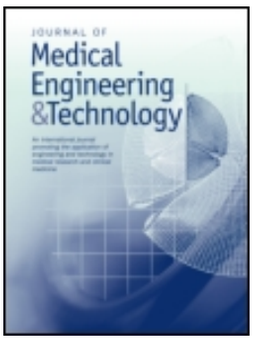

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INVITED REVIEW

Technology innovation for patients with kidney disease

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Abstract

The loss of kidney function is a life-changing event leading to life-long dependence on healthcare. Around 5000 people are diagnosed with kidney failure every year. Historically, technology in renal medicine has been employed for replacement therapies. Recently, a lot of emphasis has been placed on technologies that aid early identification and prevent progression of kidney disease, while at the same time empowering affected individuals to gain control over their chronic illness. There is a shift in diversity of technology development, driven by collaborative innovation initiatives such the National Institute's for Health Research Healthcare Technology Co-operative for Devices for Dignity. This has seen the emergence of the patient as a key figure in designing technologies that are fit for purpose, while business involvement has ensured uptake and sustainability of these developments. An embodiment of this approach is the first successful Small Business Research Initiative in the field of renal medicine in the UK.

Keywords

Haemodialysis, innovation, nephrology, renal, technology

History

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1. Introduction

The kidneys are one of the body's most vital organs. They are responsible for the excretion of most water-soluble metabolic waste products and toxins from the body and maintaining the balance of its fluid and electrolyte composition. They are also an important metabolic organ, secreting and activating hormones involved in blood pressure control, red blood cell production and bone turnover. Therefore, it is not surprising that kidney failure has a detrimental effect on bodily function.

Up until the late 1950s kidney failure was considered a fatal condition, but, due to leaps in technology, the development of renal replacement therapies (RRT) has meant that sufferers can live for many years with their condition.

Kidney failure can impose life-long dependence on healthcare on affected individuals. Currently ~5000 people are diagnosed with kidney failure every year [1] and, according to the last UK Renal Registry Report, in 2012 there were ~55 000 adults receiving RRT in the UK [2]. Although end-stage kidney failure affects only 0.05% of the general population, it commands 1–2% of the annual NHS budget [3]. Despite this and advances in the field, the 1-year survival on dialysis remains less than 88% [4].

Kidneys can fail both acutely or follow a chronic decline in function. Although chronic kidney disease (CKD) is an irreversible process, only 4% of sufferers will ultimately need RRT [5]. In contrast, acute kidney failure (acute kidney injury) is a potentially reversible and, in many cases, preventable condition (20–30% [6]). One out of five hospital emergency admissions is associated with acute kidney injury (AKI) [6] and carries a mortality of 10% [7,8]. This can rise to 50% [9] in patients with AKI requiring Intensive Care Unit admission and 80% if RRT is required [10]. More than 65% of patients affected by AKI will recover kidney function, although up to 10% will become dependent on long-term RRT [11].

In this review of the role of technology in renal medicine we will see how, over the past 60 years, a terminal and incurable illness has been turned into a manageable chronic condition. Now the emphasis is shifting towards prevention and making the life of affected individuals as close to what is considered normal as possible. This calls for smart technologies that will empower these individuals to gain their independence from the hospital setting. Key in this new direction is the emergence of collaborations for innovation and the National Institute's for Health Research Healthcare Technology Co-operative for Devices for Dignity (NIHR HTC D4D) is such an initiative.

2. A journey down memory lane

Although the beginnings of haemodialysis are found in the 1800s with Thomas Graham [12] and Adolph Fick [13] describing the principles behind blood purification techniques, the first documented attempt of RRT was by Christopher Warrick, an English surgeon, in the early 1740s [14].

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He treated a woman suffering from severe ascites by instilling water and claret wine into her peritoneum through a leather pipe. The patient did not tolerate this early form of peritoneal dialysis and, although the therapy was discontinued early, she recovered from her ascites and, according to Warrick, in a short time she was able to walk 7 miles in a day without difficulty [14]. The use of the peritoneum for infusing and removing substances from the body continued to be explored and, in 1923, George Ganter treated the first patient with kidney failure using peritoneal dialysis [14].

At the same time, in Germany, Georg Haas produced his clinical system for blood purification in 1926 [15]. However, it was not until two decades later that Willem Kolff in the Netherlands developed a haemodialysis machine that was able to save a life for the first time [16]. Blood was taken from an artery using a glass cannula and passed through a semi-permeable cellulose tube (artificial sausage skin) wound round a wooden drum. The drum was immersed in a bath containing an electrolyte solution. Molecules, such as urea, the product of protein breakdown, passed easily through the cellulose membrane into the electrolyte solution, but cells and protein were retained. The purified blood was returned to a vein. Kolff used this machine to treat people with AKI and, in 1945, after 15 failures, he succeeded in saving the life of 67-year-old Sofia Schafstadt [16].

Meanwhile, following the success of the Wisconsin General Hospital Group (1936) in using peritoneal dialysis to prevent mortality from kidney disease, P.S.M Kop created an integrated system in the mid-1940s that used gravity to instill the dialysis solution into a patient's peritoneal cavity [14]. The system used components that could be easily sterilized: porcelain containers to hold the solution, latex rubber tubing to carry the solution down to the patient and a large glass catheter to instill the solution into the peritoneum [14].

The next major milestone in haemodialysis was the development of a vascular access for long-term use. Following initial treatment with dialysis, the artery used had to be tied-off, meaning that the procedure could not be repeated. The development of the arterio-venus shunt from Teflon attached to rubber tubing by Belding Scribner and Wayne Quinton in 1960 meant that now dialysis could be used as a treatment for people with chronic kidney failure [17]. The shunt could remain in place in-between treatments and was shortly followed by the establishment of the first haemodialysis outpatient unit, the Seattle Artificial Kidney Centre, in 1962 [17]. A few years later, in 1966, Brescia and Cimino et al. [18] described a technique for forming an internal 'arterio-venous fistula' by joining an artery in the arm directly to a vein. The vein swells under the abnormally high pressure and can be punctured repeatedly, while the overlying skin provides a natural barrier to infection. Today the fistula is still the first choice for vascular access for haemodialysis.

By the mid 1960s, dialysis no longer had to be performed in hospital, giving birth to home-based RRTs. In fact, until the mid-1970s, home haemodialysis was the principle modality for RRT [19].

In 1976, Jack Moncrief and Bob Popovich from Austin, Texas made peritoneal dialysis (PD) also available as a home treatment when they described a technique which involved manually draining and refilling the peritoneal cavity several times each day using a specially designed catheter inserted through the abdomen [14]. This technique of 'continuous ambulatory peritoneal dialysis' (CAPD) was followed some years later by the development of automated PD (APD), in which a machine carries out the fluid exchanges while the patient sleeps.

Although dialysis made life possible for people with kidney failure, the best available treatment to date remains transplantation. In 1954 the first successful kidney transplant operation between identical twins was performed in Boston, followed 8 years later by the first successful cadaveric transplant by the same group. However, it was not until the 1980s, with the licensing of cyclosporine as an immunosuppressive agent, that transplantation became a more accessible and viable treatment choice [20].

From the humble beginnings of RRT, the development of new technologies has helped propel the treatment of this group of patients to the next level, one step at a time. We are now not only looking to keep people with kidney failure alive, but also to keep them out of hospital and integrated with their community, active and engaged with both their treatment and social commitments. We are also looking into identifying, preventing and delaying the progression of kidney disease. A review of the advances in technology in all areas of renal medicine in the last decade reveals the deployment of new approaches in innovation to fulfil the unmet needs in our practice.

3. Advances in haemodialysis

Since the early days of maintenance haemodialysis in the 1960s, developments in this area have focused on improving dialysis efficiency, biocompatibility and safety and preservation of vascular access.

The artificial kidney has continuously evolved and the wooden drum and sausage skins on Kolff's machine have been replaced by a cylindrical container of just over 30 cm in length encasing up to 2.5 m^2 of hollow fibres. Reactions to components of the haemodialysis circuit are now a thing of the past as cellulose has given place to synthetic biocompatible materials [21–23].

During haemodialysis, blood is pumped across a hydrostatic gradient through the artificial kidney separated from the dialysate solution by a semi-permeable membrane. As blood and dialysate are flowing in a countercurrent manner, toxic substances are removed from the body in two ways: either by diffusion or convection during the process of fluid removal (ultrafiltration). Diffusion has historically been the more dominant of the two processes. While small molecules pass across the diffusion gradient well, the rate of diffusion decreases as molecular weight increases. Medium size molecules are cleared much more effectively by convective transport. The measure of how well toxins are cleared from the blood by dialysis is known as dialysis adequacy, but this tends to reflect mainly the clearance of small particles such as urea. Although our understanding of the toxic effects of different metabolites still remains largely incomplete, it is increasingly recognized that larger particles play a significant role in the uraemic milieu [24,25]. Use of synthetic

microfibres has allowed the production of membranes with larger size pores that enable the removal of more middle molecular size particles (known as the middle molecules). Because of the general correlation between water flux and the clearance rate of middle molecules, the term 'high-flux membrane' has been used commonly to denote these high-permeability membranes and the ultrafiltration coefficient to describe their permeability [26]. An example of a middle molecule is Beta-2-microglobulin. This 12 kD molecule produced during normal cellular turnover is primarily cleared by the kidney and in kidney failure it can accumulate and lead to amyloid fibril formation, carpal tunnel syndrome and generalized joint stiffness and pain [27]. This previously common problem for patients on long-term dialysis has now become scarce with the increased use of high-flux haemodialysis.

However, even with the use of high-flux membranes, middle molecule clearance is still limited by the amount of ultrafiltration required during a dialysis session. On a 4-h, three times per week schedule this can be as little as 0.5 L and can rarely rise above 3 L. If on the other hand a substitution fluid is added to the blood to replace some of the fluid volume removed, ultrafiltration can effectively be increased to tens of litres and so increase the convective clearance and middle molecule removal. These are the principles utilized by haemodiafiltration, a renal replacement technique that is now used by many haemodialysis units and could lead to better outcomes [28–33]. The safe delivery of high-flux haemodialysis and haemodiafiltration were only made possible following the development of automated ultrafiltration control systems and the ability to deliver highly purified dialysis fluid that can be used to make substitution fluid and in turn requires ultra-pure water [34]. To ensure water purity, most dialysis units have a water purification plant and utilize a reverse osmosis system [35].

Attempts to remove large size molecules (more than 60 kDa) either by dialysis through super high-flux dialysers [26,36] or absorption [37] techniques have been foiled by their inability to select between toxic elements and plasma proteins such as albumin (molecular weight of 50 kDa) [37]. Albumin and plasma proteins in general also have another category of uraemic toxins bound to them (protein-bound molecules) [37]. These tend to be of small molecular size, but their affinity to proteins makes them impermeable through high-flux membranes. A number of protein-bound particles such as P-cresol and indoxyl sulphate have been linked with cardiovascular mortality and morbidity [38–41]. Although these could be removed together with the proteins they are bound to by the process mentioned earlier, such interventions have a significant effect on the normal body physiology. It is now thought protein-bound particles can be removed by more intensive haemodialysis regimes (more than 12 h of dialysis per week) [42]. As these intensive haemodialysis regimes are more frequently practiced at home, this has generated further interest in home-haemodialysis.

Most haemodialysis was initially performed at home, but as the demands for more dialysis availability increased, treatments had to be scheduled and delivered in outpatient dialysis units. This allowed the expansion of kidney services. However, although the development of satellite dialysis units did bring haemodialysis closer to their homes, the increased desire of patients to maintain their independence and plan their treatment around their way of living rather than the other way around has led to the re-birth of this modality. This was followed by the development of smaller and more portable dialysis machines to simplify the process of home haemodialysis without the necessity for patients to over-medicalize their home environment (example of small and portable dialysis machine shown in Figure 1). These machines might be less efficient than conventional haemodialysis machines, but provide easier set up and make haemodialysis at home possible for people with limited living space. The inefficiency of the dialysis delivered tends to be supplemented either by increased frequency or duration of treatment. In fact, home haemodialysis is all about flexibility and patient choice. Patients can dialyse as frequently and for as long as they wish provided they achieve good clearance of uremic toxins. Patients empowered with this choice tend to opt for longer or more frequent treatment sessions as this allows them to have a more relaxed fluid intake allowance and, due to better clearance of phosphate and potassium, enjoy food that would normally be restricted. The documented positive impact on quality-of-life is coupled with improvement in physical activity and, together with the cardiovascular benefits [43–47], have led patient groups, clinicians and government bodies to advocate a return to home haemodialysis. While maintaining financially affordable technologies for home treatment delivery had been the primary obstacle for many healthcare providers, the ability to self-care and, in particular, self-cannulate has kept many patients from considering home haemodialysis as their treatment modality [48–50]. So the vascular access that was instrumental in the birth of outpatient haemodialysis is playing a key role in the uptake of home haemodialysis.

Figure 1. The Quanta Fluid Solutions' Selfcare + (SC+) dialysis machine is an example of smaller and more portable technology for Home Haemodialysis. Picture reproduced with permission from Quanta Fluid Solutions.

Since the development of the arteriovenous fistula nearly 50 years ago, no better alternative vascular access has been developed. The Gore-tex® graft, used to bridge the space between an artery and a vein, can be used in the same way as a fistula and is a good alternative for patients whose vascular anatomy is not suitable for fistula formation. Experience from the US has shown that grafts have a considerably higher complication profile (high incidence of clotting and

infections) and should be reserved for patients with no alternative option for fistula formation [51]. However, grafts still remain a better alternative to semi-permanent central venous catheters [52]. These have an even higher rate of complications, especially infections. Even with the use of antiseptic line locks [53–56] and antibiotic containing dressings [57], the incidence of line related infections still remains a significant problem. Unfortunately, lines are considered a necessary evil as many patients will require RRT either unexpectedly or before their fistula is ready for use. For an arterio-venous fistula to 'mature' and the venous limb to develop a vascular endothelium, a period of 6–8 weeks is required; this can take longer in patients with poor arterial circulation. Although grafts can be used shortly after their insertion, they require surgical insertion, while lines can be inserted under only local anaesthesia and at very short notice [58].

Taking into account the importance of vascular access and the lack of suitable alternatives, the focus of technology development in this area has been to improve arterio-venous fistula survival and development of devices to aid safe fistula cannulation and the uptake of home haemodialysis.

Fistulas fail either because they fail to develop in the first place or because years of cannulation and high blood flows generated by dialysis lead to stenosis and repeated episodes of thrombosis and eventual failure [59,60]. Venous mapping for fistula formation using ultrasound imaging has improved vein selection [61,62], while devices that utilize far-infrared radiation have been linked with promoting fistula maturation as well as overall patency outcomes [63].

Repeated vascular injury and the subsequent healing process due to needling for haemodialyis play a significant part in the development of stenosis and clot formation. To a degree, poor needling technique and cannulation difficulties can add to the risk of vascular access failure [64]. The buttonhole needling technique allows for a needle track to form from the skin down to the blood vessel following repeated cannulation at the same position. Once the track has been formed, cannulation can occur using a blunt needle. This is a technique very much preferred by home haemodialysis patients. However, it has been linked with increased incidence of infections of the track [65]. Thus, there is an increase in the emphasis placed on improving safe and easy cannulation and steps are being taken for the development of devices to aid this.

Another way of preventing vascular access loss is by developing monitoring programmes. Both ultrasound and thermodilution techniques have been used to monitor fistula blood flow and recirculation to identify early fistula stenosis [66,67]. However, there is an ongoing debate as to the significance of anatomic vs functional stenosis and, therefore, the clinical significance of monitoring.

In the past when fistulas failed (mainly thrombosed) there was a short time-window to intervene. With the development of rheolytic thrombectomy technology, fistulas can now be salvaged even a week after they fail [68]. Also, for stenotic lesions that do not respond to conventional balloon angioplasty, cutting balloons [69] and stents have been developed to keep the vessels patent [70,71].

As the number of vessels that can be used for vascular access formation is limited, some people inevitably will run out of vascular access, either due to multiple access failures because of dialysis vintage (years on haemodialysis) or poor vasculature. The HeRO® graft (CryoLife Inc. Kennesaw, Georgia, USA) provides a lifeline to such individuals. This device is a cross between a dialysis line and graft. Although the risk of infection and thrombosis is likely to be high, this will be the only option for some individuals to continue performing dialysis [72–75].

One other factor that has been linked with a number of haemodialysis complications, including vascular access failure and hemodynamic instability, has been our limitations in accurately measuring body's fluid excess. As most dialysis patients do not pass sufficient volumes of urine to maintain fluid balance, it is usually necessary to remove excess fluid from the body during haemodialysis. Unlike most blood toxins, which can be measured by laboratory assays, the assessment of fluid retention is usually subjective. Optimal fluid management is achieved by adjusting the post-dialysis 'target' weight and, if required, limiting the fluid gained between dialysis sessions. The accumulation of fluid in the body is assessed by weight measurement before each dialysis session. The patients are restored to their target weight with ultrafiltration of any excess.

The prescription of target weight is based on clinical assessments. Hypertension, puffy tissue and breathlessness usually indicate over-hydration, whereas hypotension, cramping, dizziness or nausea can be signs of dehydration. Unfortunately, these indicators are not always present and patients can be fluid overloaded or dehydrated with no obvious symptoms. If target weight is set too high a patient can be chronically fluid overloaded with consequent cardiovascular risks, while if it is set too low it can worsen post-dialysis fatigue and accelerate the loss of any residual kidney function.

The development of bioimpedance analysis (BIA) techniques has, for the first time, offered an objective approach to measuring fluid status (example BIA in Figure 2). This can be combined with conventional clinical assessment to improve fluid management [76] and has been shown to improve outcomes [77]. The technique is based on measuring the resistance and reactance of the body to small electric currents. However, BIA is a measure of tissue hydration and, in some conditions, this does not reflect the intravascular volume.

While monitoring changes in blood volume (BV) during dialysis can provide important information about the capacity for vascular refilling, it lacks the evidence base to be used in isolation for fluid management [78]. BV monitors are easily incorporated in haemodialysis machines and, as the information provided is complementary to BIA, it is possible that systems combining these technologies will be used in future to aid clinicians with the management of fluid status in most patients.

4. Advances in peritoneal dialysis

Unlike haemodialysis, the technical advances in peritoneal dialysis have been more modest. Since the development of CAPD and the Tenchkoff Catheter in the 1970s and later the

Figure 2. The Fresenius' Body Composition Monitor (BCM) is an example of multi-frequency Bio-impedance analysis technology. Picture reproduced with permission from Fresenius Medical Care.

development of APD, efforts had focused in limiting connections to minimize peritoneal infections and developing solutions with different glucose concentrations [14]. Peritoneal dialysis follows a more simplistic approach to dialysis. The peritoneal membrane becomes the semipermeable membrane and the dialysate is placed in the peritoneal cavity and left for a period of time. Solutes diffuse between blood vessel, peritoneal membrane and peritoneal solution and fluid is ultrafiltered across an osmotic gradient that decreases as the peritoneal fluid osmotic concentration equilibrates with that of the circulating blood. As glucose is the main osmotic agent and readily crosses the peritoneum, ultrafiltration depends on the peritoneal membrane's characteristics and its ability to facilitate transport of glucose. People with fast glucose transport achieve very little ultrafiltration as the osmotic gradient driving fluid removal is quickly reduced. Therefore, arguably, the most important innovation in peritoneal dialysis had been the introduction of icodextrin containing solutions (a polysaccharide that does not cross the peritoneum) that maintained osmotic gradients and so enabled better ultrafiltration, even allowing people with little urine output to continue their treatment.

Another important development was the two-compartment peritoneal solution bag. This allows mixing of the buffer bicarbonate and lactate solutions with the acid glucose solution at the time of use, preventing the build-up of advanced glycosylation end (AGE) products, formed in premixed PD fluid at physiological pH [79]. AGE have been linked to encapsulating peritoneal sclerosis, a potentially fatal complication [80,81].

5. Advances in transplantation

Once transplantation became feasible the challenges were to make it available for as many people as possible and to maintain the lifespan of the donated organ. Immunossupressives, such as azathioprine, ciclosporin and sirolimus, were developed, but it was the introduction of the combination tacrolimus with mycofenolate that significantly improved the long-term survival of transplanted organs [82]. However, all of the immunosuppressive agents in current use still have a significant side-effect profile and there is a continued development to reduce the side-effect profile of these drugs.

The advent of powerful biological agents that act as monoclonal antibodies and bind to key immune system components to produce immunosuppression saw the introduction of agents such as basiliximab [83] and alemtuzumab [84]. Used as an induction regimen, they have significantly decreased the episodes of early rejection. Although the introduction of more accurate crossmatch techniques such as flow cytometry and virtual crossmatch by Luminex has improved the identification of tissue mismatch and antibody sensitization [85], the leaps in the development of immunosuppressive therapies and strategies means that mismatches that were previously considered incompatible can now be successfully transplanted. Even individuals with blood group incompatibility [86] or a high level of antibodies are being transplanted. These approaches have been made possible with, again, the introduction of biologic agents such as Rituximab and antibody removal techniques such as double filtration plasma apheresis and antibody absorption [87–89]. These techniques are similar to dialysis with super-high flux pores, but the microfibres can also be coated with binding agents for specific antibodies. Although there is increasing success in this area, these options are maintained for patients whose transplantation chances by other means are limited.

At present, the main limiting factor is organ availability. Live donor nephrectomy can even be done laparoscopically, reducing the donor's time in hospital to just a couple of days [90,91]. Despite this and the evidence that organs donated by living donors, even unrelated, have better outcomes, the number of organs donated do not match demand [92]. This is also despite the introduction of paired-pool schemes. Advances in technologies have enabled individuals that have a willing live donor available, but with poor organ match to enter a computer run matching scheme that identified suitable live donors elsewhere, in a similar situation. Two-, three- or even four-way swaps are arranged where the donation and transplantation operations for all the involved parties take place at different centres simultaneously. These can be countries and even oceans apart [93–96].

The success of kidney transplantation programmes, to a large extend depends on deceased donors. Most important in the outcome of this type of transplantation is the time the donated kidneys remain without circulation. Part of that 'ischaemia time' is when the kidneys are inside the body. Once the kidneys are out of the donor's body a period of 'cold ischaemia' begins. This is referred to as 'cold ischaemia' because during this period the kidneys are infused with cold saline and stored in ice. The duration of this period would depend on the distance to their intended destination, theatre and surgical team availability and final screening of potential recipients. The longer the period of ischaemia, the worse are the outcomes. The development of machine kidney perfusion allows the kidneys to be stored under hypothermic perfusion using plasma protein fraction perfusate and has been shown to

be able to preserve the kidney for a longer period of time with good outcomes [97].

Organ transplantation has evolved hugely in the last 20 years and with such good outcomes and increasing demand technology has a significant role to play.

6. Advances in prevention of kidney disease

Despite all the technology advances in the management of kidney disease it has been proven difficult to make big steps in disease prevention. The search for biomarkers of early kidney injury has yet to yield one that can be used in clinical practice, other than urinary albumin. Monitoring for the excretion levels of urinary albumin in the diabetic population in the community allows early identification of diabetic nephropathy, the second most common cause of CKD [1]. Early treatment can lead to disease regression [98–100]. The list of proposed biomarkers for the diagnosis and progression of kidney disease is endless, with Cystatin C being the most notable one [101]. However, none of them, other than urinary albumin, have made it into clinical practice. With the lack of reliable biomarkers for the prevention of CKD, we resort to public awareness and focus in delaying progression at earlier stages, by good blood pressure control and modification of cardiovascular risk factors.

Although CKD at the time of diagnosis is mostly an irreversible state, this is not the case with acute kidney injury. Early identification of patients developing AKI on admission to hospital or during their inpatient stay has been one of the focuses of technology development in the field. While the search for novel biomarkers is still ongoing, algorithms are being designed to utilize information from patient records, blood tests and clinical observation using computer interfaces (as most medical patient information is now electronic) and generating alerts with a calculated risk of AKI [102]. This will help prompt management and prevention of a large number of avoidable cases.

Not all causes of acute kidney injury are avoidable or preventable. Some conditions that affect the kidneys have an autoimmune and inflammatory component. As with transplantation many of these conditions have benefitted from the development of biologic agents and the accessibility of techniques like plasma apheresis [103–106]. However, these conditions are rare and this makes large studies to assess treatments impossible. In 1995 the UK Renal Association set up the Renal Registry, a large database that has been continuously collecting data on renal disease from all UK renal centres. Following the success of the registry's annual reports in providing a great insight into chronic kidney disease, the development of the Rare Disease Registry, to collect data on rare glomerular pathologies and familial conditions, promises to provide valuable information to aid future management.

7. Facing up to the patient burden: The unmet need

Technological developments in renal medicine have come far in making the impossible possible. We are now at a crossroads trying to decide on a new direction. Undoubtedly, some of the challenges are now different than in the past. In the last few years, despite advances in the efficiency of RRT equipment, patient outcomes have not significantly improved. We are beginning to re-think some of the processes that have remained unchanged for too long. We are now exploring the unmet needs. Lost in our success of maintaining life in kidney failure we might have forgotten the people at the centre of our quest; the growing number of people entering end-stage kidney failure to begin a life of dependence on the health service with detrimental effects on their quality-of-life. We have achieved RRT on such a large scale that it often feels that patients enter a conveyor belt and every one of them is processed in exactly the same way. Understanding and managing the patient burden through their disease journey is becoming an urgent priority. The kidney dialysis units that helped provide affordable RRT for so long are in desperate need of innovative solutions to deliver a more flexible patient-friendly approach. Patient transport to and from their dialysis treatment has been a key hindrance and stress factor for both patients and staff and affects the smooth running of renal units. This is an area where technology can be applied to provide personalized solutions.

For better flexibility and quality-of-life, dialysis treatment is better delivered at home. However, this is a decision that patients have to take themselves and often patients do not have sufficient support to give them the confidence to share in the management of their own condition. Patient education and support has been an evolving and flourishing part of our practice, but in most cases the service is found to be stretched and falls short of the ideal. Ideas for using self-help websites and support call lines have been explored for improving patient education.

Patients with kidney disease come to hospital too often and that results in the development of a hospitalized behaviour and impaired quality-of-life. Telemedicine and virtual clinics are increasingly being used to provide ongoing good quality of care without the customary visit to the hospital.

By reducing the patient burden, we will improve patients' quality-of-life and generate a positive patient view towards their health, stimulating better uptake and adherence to treatments suited to individuals' needs and, therefore, improvement in outcomes.

8. Innovating technology innovation

Historically research provided us with the knowledge of the guiding principles behind our treatments, but the biggest innovations materialized through collaborative approaches that arose as a result of the drive of individuals to see their work to completion. A lot of research work never translated itself into clinical practice and that is partly to blame for the lack of recent breakthroughs that would influence patient outcomes. Before embarking on a technology development, it is essential to understand the unmet requirements of all the technology stakeholders. Consideration must be given to the needs of patients, industry and clinicians in addition to the views of academic researchers. Patients should be engaged because they are the users or beneficiaries of the particular innovation and the industry should be engaged because of their expertise in development products that are marketable and, therefore, reproducible at large scale. The earlier this engagement teas place, the higher the chances of the end-

product being something meaningful. The final product will still have to go through all the stages of development, from invention and prototype development to its clinical evaluation, adoption and large-scale uptake.

These are the guiding principles that drive innovation co-operative initiatives such as NIHR HTC D4D. Utilizing this innovation methodology NIHR HTC D4D has worked with patients, clinicians, academics and the industry to deliver innovative solutions to some of the burning unmet needs in renal medicine. Collaborative work with Quanta Fluid Solutions has led to the development of Selfcare+, a small portable dialysis machine that is ideal for home use, while NIHR HTC D4D's involvement with the Healthcare Economics academic field is striving to deliver a business model to make home haemodialysis more financially attractive to healthcare commissioning. Also NIHR HTC D4D's work with BIA technology has provided significant insight to its use as a clinical tool for measuring body fluid composition and has helped his adoption us such. The contribution of NIHR HTC D4D in raising awareness of the importance of patient empowerment has been been equally important and the source of a number of ideas. Figure 3 illustrates this innovation methodology.

When it comes to the development and adoption of new ideas, financial constraints have always been a barrier to innovation adoption and traditional funding pathways have often been restricting, failing to factor-in the element of project sustainability. The use of innovation methodology has also seen the rise of 'unconventional' funding pathways derived from business entrepreneurship models (bootstrapping, seed round, angel round, etc.). This marriage between healthcare technology development and business entrepreneurship generated a new, more agile school of thought to help filter and select ventures with the greatest likelihood of success.

Figure 3. NIHR HTC D4D innovation methodology.

Such a marriage was put together earlier this year when NIHR HTC D4D partnered the Department of Health to run a Small Business Research Initiative (SBRI) and support the winners through a 2-phase venture. Although a lot of innovation ventures serve in sustaining existing markets and technology outlets, SBRI is considered as a disruptive innovation pathway that aims to generate new markets and introduce new blood, energy and ideas to the existing scene.

This was the first time an SBRI competition involving kidney care was run in the UK. It attracted interest from 41 applicants and, after a selection process by leading field experts and patient representatives, 14 projects were awarded funding for 6 months to complete the first phase of their proposed technology development. These were all collaborations between industry, academia and healthcare and had healthy patient involvement. Reflecting the drivers and unmet needs identified earlier in the text:

- Four projects aimed at early diagnosis and disease prevention:
  - Three in AKI, and
  - One in diabetic nephropathy;
- Six projects aimed at empowering patients and reducing patient burden:
  - One through Telemedicine,
  - One through improving the dialysis patient pathway,
  - One by promoting self-cannulation,
  - One through self-help technology,
  - One though patient empowerment over their medical records, and
  - One by personalizing patient transport to and from their dialysis treatment;
- One project involved the development of a point of care test for creatinine using interstitial fluid;
- Two projects were in the field of transplantation; and
- One project involved the development of an infection sensor for peritoneal dialysis.

All teams received advice and support by NIHR HTC D4D and made use of their experience in technology development. All but one project successfully completed the first phase, which is an unusually high success rate.

9. Conclusion

Through our journey through time, from the beginnings of modern nephrology to the present time, we can appreciate how technology has changed the life of people with kidney failure. The partnership between clinical medicine and technology has been so successful that a life-ending condition has become a manageable chronic illness. However, more recently, technology developments have failed to translate into further improvements in outcomes. In renal medicine, we are increasingly recognizing that, if we are to progress in our field, we will have to re-assess our approach in the way we explore unmet needs and develop new technologies. Collaborative initiatives like NIHR HTC D4D are increasingly successful in fuelling technology innovation. Our experience with the SBRI competition would suggest that, with the right guidance, this is a very good model for funding innovation. Although

we had to search for our way, the future looks bright for renal technology development.

Declaration of interest

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