability to follow them through. I was lucky to link up with two fantastic clinical geneticists early on, Sue White and Zornitza Stark, as well as a genetic counsellor, Ella Wilkins, and we opened the doors of our clinical service in 2016 with the support of the Royal Children's Hospital (RCH) Foundation. This service now offers 26 multidisciplinary clinics per year, and provides a new model of care for the diagnosis and management of genetic kidney disease. From the beginning, we have integrated research into our clinical service and have worked closely with Melissa Little at Murdoch Children's Research Institute (MCRI), recruiting patients to kidney organoid modelling projects that have expanded our understanding of the pathogenetic mechanisms of kidney disease.

I am passionate about equity, and my early driver on the research side of the clinic was to generate an evidence base to support an application for federal funding for genetic testing in patients with kidney disease. Within a year, we had the data to support a move into adult services with the support of Melbourne Genomics, and since then we have gone from strength to strength.

Q4 What impact has this service had on patient care since its inception?

Since its inception, our kidney genetics service has reviewed over 500 patients, and we have set a new benchmark for diagnostic yield, while generating the evidence base to support a successful application for federal funding of genetic sequencing for patients with kidney disease in Australia.

Further outputs from the service have included guidelines for the diagnosis and management of patients with kidney disease, the development of visual genomic explainers and decision support tools, the addition of new genes to the PanelApp kidneyome (Australian Genomics, Melbourne, Australia), and the development of a registry of patients with genetic kidney disease.

Q5 You lead the Kidney Flagship at the MCRI. Could you tell us more about the Kidney Flagship, and discuss its aims and goals?

The Kidney Flagship is a multidisciplinary collaboration of clinicians and scientists at Melbourne Children's with a focus on kidneys. The flagship is a comprehensive clinical research pipeline spanning multiple research groups at MCRI, and linking with clinical services at RCH. The flagship built on my ongoing work examining genetic kidney disease from multiple perspectives: clinical outcomes, qualitative assessment, clinical utility, health economics, implementation science, research genomics, pathophysiology, functional genomics, disease modelling, drug screening, and, ultimately, the development of clinical trials.

Our vision is to end kidney failure in childhood, and our mission is to find new ways to prevent kidney failure in childhood while developing better alternatives to dialysis. We are approaching this from five different directions: aiming to empower families to drive research and clinical interventions; to provide an early and accurate diagnosis for children based on research genetics; to develop data-led approaches to manage kidney disease; to discover and repurpose therapies to treat kidney disease; and to develop transplantable stem cell-derived kidneys.

There have been two key papers[1,2] that have been major outputs from the Melbourne Genomics flagship, showing the significant clinical impact of a genetic diagnosis, and which formed a significant portion of Kushani Jayasinghe's PhD under my supervision. The first paper set a new benchmark for diagnostic yield (39%), and the second demonstrated the cost-benefit to the early application of genomic sequencing for children with glomerular disease, demonstrating an incremental cost saving of 3,230 AUD per additional diagnosis when compared to standard of care. These papers formed the evidence summary quoted by the Medical Services Advisory Committee (MSAC) in their recommendation that genomic sequencing for patients with kidney disease should be funded by Medicare in Australia. These papers were also key to the initiation of three new Medicare Benefits Schedule (MBS) item numbers, which fund genomic sequencing for patients suspected to have genetic kidney disease, along with their families and reproductive partners.

I am now fortunate to collaborate with Jayasinghe, as we are working to mainstream genomics in nephrology, and to support all nephrologists in Victoria to request and interpret genetic tests for appropriate patients in general nephrology clinics, another project funded by Melbourne Genomics.

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Q6 Your current research focuses on the use of electronic medical record (EMR) data to locate patients at risk of kidney disease. Could you tell us more about this work, and how you foresee this being rolled out across healthcare systems?

I am passionate about achieving an early, accurate diagnosis for children, believing that this leads to the best outcomes. As our hospital moved to an electronic health record (EMR), I realised that there was an enormous amount of healthcare data sitting in the system that could be used to identify children at risk of kidney disease, if we only knew the right question to ask. In collaboration with the Centre for Health Analytics and a brilliant PhD

student, Gráinne Butler, we have utilised data in the EMR to detect a signature for early kidney disease in patients who are undiagnosed and unknown to the nephrology team. This enables us to proactively reach out to patients to offer genomic sequencing.

I believe that data-driven decision-making about healthcare can drive a new era for medical care. The power of data enables us to identify patients before they are symptomatic to proactively intervene early on, so that patients do not have to experience the impact of their disease, and improve outcomes. An example of this in practice at the RCH is the utilisation of EMR data to identify patients with haematuria who have not had follow-up samples or been referred to nephrology. If sustained, haematuria could signify a future risk of adult kidney disease, such as Alport syndrome. Once we have identified these patients, we proactively contact them to arrange a follow-up urine test, offering genomic sequencing to those with sustained haematuria. Through this programme we have identified children with Alport syndrome who were unknown to our nephrology service, or any medical team, enabling us to intervene at an early stage and improve longer-term outcomes for these children.

This programme has the potential to drive a paradigm shift in medicine as we use the power of data to identify patients at risk, rather than waiting for them to develop symptoms. Essentially, we are shifting the focus from treating sick children to working to keep them well, while proactively using the EMR data-lake to identify at-risk patients, rather than waiting for them to be referred to our care.

Q7 You recently co-authored a paper entitled 'Clinical and diagnostic utility of genomic sequencing for children referred to a Kidney Genomics Clinic with microscopic haematuria'. Could you summarise the key findings from this article?

I loved this paper, not least because the lead author, Josiah Shanks, was a medical student when he started the project, and I always enjoy introducing students to the exciting world of research. This was a retrospective review of all patients with microscopic haematuria referred to our Kidney Genomics Clinic from January 2016–December 2021. We demonstrated a substantial diagnostic yield (48%) and clinical utility (60%) of genomic analysis for children with microscopic haematuria.

Q8 What are some of the main challenges in implementing genomic testing into routine nephrology practice?

The challenges differ across the world depending on the availability of genomic sequencing, and the knowledge base of healthcare providers. In Australia, where genomic sequencing is now funded for patients with kidney disease, and where we have been providing nephrology-specific genetic education through the KidGen collaborative for many years, the main challenges remain confidence and finding the time in a busy consultation to appropriately consent, request, and explain genetic testing.

In Victoria, with the support of Melbourne Genomics, we have developed a suite of decision support tools, visual explainers, and an

education programme alongside the development of genomic champions and funded genetic counsellors. At RCH, we are fortunate to have two genetic counsellors, equating to a full-time position, embedded in our nephrology team, providing invaluable support for all the paediatric nephrologists in requesting and interpreting genetic tests on the wards and in the clinic. Recognising the distances that patients can travel in Australia, we have developed our service so that we can provide appointments via telehealth and genomic sequencing on saliva samples that patients collect at home and post to us.

The pace of change in genomics is breathtaking, and I am grateful to work with a flexible team who are endlessly willing to try new approaches to patient care, and research as the knowledge base expands.

Q9 What do you feel are the main gaps within the field of nephrogenetics?

Knowledge, knowledge, knowledge. While the diagnostic yields have increased and there are new therapies available, such as sodium-glucose cotransporter-2 inhibitors and vasopressin 2 receptor antagonists, so many of our patients do not have an identifiable genetic cause, and many do not have an available disease-modifying agent.

I would like to better understand the genetics that underly a predisposition to kidney disease, and the development of data-analytics tools that can be deployed to identify at-risk children before the development of disease. I am excited to think about how the use of data-driven artificial intelligence approaches could make this a reality.

Internationally, the main gap remains equitable access to genomics, including both funded genetic testing and the clinical knowledge required to identify patients who will benefit from a genetic test, provide genetic counselling, and interpret the results. The expansion of genomics education at medical conferences, in undergraduate curricula, and through free online resources, such as GlomCon and NephMadness, will hopefully continue to bridge this gap.

Q10 What direction would you like to see the field of renal genomics take in the future?

I would like to see genomics adopted broadly by nephrologists as another diagnostic tool in our kit, similar to histopathology or ultrasound. Further to this, I would like to see more data-driven approaches to the identification of children at risk of kidney disease, and a shift towards proactive, preventative kidney healthcare in childhood rather than the management of disease.

Q11 To conclude, what has been your proudest achievement in your inspiring career thus far?

I am proud to have developed a kidney genetics service that has provided answers to so many families, and to have developed the evidence base to ensure equitable access to genetic testing for patients with kidney disease across Australia. I am also very proud of my role in developing the Kidney Flagship and in developing data-informed approaches to the early detection of kidney disease.

But if you asked me what makes me happiest at this stage of my career then my answer would be different. Working with children never ceases to be fun and I adore meeting them again as secure, confident adults with the world at their feet. Similarly, I love supporting and nurturing the next generation of researchers, and the achievements of my students bring me the greatest joy. I am fortunate to have been inspired and supported throughout my career by some incredible clinicians, and hope that I will similarly inspire and support the next generation of nephrologists to be the best version of themselves.

References

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