BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Genomic testing in patients with renal disease

Katya Lyulcheva-Bennett[1]

Simon Williams[2]

Matthew Howse[2]

Emma McCann[1,3]

Author details can be found at the end of this article

Correspondence to:
Emma McCann;
emma.mccann@olchc.ie

Abstract

Inherited kidney disease accounts for a significant proportion of chronic kidney disease and end-stage renal failure. There is increasing evidence that genetic testing for inherited kidney disease should be integrated into clinical care pathways at the earliest opportunity so that patients and their families can maximally benefit from carefully tailored care. Despite increased availability of genetic testing, the proportion of patients with renal disease undergoing genetic investigations remains low. This article introduces key concepts of genetic and genomic testing to the renal physician and addresses some common barriers to the wider integration of genetic testing in routine clinical practice to fully capitalise on recent advances in genomic medicine and improve patient outcomes.

Key words: Genetic testing; Genomics; Kidney diseases; Nephrology

Submitted: 3 March 2023; accepted following double-blind peer review: 24 March 2023

Introduction

In 2020, the four nations of the UK outlined their commitment to lead the most advanced genomic healthcare system to improve patient outcomes (HM Government, 2020). NHS England is committed to harnessing the potential of genomic medicine, which involves the comprehensive analysis of an individual's entire genome, by embedding it in mainstream specialities to achieve earlier diagnoses, predict and or prevent genomic conditions and their complications, and use genomic data to improve individualisation treatment. The most recent NHS England (2022) strategy, Accelerating Genomic Medicine in the NHS, considers the broader context of the entire genome, to provide a world-leading, equitable service to the population.

While inherited kidney diseases are individually rare, collectively they represent the fifth most common cause of end-stage renal disease, accounting for approximately 10% of cases of end-stage renal disease in adults in Europe (Devuyst et al, 2012, 2014; Hays et al, 2020). Groopman et al (2019) demonstrated the utility of exomic testing in identifying a genetic diagnosis in nearly 10% of individuals in a cohort of over 3000 adults with chronic kidney disease, highlighting the importance of genomic testing in this group. Jayasinghe et al (2021) found a similar diagnostic rate in their smaller Australian adult cohort. The utility of genetic and genomic testing in the paediatric population is also established – Mann et al (2019) reported a diagnostic rate of around 20% in those under 25 years of age presenting with chronic kidney disease.

Approximately 200 rare disorders primarily affect the renal system and the majority of these have a genetic basis. Until recently, genetic testing was costly and difficult to access. It was traditionally only available through referral to a clinical genetics service and would typically take place at the end of a long diagnostic journey, after the phenotype was fully established. The paradigm is shifting, and secondary care specialists are now encouraged to organise genetic and genomic testing for patients as soon as a genetic disorder is suspected as the underlying cause of their presentation.

The Genomic Test Directory for Rare and Inherited Disease, published and updated regularly by NHS England (2023), describes the genetic or genomic tests available to request, where in the pathway to request them (typically at an earlier stage than previously), who can request them and the appropriate clinical indications. The document includes a dedicated renal section that lists comprehensive indications for genetic testing in renal conditions, such as renal ciliopathies, glomerular diseases, tubulopathies, complement disorders and structural renal disease (Table 1).

How to cite this article:
Lyulcheva-Bennett K, Williams S, Howse M, McCann E. Genomic testing in patients with renal disease. Br J Hosp Med. 2023. https://doi.org/10.12968/hmed.2023.0085

Table 1. National test directory

Condition		R number	Test modality
Primary renal pathology	Cystic renal disease	R193	Whole genome sequencing
	Haematuria	R194	Panel testing
	Proteinuric renal disease	R195	Panel testing
	CFHR5 nephropathy	R196	Single gene testing
	Membranoproliferative glomerulonephritis including C3 glomerulopathy	R197	Panel testing
	Renal tubulopathies	R198	Panel testing
	Atypical haemolytic uraemic syndrome	R201	Panel testing
	Tubulointerstitial kidney disease	R202	Panel testing
	Hereditary systemic amyloidosis	R204	Panel testing
	Nephrocalcinosis or nephrolithiasis	R256	Panel testing
	Unexplained young onset end-stage renal disease	R257	Whole genome sequencing
Neoplastic	Inherited renal cancer	R224	Panel testing
	von Hippel–Lindau syndrome	R225	Gene sequencing
	Fumarate hydratase-related tumour syndromes	R365	Gene sequencing
	Tuberous sclerosis	R228	Gene sequencing
Metabolic	Cystinosis	R334	Single gene testing
	Fabry disease	R335	Single gene testing
Congenital syndromes	Bardet–Biedl syndrome	R107	Panel testing
	Congenital anomalies of the kidney and urinary tract – familial	R199	Genome-wide microarray
Other conditions seen in renal medicine	Monogenic diabetes	R141	Panel testing
	Hereditary systemic amyloidosis	R204	Panel testing
	Glucocorticoid-remediable aldosteronism	R183	Single gene testing
	Primary hyperaldosteronism KCNJ5	R344	Gene sequencing
	Acute rhabdomyolysis	R419	Panel testing

From NHS England (2023)

Despite the increased availability of genetic and genomic testing, this continues to be underused in renal medicine (Jayasinghe et al, 2021). Epidemiological data taken from the European Rare Kidney Disease registry showed that only a small proportion of patients with rare renal conditions, most of which are genetic in origin, underwent genetic testing (14% and 31% of all adult and paediatric patients respectively) (Bassanese et al, 2021).

This article introduces genetic and genomic testing to the renal physician and addresses some of the barriers identified. It is hoped that this will encourage integration of genetic and genomic testing into clinical practice so that renal patients may benefit from advances in genomic medicine.

Current barriers to routine use of genomic testing in nephrology

While evidence is mounting for the benefits of early genetic diagnoses in patients with renal disease, a number of barriers limit the wider uptake of genetic or genomic testing.

A survey of nephrologists working in northwest England was conducted to assess attitudes towards genomic medicine and the perceived barriers to genetic testing (Dr S Williams, 2022, personal communication). Adult and paediatric nephrologists, along with higher specialty trainees, were invited to complete the survey (40 responses were received, 90% of which were from those working in adult services). The survey revealed that 34% of respondents had never organised genomic testing for their patients, while 45% only requested genetic testing very infrequently (yearly). Barriers included limited genetic or genomic literacy, perceived lack of benefit, difficulties in organising appropriate tests and/or interpreting the results, as well as the time commitment required for pre- and post-test counselling (Knoers et al, 2022). However, 63% of respondents were aware of how to access local genetic services and 55% reported having a local renal genomics multidisciplinary team. Just under a quarter of survey respondents were aware of there being a dedicated renal genomics clinic locally.

Why offer a genomic test?

The importance of a genetic diagnosis should not be underestimated. Genetic testing can, at least in part, address the unmet need for establishing specific diagnoses in kidney disease to improve patient experience, outcomes and offer reproductive choices for affected individuals and their at-risk relatives.

Earlier consideration and identification of a pathogenic or likely pathogenic genetic alteration may help to predict the clinical course and prevent complications. This will also lead to a better understanding of disease and its pathogenesis and negate the need for extensive (often invasive) investigations (Mann et al, 2019). A genetic diagnosis can also aid prognostication and inform surveillance of renal and extra-renal manifestations or complications of a given inherited disorder (such as intracranial aneurysms in autosomal dominant polycystic kidney disease or progressive hearing loss in Alport syndrome). Furthermore, genetic testing can help to inform clinical management decisions (including considerations around renal replacement therapy and transplantation), which can differ considerably from the acquired forms of renal disorders (Aymé et al, 2017). In the future, increased use of genomic testing in renal disorders may also facilitate aetiology-based disease classifications to develop and support clinical trials, and offer opportunities for personalised medicine (NHS England, 2016; Bullich et al, 2018).

Another important benefit of timely genetic testing is facilitation of reproductive choices and prenatal testing (Table 2) for affected individuals, as well as identification, and in some instances, pre-symptomatic screening or treatment, of at-risk family members. Patients with confirmed inherited kidney disease should be made aware that a range of prenatal testing and reproductive choices may be available through referral to the local genomics service.

When to consider testing

The possibility of a genetic cause of renal disease should be considered in all nephrology consultations but particularly in new patient consultations so that the benefits for affected individuals and their families are fully realised. Accordingly, genetic and/or genomic testing

Table 2. Prenatal choices

Pre-implantation genetic testing	This can be used to identify genetic alterations in embryos created through in vitro fertilisation. It is available when one or both genetic parents have, or are carriers of, a pathogenic or likely pathogenic variant
Non-invasive prenatal diagnosis	This uses maternal blood samples to analyse cell-free fetal DNA from 9 weeks of pregnancy. It can be used for certain single gene conditions and fetal sex determination in X-linked conditions
Chorionic villous sampling	This is an invasive test available from 11 weeks of pregnancy
Amniocentesis	This is an invasive test available from 16 weeks of pregnancy
Cord blood	Cord blood can be collected for genetic testing of at-risk newborns

should be considered in any patients with renal disease who have any of the following features (this is not an exhaustive list):

- Younger age of onset than typical for that condition
- Atypical presentation of renal condition
- Additional renal or extra-renal features, even if not obviously linked to the presenting condition
- Congenital anomalies, dysmorphism, learning or behavioural difficulties
- Family history of similar kidney condition and/or extra-renal features as above
- Absence of any other identifiable cause.

Which test?

As discussed above, the National Genomic Test Directories (both rare disease and cancer) outline the range of genetic and genomic tests available in England. Table 1 outlines the indications for testing in the rare disease test directory that the nephrologist may use, although there may be others depending on specific interests.

Details of the specific gene(s) in any particular indication can be determined using the PanelApp resource (https://nhsgms-panelapp.genomicsengland.co.uk/). The genetic and genomic testing offered is reviewed annually; clinicians can suggest additional genes and tests and submit evidence for their inclusion to be assessed.

When using the test directory, it is important to consider:

1. Whether there is a well-defined clinical phenotype, eg haematuria or proteinuria, as this will direct the clinician to the most relevant indication
2. Whether there is a specific gene the clinician is interested in – eg COL4A5. In this situation it is important to use PanelApp; this will alert the clinician as to which panels this gene is included in and allow selection of the most appropriate panel that closely fits the patient's phenotype
3. The best test may not be in the renal section
4. The technology used to deliver the test – different technologies require different documentation and consent (such as whole genome sequencing vs panel testing).

Possible results and their interpretation

The American College of Medical Genetics and Genomics has developed detailed guidelines for the interpretation of variants in clinical genetics that were subsequently adopted by the Association for Clinical Genomic Science (Richards et al, 2015; Ellard et al, 2020). The guidelines provide a framework for the classification of genetic variants based on the level of evidence and the potential impact on health. They divide variants into five categories: pathogenic, likely pathogenic, uncertain significance, likely benign and benign. The classification is based on multiple criteria including frequency in the population, functional studies, segregation studies, the presence or absence of the variant in affected individuals or family members and computational predictions to determine the probability that the variant is damaging to the protein or not. Table 3 details the possible results from a genetic or genomic test and its potential implications.

Reports will contain details of any pathogenic or likely pathogenic variants. Both classifications are considered disease-causing and can be used to guide management. Conversely, variants that are benign or likely benign are not reported.

Variants of uncertain significance are genetic alterations that have not been confirmed to have an effect on a person's health, because there is not enough evidence to determine whether they are benign or pathogenic. Only variants of uncertain significance that have narrowly missed out on a 'likely pathogenic' classification (so-called 'hot variants of uncertain significance') will be reported. A variant of uncertain significance cannot be used to confirm diagnosis or guide management. However, reporting selected variants of uncertain significance may highlight the need for further testing (of the affected individual and/or their family members) or research to determine the clinical significance. Such work may generate additional evidence, potentially resulting in reclassification of these variants. Discussion of such variants with genomic medicine colleagues may be beneficial.

Table 3. Possible outcomes of genetic testing	
A pathogenic or likely pathogenic variant is identified	There is a high probability that a disease-causing variant has been found in the affected individual
	Patient and/or close relatives should be referred to their local genetics service to discuss the implications
	Predictive and prenatal genetic testing may be available
No significant variants are identified	No predictive or prenatal testing is possible. Depending on presentation, further genetic testing may be appropriate
A variant of uncertain significance is identified	There is insufficient evidence to confirm or exclude the variant as disease-causing. The clinical significance of such genetic variants is unknown, and they should not be used to confirm diagnosis or guide management
	Further investigations may be required. Predictive or prenatal testing cannot be offered. Consider referring to the local clinical genomics service if family studies or further phenotyping is indicated
An unexpected result	A significant variant has been found in a gene that does not account for the patient's presentation but may have implications for their health, surveillance or drug treatment(s). Referral to the local clinical genomics service would be appropriate

Table 4. Modes of inheritance	
Autosomal dominant (eg autosomal dominant polycystic kidney disease)	Risk to first degree relatives: 50%
Autosomal recessive (eg nephronophthisis)	Patient's full siblings at 25% risk of being affected. Patient's parents and offspring likely unaffected carriers
X-linked (eg X-linked Alport syndrome)	Males usually more severely affected at a younger age than females. Females are more variably affected. Typically, females are more mildly affected than males with and can be unaffected carriers. Some females are severely affected. All females have a 50% risk of having an affected son
Mitochondrial inheritance (eg maternally inherited diabetes and deafness or mitochondrial encephalopathy, lactic acidosis and stroke-like episodes)	Alterations in mitochondrial DNA are maternally inherited. All children of an affected female will inherit the mitochondrial DNA change. Males cannot pass mitochondrial conditions on to their children

NB: genetic variants can be inherited or occur in the affected individual for the first time (de novo), therefore a lack of family history does not rule out a genetic condition.

Once a pathogenic or likely pathogenic variant is identified, patients and their families can be referred to the local genomics service for advice on the mode of inheritance (Table 4), counselling regarding reproductive choices and prenatal testing options (Table 2), as well as predictive genetic testing for close family members and, if appropriate, pre-symptomatic screening and treatment in some renal conditions (eg autosomal dominant polycystic kidney disease, Alport syndrome).

The Case study illustrates the importance of genetic testing in a family with a history of renal disease. The testing aims to confirm a diagnosis, assess the risk for family members and guide treatment decisions. The Case study also highlights the need for careful reproductive planning and emphasises the implications of genetic findings on family members, including the exclusion of certain relatives as potential kidney donors based on their genetic status.

Genomic test results can also be unexpected. It is important that individuals undergoing genetic or genomic testing are made aware of the possible outcomes as part of the consent process.

The absence of a confirmed pathogenic or likely pathogenic variant does not mean that person does not have an underlying genetic condition, only that it is less likely to be in the genes tested. It may be worth reviewing if there are other genomic tests more relevant either now or in the future, particularly if the phenotype evolves.

Case study: Alport syndrome

Clare attended her GP as she was planning her first pregnancy. She was worried as her brother Harry, aged 25 years, was awaiting a kidney transplant for end-stage renal failure. The GP noted that Clare had had persistent microscopic haematuria since childhood.

Why test?

There are several reasons to test in this situation:

1. To confirm a diagnosis in the affected individuals and ensure they receive optimal care
2. To determine whether surveillance of extra-renal manifestations is indicated
3. To allow close family members to be tested to assess their risk (if significant variant detected only)
4. To give an accurate risk assessment to any future pregnancy that Clare may have
5. To help identify suitable family members as potential kidney donors

Who to test?

The best person to test is the person most likely to have the genetic condition – ie Harry, as he has the most significant features of renal disease. Clare's haematuria could have several causes, but she could also be tested if her brother was not available or refused consent.

Which test?

The latest guidelines (Savige et al, 2022) advise that testing of COL4A3, COL4A4 and COL4A5 is completed in people with persistent haematuria, especially where there is a family history of renal insufficiency. Using PanelApp and searching for each gene reveals that all three genes are included in the following tests:

- R194 Haematuria (five genes – gene panel test)
- R195 Proteinuric renal disease (55 genes – gene panel test)
- R257 Unexplained young onset end-stage renal disease (183 genes – whole genome sequencing).

The phenotype(s) in the patient and their relatives helps guide test selection. The clinical features are consistent with Alport syndrome and there are no unusual features, so R194 is the most appropriate investigation.

Results

Harry was found to have two alterations in the COL4A4 gene. One was reported to be pathogenic, while the other was classified as a 'hot' variant of uncertain significance. The diagnosis of autosomal recessive Alport syndrome was likely but could not be confirmed. Harry's case was discussed at the renal genomics multidisciplinary team and Harry and his family were referred to genomic medicine. Parental testing confirmed that Harry's COL4A4 variants were in trans (one inherited from each parent). Subsequently, Harry's father, who was heterozygous for a pathogenic COL4A4 variant, was found to have haematuria, hypertension and renal impairment. Further family studies, involving Harry's maternal relatives and in silico modelling, have enabled re-classification of the variants of uncertain significance as a 'likely pathogenic' variant, confirming the diagnosis of autosomal recessive Alport syndrome.

Implications

Clare was found to be a COL4A4 heterozygote. She was advised that there was a 50% chance that any children she may have will inherit the familial variant and have an increased risk of developing renal disease, requiring surveillance. As Clare's partner reported a family history of renal failure in a first-degree relative, he was offered genetic testing of the COL4A3–COL4A5 genes because of the risk of autosomal recessive or digenic Alport syndrome any children he may have with Clare. Reproductive risks and options were discussed in detail to help the couple make an informed decision.

- Harry's immediate and wider family were referred to their respective genetic services for counselling and/or testing and, where appropriate, renal screening. All individuals with a heterozygous familial COL4A4 variant and evidence of microalbuminuria, hypertension or kidney impairment were commenced on renin–angiotensin–aldosterone system blockade.
- Any relatives with a familial COL4A4 variant were automatically ruled out as potential kidney donors for Harry

Close collaboration between nephrology and genomic medicine services in a dedicated renal genomics multidisciplinary team meeting or clinic provides an important forum

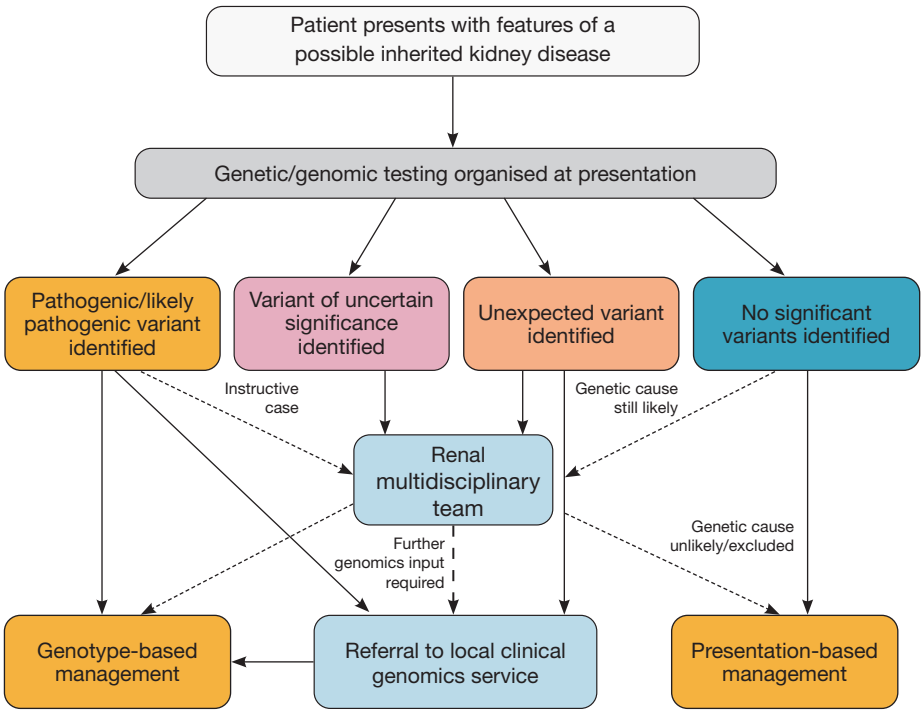

Figure 1. Role of renal genomics multidisciplinary team meetings and clinics.

to discuss cases and results (Figure 1) and plays a central role in integrating genetic or genomic testing in renal medicine (Alkanderi et al, 2017). Possible pathways for using the renal genomic multidisciplinary team meeting to facilitate interpretation of genetic or genomic results are shown in Figure 1.

Alternative models of renal genomics services may be better suited to specific regions and support is also available via the National Renal Genetic Network (@rengenUK).

Utility of genomic testing in nephrology

Genomic testing to aid diagnosis and personalised management

Personalised medicine aims to combine genomic and clinical information to secure a precise diagnosis, managed with targeted interventions. Steroid-resistant nephrotic syndrome is the second most common cause of end-stage renal disease in the first two decades of life and causative genetic alterations have been identified in 25–29% of cases of steroid-resistant nephrotic syndrome (Sadowski et al, 2015; Warejko et al, 2018).

Standard management involves immunosuppressive agents to treat the underlying histological diagnosis identified on renal biopsy. However, identification of a genetic cause, for example via a proteinuric renal disease gene panel test (R195, Table 1), would allow discontinuation of unnecessary immunosuppressive treatment, reducing the risk of significant side effects occurring. Murray et al (2020) reported that genetic testing following biopsy altered the understanding of the underlying disease mechanism in 54% of patients and changed medical management in 26% of cases of steroid-resistant nephrotic syndrome, demonstrating the impact of a genetic diagnosis on clinical management and highlighting the importance of genetic testing in patients presenting with nephrotic syndrome

Genomic testing to aid prognostication and reproductive counselling including prenatal genetic testing

Alport syndrome is a common inherited kidney disease caused by pathogenic variants in the genes COL4A5 (X-linked), COL4A3 or COL4A4 (autosomal recessive), which code for the collagen IV α5-, α3- and α4-chains forming the major constituent of basement membranes. Clinical features of X-linked Alport syndrome include kidney failure, hearing loss, lenticonus and fleck retinopathy. Autosomal recessive Alport syndrome is diagnosed in individuals with two pathogenic variants in COL4A3 or COL4A4 and is characterised

by haematuria, proteinuria, hypertension and kidney impairment but without the hearing loss or ocular abnormalities seen in X-linked Alport syndrome (Kashtan et al, 2018).

Most men and 15–30% of women with X-linked Alport syndrome and most patients of either gender with autosomal recessive Alport syndrome develop kidney failure, while the risk for COL4A3 and COL4A4 heterozygous carriers has been estimated to be 10–20% (Savige et al, 2022). Expert opinion advises that individuals with a heterozygous COL4A3 or COL4A4 variant and women with pathogenic COL4A5 variant should not act as kidney donors because of their own risk of kidney impairment as well as a risk of further deterioration after donation (Savige et al, 2022).

Diagnosing Alport syndrome is critical for effective treatment with RAAS blockade and other agents, implementation of extra-renal screening and reproductive counselling. Exact diagnosis can be difficult based on clinical features and family history alone, highlighting the importance of genetic testing in this heterogenous condition.

Genomic testing to confirm diagnosis, reduce unnecessary screening and facilitate presymptomatic treatment

Autosomal dominant polycystic kidney disease is the most common cause of inherited chronic kidney disease and is associated with pathogenic alterations in the PKD1 or PKD2 genes. Although autosomal dominant polycystic kidney disease can be clinically diagnosed based on imaging criteria (Lanktree et al, 2021), identification of a pathogenic or likely pathogenic variant can help to reduce the risk of other causes of cystic kidney disease that require different management (eg HNF1B-associated renal disease), aid prognostication (Mantovani et al, 2020) (eg PKD1 is usually more severe than PKD2), and enable timely reproductive counselling and/or testing. Furthermore, predictive genetic testing of at-risk family members allows identification of at-risk relatives, negating the need for annual screening and ensuring they receive optimal management (Marlais et al, 2016). This is not only cost effective, but also helps to reduce anxiety associated with prolonged diagnostic uncertainty and enables individuals to make informed reproductive choices.

Genetic testing to facilitate selection of a suitable related live donor

Careful selection of live related donors for renal transplantation is important for a successful long-term outcome for the (living) donor and recipient. Live donation requires thorough pre-donation assessment to mitigate the risk to the donor, both immediate and long term (Mjøen et al, 2014). Where a genetic cause of kidney disease is confirmed, donation by a related donor could increase their own risk of end-stage renal disease. KDIGO guidelines advise that donor candidates should be questioned about their family history of kidney disease (Lentine et al, 2017). Genetic testing for the familial variant should be undertaken and form part of the assessment of suitability to be a donor. For this to occur in a timely manner, the familial pathogenic variant should ideally have been already identified (Savige et al, 2022).

Overcoming barriers

There are many benefits of timely genomic testing in renal medicine. However, there remains a hesitancy among renal specialists to undertake genetic or genomic testing as part of their routine practice.

Increased collaboration between renal physicians, genomic clinical scientists and clinical geneticists is key to overcoming such hesitancy and increasing use of genomic testing in renal medicine. This could be achieved through a dedicated joint renal genomics multidisciplinary team meeting and/or clinic and involvement in the national renal genomics meetings.

Ongoing education to increase nephrologists' knowledge and confidence around genetic and genomic testing, supported by regular interactions with local clinic genetics specialists and national meetings, will continue to promote integration of genomics within nephrology services. Although multidisciplinary renal genomics clinics are slowly increasing in number nationally, they remain patchy, leaving inequity of access to genomic testing in certain areas, which needs addressing in future. Establishing a dedicated renal genomic service, similar to inherited cancer and cardiac services, will allow clinicians to better address the needs of the local population and offer a forward-thinking, comprehensive and responsive service for patients with inherited kidney disease.

The potential for the future

To realise the potential of genomic medicine in nephrology, it is critical that genomic testing becomes embedded in mainstream renal services. Renal specialists should be supported to use genomic investigations at the earliest appropriate time, so that patients and their families can maximally benefit from personalised care. Increased use of genomic testing will increase genomic knowledge and elucidate genotype–phenotype correlations to further enhance clinicians' ability to diagnose, prognosticate, screen and improve outcomes for patients and their families.

Going forward, advances in renal genomics will extend beyond rare monogenic conditions and facilitate the development of polygenic renal risk scores for patients with renal disease and the general population. Better understanding of underlying molecular mechanisms will identify novel targets for therapeutic intervention and help develop genetically targeted therapies for inherited kidney disease.

Author details

[1]Liverpool Centre for Genomic Medicine, Liverpool Women's NHS Foundation Trust, Liverpool, UK

[2]Department of Nephrology, Royal Liverpool Hospital, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

[3]The North West Genomic Laboratory Hub, Manchester University NHS Foundation Trust, St Mary's Hospital, Manchester, UK

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Alkanderi S, Yates LM, Johnson SA, Sayer JA. Lessons learned from a multidisciplinary renal genetics clinic. QJM. 2017;110(7):453–457. https://doi.org/10.1093/qjmed/hcx030

Aymé S, Bockenhauer D, Day S et al. Common elements in rare kidney diseases: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int. 2017;92(4):796–808. https://doi.org/10.1016/j.kint.2017.06.018

Bassanese G, Wlodkowski T, Servais A et al. The European Rare Kidney Disease Registry (ERKReg): objectives, design and initial results. Orphanet J Rare Dis. 2021;16(1):251. https://doi.org/10.1186/s13023-021-01872-8

Bullich G, Domingo-Gallego A, Vargas I et al. A kidney-disease gene panel allows a comprehensive genetic diagnosis of cystic and glomerular inherited kidney diseases. Kidney Int. 2018;94(2):363–371. https://doi.org/10.1016/j.kint.2018.02.027

Key points

- Inherited kidney disease accounts for approximately 10% of adult cases of end-stage renal disease in Europe and an even higher proportion of paediatric cases.
- Genetic testing for inherited kidney disease should be integrated into clinical care pathways at the earliest opportunity; this will need renal physicians to organise testing at presentation. Support is available from local clinical genomics services.
- Establishing a genetic diagnosis may streamline the diagnostic journey, provide a better understanding of disease pathogenesis, aid prognostication, inform surveillance and management of renal and extra-renal manifestations, offer opportunities for personalised medicine, facilitate reproductive choices, identify at-risk family members and facilitate clinical trials.
- Renal physicians will need to evaluate the required skillset to fully use recent advances in genomic medicine.
- Local clinical genetic or genomic services are available for advice, cascade testing and prenatal counselling.

Useful resources

- Test directory: https://www.england.nhs.uk/publication/national-genomic-test-directories/
- NHS Genomic Medicine Service Signed Off Panels Resource: https://nhsgms-panelapp.genomicsengland.co.uk/
- Health Education England's Genomics Education Programme: https://www.genomicseducation.hee.nhs.uk/
- GeNotes (genomics notes for clinicians): https://www.genomicseducation.hee.nhs.uk/genotes/
- GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1116/
- OMIM: https://www.omim.org/
- MedlinePlus Genetics: https://medlineplus.gov/genetics/
- Genetic Alliance: https://geneticalliance.org.uk/
- Rare Disease Groups: https://ukkidney.org/rare-renal/rare-disease-groups
- Renal Genetics UK: https://twitter.com/rengenuk

Devuyst O, Antignac C, Bindels RJM et al. The ERA-EDTA Working Group on inherited kidney disorders. Nephrol Dial Transplant. 2012;27(1):67–69. https://doi.org/10.1093/ndt/gfr764

Devuyst O, Knoers NVAM, Remuzzi G, Schaefer F, Board of the Working Group for Inherited Kidney Diseases of the European Renal Association and European Dialysis and Transplant Association. Rare inherited kidney diseases: challenges, opportunities, and perspectives. Lancet. 2014;383(9931):1844–1859. https://doi.org/10.1016/S0140-6736(14)60659-0

Ellard S, Baple EL, Callaway A et al. ACGS best practice guidelines for variant classification in rare disease 2020. 2020. https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf (accessed 20 May 2023)

Groopman EE, Marasa M, Cameron-Christie S et al. Diagnostic utility of exome sequencing for kidney disease. N Engl J Med. 2019;380(2):142–151. https://doi.org/10.1056/NEJMoa1806891

Hays T, Groopman EE, Gharavi AG. Genetic testing for kidney disease of unknown etiology. Kidney Int. 2020;98(3):590–600. https://doi.org/10.1016/j.kint.2020.03.031

HM Government. Genome UK: the future of healthcare. 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/920378/Genome_UK_-_the_future_of_healthcare.pdf (accessed 20 May 2023)

Jayasinghe K, Stark Z, Kerr PG et al. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. Genet Med. 2021;23(1):183–191. https://doi.org/10.1038/s41436-020-00963-4

Kashtan CE, Ding J, Garosi G et al. Alport syndrome: a unified classification of genetic disorders of collagen IV α345: a position paper of the Alport Syndrome Classification Working Group. Kidney Int. 2018;93(5):1045–1051. https://doi.org/10.1016/j.kint.2017.12.018

Knoers N, Antignac C, Bergmann C et al. Genetic testing in the diagnosis of chronic kidney disease: recommendations for clinical practice. Nephrol Dial Transplant. 2022;37(2):239–254. https://doi.org/10.1093/ndt/gfab218

Lanktree MB, Haghighi A, di Bari I, Song X, Pei Y. Insights into autosomal dominant polycystic kidney disease from genetic studies. Clin J Am Soc Nephrol. 2021;16(5):790–799. https://doi.org/10.2215/CJN.02320220

Lentine KL, Kasiske BL, Levey AS et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Transplantation. 2017;101(8):1783–1792. https://doi.org/10.1097/TP.0000000000001769

Mann N, Braun DA, Amann K et al. Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. J Am Soc Nephrol. 2019;30(2):201–215. https://doi.org/10.1681/ASN.2018060575

Mantovani V, Bin S, Graziano C et al. Gene panel analysis in a large cohort of patients with autosomal dominant polycystic kidney disease allows the identification of 80 potentially causative novel variants and the characterization of a complex genetic architecture in a subset of families. Front Genet. 2020;11:464. https://doi.org/10.3389/fgene.2020.00464

Marlais M, Cuthell O, Langan D et al. Hypertension in autosomal dominant polycystic kidney disease: a meta-analysis. Arch Dis Child. 2016;101(12):1142–1147. https://doi.org/10.1136/archdischild-2015-310221

Mjøen G, Hallan S, Hartmann A et al. Long-term risks for kidney donors. Kidney Int. 2014;86(1):162–167. https://doi.org/10.1038/ki.2013.460

Murray SL, Dorman A, Benson KA et al. Utility of genomic testing after renal biopsy. Am J Nephrol. 2020;51(1):43–53. https://doi.org/10.1159/000504869

NHS England. Improving Outcomes through Personalised Medicine. 2016. https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf (accessed 20 May 2023)

NHS England. Accelerating Genomic Medicine in the NHS. 2022. https://www.england.nhs.uk/long-read/accelerating-genomic-medicine-in-the-nhs/ (accessed 20 May 2023)

NHS England. National Genomic Test Directory. 2023. https://www.england.nhs.uk/publication/national-genomic-test-directories/ (accessed 28 June 2023)

Richards S, Aziz N, Bale S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–424. https://doi.org/10.1038/gim.2015.30

Sadowski CE, Lovric S, Ashraf S et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2015;26(6):1279–1289. https://doi.org/10.1681/ASN.2014050489

Savige J, Lipska-Zietkiewicz BS, Watson E et al. Guidelines for genetic testing and management of Alport syndrome. Clin J Am Soc Nephrol. 2022;17(1):143–154. https://doi.org/10.2215/CJN.04230321

Warejko JK, Tan W, Daga A et al. Whole exome sequencing of patients with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2018;13(1):53–62. https://doi.org/10.2215/CJN.04120417