Institution: University of Bristol		
Unit of Assessment: 1) Clinical Medicine		
Title of case study: Transforming the care of children and adults with nephrotic syndrome throughout the world		
Period when the underpinning research was undertaken: 2002 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Moin Saleem Richard Coward	Professor of Paediatric Renal Medicine Professor of Renal Medicine	1999 - present 2001 - present
Period when the claimed impact occurred: 1st August 2013 – 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Steroid resistant nephrotic syndrome (SRNS) is a devastating renal disease which, until the last 5 years, was blindly treated with heavy immunosuppressive regimes, with massive morbidity. University of Bristol research revealed underlying molecular mechanisms based on the target cell, the glomerular podocyte. By establishing both a gene panel testing for podocyte monogenic disorders and a national nephrotic syndrome patient register with over 3,500 participants, we enabled rapid diagnosis and precision targeting of therapies, including gene therapy approaches, and informed new international clinical practice guidelines. In the UK, over 1,000 patients have benefited from genetic testing, with an estimated saving of GBP68,900 per patient (GBP5-10 million total per year) for the NHS. This has stratified patients to permit targeted, less toxic therapies, improved kidney transplant outcomes and established a resource for industry which has generated inward UK investment totalling over GBP50,000,000 in academic and spin out partnerships.

2. Underpinning research

The glomerular podocyte is the central cell of the kidney filtration barrier, and the primary target of most forms of proteinuric kidney disease. The University of Bristol (UoB) Renal research group led by Prof Moin Saleem is an acknowledged world leader in podocyte biology and translational research.

In 2002, Bristol Renal were the first to develop conditionally immortalised human podocyte cell lines [1]. Previously, podocyte cell lines had been unrepresentative of the *in vivo* specialised cell types. The UoB cell lines have since become the international gold standard tool used by academia and industry for developments in podocyte biology. The underpinning study [1] is the 5th most cited paper of all time in the *Journal of the American Society of Nephrology*, the world's leading kidney journal. Development of this integral tool has led to understanding fundamental podocyte disease pathways relevant to many disease processes (e.g. Insulin signalling/resistance and diabetic kidney disease), as well as enabled the discovery and validation of gene mutations causing glomerular disease.

Steroid Resistant Nephrotic Syndrome (SRNS) is a disease of kidney filtration, resulting in substantial and unremitting protein loss into the urine. It is managed with heavy immunosuppression, but despite this over 60% of patients eventually suffer irreversible kidney failure. It is a rare disease (incidence 2-5/100,000), but arguably the most difficult clinical

condition that nephrologists manage, and accounts for 10% of the 67,000 dialysis patient population. The initial diagnosis is made clinically, and our work [2, 3, 4, 5] has made it clear that the disease segregates into genetic and several non-genetic forms.

Our underpinning research (using cell lines and patient cohorts) has identified new genes responsible for genetic/familial SRNS, as well as establishing Next Generation Sequencing (NGS) technology as the optimal clinical testing pathway [2]. We published the first description of NGS to test patients for SRNS [2] and demonstrated its clinical utility [3]. By applying this testing to UoB-led national patient cohorts, in conjunction with detailed genotype-phenotype correlations, we have stratified SRNS patients into genetic and clinical groups and subgroups to guide new management paradigms [4, 5, 6].

3. References to the research

1) **Saleem MA,** O'Hare MJ, Reiser J, **Coward RJ,** Inward CD, Farren T, Xing CY, Ni L, Mathieson PW, Mundel P. (2002). A conditionally immortalized human podocyte cell line demonstrating nephrin and podocin expression. *Journal of the American Society of Nephrology,* 13, 630–638. Available at: https://jasn.asnjournals.org/content/13/3/630

2) McCarthy HJ, Bierzynska A, Wherlock M, Ognjanovic M, Kerecuk L, Hegde S, Feather S, Gilbert RD, Krischock L, Jones C, Sinha MD, Webb NJA, Christian M, Williams MM, Marks S, Koziell A, Welsh GI, **Saleem MA** on behalf of RADAR the UK SRNS Study Group (2013). Simultaneous sequencing of 24 genes associated with steroid-resistant nephrotic syndrome. *Clinical Journal of American Society of Nephrology,* 8, 637–648. DOI:10.2215/CJN.07200712

3) Sen ES, Dean P, Yarram-Smith L, Bierzynska A, Woodward G, Buxton C, Dennis G, Welsh GI, Williams M, **Saleem MA.** (2017). Clinical genetic testing using a custom-designed steroid-resistant nephrotic syndrome gene panel: analysis and recommendations. *Journal of Medical Genetics,* 54, 795–804. DOI:10.1136/jmedgenet-2017-104811

4) Bierzynska A, McCarthy HJ, Soderquest K, Sen ES, Colby E, Ding WY, Nabhan MM, Kerecuk L, Hegde S, Hughes D, Marks S, Feather S, Jones C, Webb NJA, Ognjanovic M, Christian M, Gilbert RD, Sinha MD, Lord GM, Simpson M, Koziell AB, Welsh GI, **Saleem MA.** (2017). Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management. *Kidney International,* 91, 937–947. DOI:10.1016/j.kint.2016.10.013

5) Mason AE, Sen ES, Bierzynska A, Colby E, Afzal M, Dorval G, Koziell AB, Williams M, Boyer O, Welsh GI, **Saleem MA.** (2020). Response to First Course of Intensified Immunosuppression in Genetically Stratified Steroid Resistant Nephrotic Syndrome. *Clinical Journal of the American Society of Nephrology,* 15, 983–994. DOI:10.2215/CJN.13371019

6) Ding WY, Koziell A, McCarthy HJ, Bierzynska A, Bhagavatula MK, Dudley JA, Inward CD, **Coward RJ**, Tizard J, Reid C, Antignac C, Boyer O, **Saleem MA**. (2014). Initial Steroid Sensitivity in Children with Steroid-Resistant Nephrotic Syndrome Predicts Post-Transplant Recurrence. *Journal of the American Society of Nephrology,* 25, 1342–1348. DOI:10.1681/ASN.2013080852

Grant Funding:

i) **Coward R.** Insulin signalling to the podocyte; pathological importance and therapeutic potential. MRC Senior Clinical Fellowship, 2013 - 2019, GBP1,463,941

ii) **Saleem M,** Kidney Research UK academic-industry award, 2017, GBP2,050,000

iii) **Saleem M.** MICA: NURTuRE: changing the landscape of renal medicine to foster a unified approach to stratified medicine, MRC, 2018 - 2022 GBP2,561,602

iv) **Saleem M.** Trans-national cohorts of nephrotic syndrome - a unified approach to a global chronic disease. MRC GCRF, 2017 – 2020, GBP532,742

4. Details of the impact

SRNS is a devastating disease disrupting the glomerular filtration barrier of the kidney, with multiple distinct pathological triggers, most of which are immune based and poorly understood. Hence traditionally it has been treated indiscriminately with heavy 'toxic' immunosuppression, with limited benefit and huge morbidity (e.g. infections, poor growth and nutrition (in children), low energy, loss of employment/schooling). 60% of these patients develop end stage kidney disease (ESKD) within 5-years of diagnosis. Our work has been based on insights into the target cell, the glomerular podocyte [1], and applied directly to clinical care via comprehensive national registries. This has distinguished genetic forms of SRNS from immune based SRNS, and further subclassified the latter in order to better target patients who will respond to specific therapies or transplantation [4-6].

Changed national and international clinical practice

The gene panel test developed by Saleem and Coward [3] was approved by UK Genetic Testing Network (UKGTN) in 2014 for clinical use. Bristol Genetics Laboratory were the first national provider of UKGTN panel testing for proteinuric renal disease and haematuria, and in 2019 were approved as one of two UK genetic testing hubs for all renal genetic disease, using gene panel technology [Aii (cites [3])]. In the UK over 1,000 patients from 81 UK and 44 international centres have been tested to date by utilising the UoB gene panel [A]. The cost saving to the NHS of implementing the results of the genetic test was estimated in the (successful) UKGTN application in 2014 to be GBP68,900 per patient, as a consequence of changing the patient clinical pathway [Ai].

Gene panel testing has been incorporated into the first International Pediatric Nephrology Association (IPNA) clinical practice recommendation for children with SRNS [B]. UoB research demonstrating clinical utility [3] and stratification [4] are cited among the evidence and rationale for genetic testing, and a *'comprehensive gene panel analysis'* using the gene list identified in [4], is recommended [B (p.1539)]. This has resulted in standardisation of care across the world (IPNA members in 105 countries, bringing together eight regional paediatric nephrology societies). Assessment of risk of transplant recurrence using clinical biomarkers that predict recurrence with 90% sensitivity in non-genetic subgroups [6], has also been incorporated in the guideline for selection of transplant recipients [B]

Benefits to health and well-being of patients and families

Availability of comprehensive and rapid genetic test results for SRNS has eliminated previous indiscriminate and harmful diagnostic and treatment routes. A survey of UK paediatric nephrologists confirmed that the improved understanding of underpinning genetics and availability of genetic testing had changed clinical practice for all respondents [H]. Respondents noted the avoidance of immunosuppression and biopsy, as particular changes in practice [H]. Kidney biopsy looking for histological changes that caused discomfort, cost, and could require up to two weeks' recovery for patients, is now no longer necessary. Harmful effects of inappropriate, trial and error immunosuppression protocols (e.g. mood changes, hypertension, poor growth, weight loss, infection, hair loss, GI disturbance), applied across the whole patient groups, have also been prevented. This management change translates to 30 new patients per year in the UK, and 150 per year in the US.

The gene panel test also predicts patients who will get recurrence of disease after kidney transplantation. 50-90% of patients with genetic or sporadic SRNS will suffer from renal failure

and require transplantation. Up to 50% of patients with non-genetic SRNS will suffer recurrence of the primary disease in the newly transplanted kidney [4], with implications for counselling and disease management, whereas <2% of patients with genetic SRNS have been reported to get post-transplant recurrence. This will affect both patient counselling and the choice of live related kidney donors. For both the patient and family members, there is the additional benefit of being able to understand the nature of their condition, provide genetic and antenatal counselling, offer specific therapy for some mutations (mitochondrial diseases) and test other family members if necessary. Prof Saleem is a founding trustee of the Nephrotic Syndrome Trust (NeST) patient community which provides information and support to patients and their families, including through annual patient days and laboratory open days which offer the opportunity to meet scientific researchers and *'help them understand the science directly'* [G]. The Director of NeST describes how UoB research is *'embedded in our activities and patient interactions'* and the importance of the information for patients which is *'impossible to find elsewhere for a rare but devasting disease'* [G].

Finally, there is a small but significant cohort of usually early onset mitochondrial disease individuals whose genetic disease is treatable by co-enzyme Q10 administration if recognised, preventing both renal disease and neurological deterioration. This impacts 5-10 patients per year across the US and Europe and is a life-transforming intervention.

Increased UK registry infrastructure

In parallel with the gene technology development and testing, in 2010 Saleem and Coward initiated the UK Renal Rare Disease Registry (RaDaR), housed in the UK Renal Registry in Bristol, and now nationally embedded within UK Renal medical practice. As of 31st December 2020, there were 26,913 UK patients in RaDaR from 104 hospitals, and 29 rare diseases covered [C]. Genomic and molecular stratification into rare disease groups is facilitating personalised medicine and evidence-based care pathways.

The RaDaR registry now forms the core repository of NURTuRE (National Unified Renal Translational research Enterprise), formed in in 2017 collaboration with industry partners and under the strategic management of Kidney Research UK. This original initiative, delivered by UoB (Saleem) and the University of Nottingham (Prof Maarten Taal), has created a national Kidney Bio Bank for collection and storage of biological samples from 3,000 Chronic Kidney Disease (CKD) patients and up to 1,000 Nephrotic Syndrome (NS) patients. The enterprise has established renal research nurses in 14 large renal centres across England, Scotland and Wales, and also integrates patient support groups including the NeST, and Renal Patient Support Group [D, G]. Patient representatives from NeST attend biannual consortium meetings and patients receive updates via 'Precision Medicine Champions' [G].

Increased industrial capacity for R&D in renal care

Since 2018, NURTuRE has established a sustainable infrastructure with collaborative industry partners AbbVie Inc, Evotec AV, UCB Celltech Biopharma, Retrophin and AstraZeneca, with a total of GBP7.7M investment [Ei]. For the industry partners this forms the basis of significant R&D strategic impact in renal disease. Each industry partner within the NURTuRE enterprise is using a different approach to identify new drug targets. All data gathered are returned to a central database and made available to all. The fibrosis leads at UCB Biopharma noted that *"This pre-competitive cooperation and combining of resources is a great model of how we should be working together to help bring benefit for patients"* [Eii].

Evotec's investment in NURTuRE, which will transfer significant clinical know-how to industry integrated with biological features, aims to form an integrated drug discovery model and high throughput patient sample analyses. The Chief Scientific Officer of Evotec noted that *"This is a very important step for Evotec to expand its leadership in kidney disease drug discovery"* [Fii]. To deliver this they have created NephTec, a virtual company within Evotec. This unique platform and business model enable unrestricted access to their leading drug discovery infrastructures and proprietary pre-clinical databases, accelerating the search for novel targets and pathways [Fiii]. Since 2012, their use of Bristol cell lines [1] and the work above has created more than 100 new jobs [Fi].

NURTuRE was further used as a partnership with NephCure Kidney International, a large US kidney charity, to participate in the Gateway Initiative – this is a multi-stakeholder partnership, including industry and the Food and Drug Administration (FDA), to optimise recruitment to industry led clinical trials in renal disease (e.g. Focal Segmental Glomerulosclerosis (FSGS)). Human podocyte and glomerular endothelial cell lines [1] have been licensed to 15 of the world's top 20 Pharma companies for internal R+D and drug screening generating [text removed for publication] income to date [I].

Gene Therapy Spinout Company

The underpinning work on renal genetic disease [2-4] has led to a significant new investment from Syncona, a major Life Sciences investment firm, to form the world's leading renal gene therapy spinout company, aiming to directly target podocyte diseases. The recently completed deal led to the creation of Purespring Therapeutics, with a Series A commitment of GBP45 million [J]. The deal involved 5 patent families. The initial pipeline of therapeutic candidates to progress to clinic has been agreed, with certain options to other programmes developed at UoB. Premises and laboratories are being built in London, with initial recruitment of 20 new staff in 2021 (researchers, management team and CEO) [J].

5. Sources to corroborate the impact

A) i) UK Genetic Testing Network (2014). Gene panel application/approval
ii) Bristol Genetics Laboratory (2019). Renal panel for Steroid Resistant Nephrotic Syndrome (SRNS), Alport syndrome and rare inherited renal disease *(cites [3]).*

B) Trautmann *et al.* (2020). IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. *Pediatr. Nephrol.* 35, 1529–1561. DOI:10.1007/s00467-020-04519-1 *(cites [3,4,6]).*

C) RareRenal (2014). RaDaR Registry and Rare Disease Groups

D) Kidney Research UK (2017). Research Update: NURTURE: breaking ground with a unique new kidney biobank

E) i) MRC (2017). MRC Industry Collaboration Agreement (MICA) Form – Evotec and UCB
ii) NIHR (2019). New biobank brings wealth of new opportunities for UK renal research

F) Evotec i) (2020). Supporting correspondence – EVP Head of Metabolic Diseases
ii) (2017). Evotec joins NURTuRE consortium to mine unique kidney disease patient biobank
iii) Drug Discovery Updates #07 (2018). Kidney Diseases 2.0

G) Nephrotic Syndrome Trust (NeST) (2021). Supporting Letter - Director

H) UK paediatric nephrologists (2020). Survey Data

I) UoB (2021). Cell Line Licensing Data

J) Syncona (2020). Syncona founds Purespring with a £45m Series A Financing