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Which patients with CKD will benefit from genomic sequencing? Synthesizing progress to illuminate the future

Andrew J. Mallett[a,b,c,d]

Purpose of review
This review will summarize and synthesize recent findings in regard to monogenic kidney disorders, including how that evidence is being translated into practice. It will add to existing key knowledge to provide context for clinicians in consolidating existing practice and approaches.

Recent findings
Whilst there are long established factors, which indicate increased likelihood of identifying a monogenic cause for kidney disease, these can now be framed in terms of the identification of new genes, new indications for genomic testing and new evidence for clinical utility of genomic testing in nephrology. Further, inherent in the use of genomics in nephrology are key concepts including robust informed consent, variant interpretation and return of results. Recent findings of variants in genes related to complex or broader kidney phenotypes are emerging in addition to understanding of de novo variants. Phenocopy phenomena are indicating a more pragmatic use of broader gene panels whilst evidence is emerging of a role in unexplained kidney disease. Clinical utility is evolving but is being successfully demonstrated across multiple domains of outcome and practice.

Summary
We provide an updated framework of evidence to guide application of genomic testing in chronic kidney disease (CKD), building upon existing principles and knowledge to indicate how the practice and implementation of this can be applied today. There are clearly established roles for genomic testing for some patients with CKD, largely those with suspected heritable forms, with these continuing to expand as new evidence emerges.

Keywords
diagnostic genomics, genetic kidney disease, genetic testing

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INTRODUCTION

The role of diagnostic genomics in mainstream nephrology practice continues to rapidly evolve. Building upon a base of substantial research discovery and technological development, we have now collectively arrived at a point where a healthy tension exists not between whether there is or is not a role for genomics in nephrology but rather whether this role should rest predominantly with subspecialists, be instead primarily integrated into general nephrology, or indeed a combination of these. This is an opportune time to reflect on recent progress and evidence in order to better inform both research and clinical pathways broadly across the space of monogenic kidney disease. Building upon a previous and complementary review focused upon the diagnosis of monogenic forms of chronic kidney disease (CKD) [1], this review will explore recent progress illuminating, which patients might benefit from genomic sequencing through the lenses of the identification of new causative genes, new indications for genomic testing, new insights into the clinical utility of such genomic testing amongst

[a]College of Medicine and Dentistry, James Cook University, Douglas, [b]Department of Renal Medicine, Townsville University Hospital, [c]Faculty of Medicine, The University of Queensland, Herston and [d]Institute for Molecular Bioscience, The University of Queensland, St Lucia, Queensland, Australia

Correspondence to Professor Andrew J. Mallett, Department of Renal Medicine, Townsville University Hospital, Douglas, QLD 4814, Australia. E-mail: Andrew.mallett@health.qld.gov.au

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KEY POINTS

- Diagnostic genomic testing is being actively implemented into contemporary nephrology practice.
- Key practices and factors indicating greater likelihood of identifying a causative genetic diagnosis are reaffirmed by new evidence.
- New genes continue to be elucidated whilst new indications for genomic testing in CKD are also emerging.
- Understanding of the clinical utility in addition to diagnostic utility of genomic testing in CKD is driving implementation into practice whilst also providing clarity around which patients with CKD benefit from diagnostic genomic testing.

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those with CKD, and emerging pathways towards implementation in nephrology practice (Fig. 1).

NEW GENES

Underpinning the ability to undertake genomic testing for patients with CKD is our understanding of which genes have a relationship to kidney disease or CKD phenotypes. This has both grown and deepened in recent years even as it has been thought that the rate of new gene discovery might plateau or slow. It is generally anticipated that whilst each newly identified gene is likely to account for a diminishing number of affected patients or families, collectively, this is successfully working towards being able to identify a diagnosable monogenic cause for the majority of instances of suspected heritable kidney disease or CKD.

In tubulopathy and electrolyte disorders, there are several key findings of note. The reporting of pathogenic variants in mtDNA causing a Gitelman-like syndrome [2▪] brings together several logical lines of understanding in terms of renal tubular physiology and mitochondrial biology, whilst the identification of biallelic variants in *KCNJ16* related to a hypokalaemic syndrome fortifies tubular potassium channel understanding whilst further linking to extrarenal phenotypes including sensorineural hearing impairment [3]. Even though inherited syndromes linking the kidney and sensorineural hearing impairment are not unknown to nephrologists, it is interesting to note that the discovery of de novo heterozygous *RRAGD* variants brings together both a hypokalaemic and hypomagnesaemic kidney syndrome with dilated cardiomyopathy owing to a shared cardiorenal mTOR-signalling pathways [4].

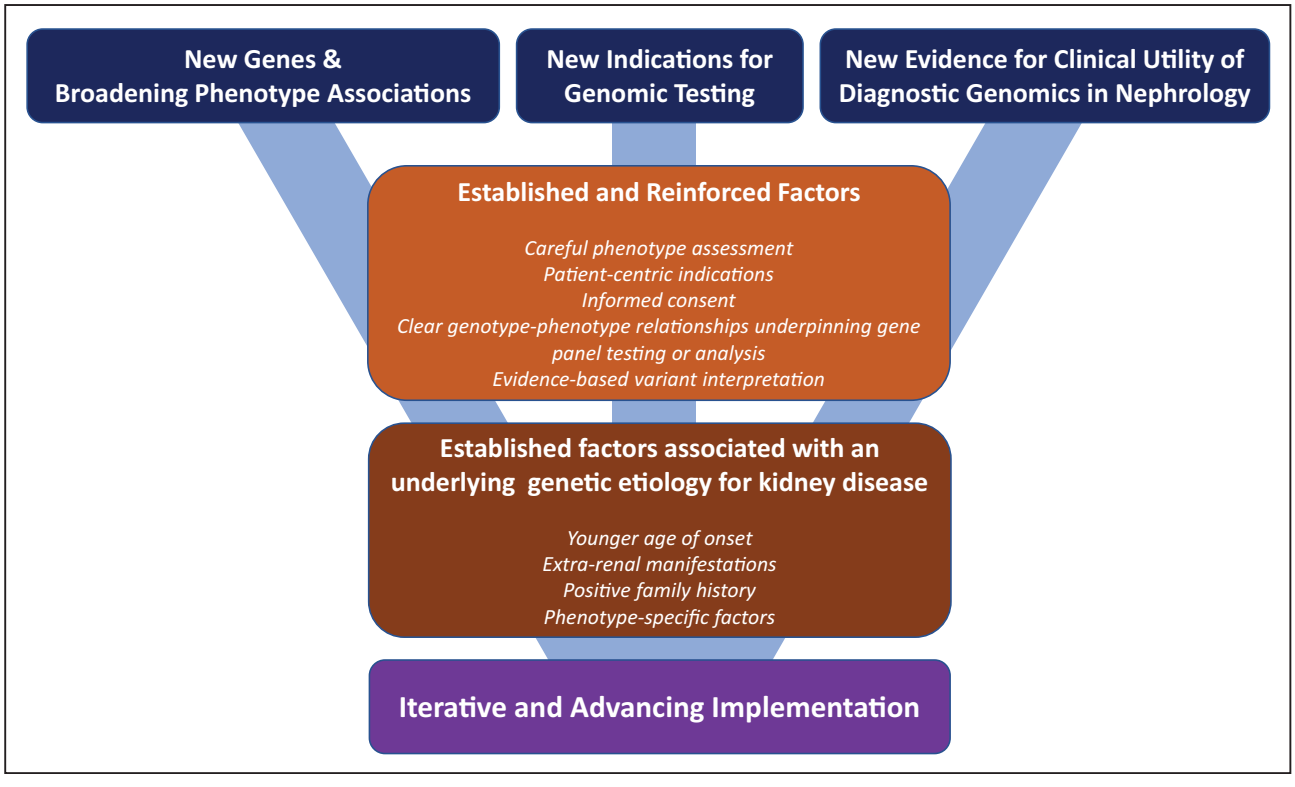

FIGURE 1. Advancing implementation of genomic testing in chronic kidney disease through new knowledge and established factors.

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Moving to heritable structural kidney disorders, iterative progress continues despite previous thinking that the proportion of cases of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) with an identifiable monogenic cause was likely to remain modest. As cohort sizes have expanded, this has enabled new ways to explore for heterozygous de novo pathogenic variants in genes and thus revealed *ZMYM2* [5], which has further eluded to potential additional genes within its broader interactome. Careful phenotyping and research investigation clarified that pathogenic biallelic *ROBO1* variants relate to a variety of CAKUT phenotypes, further confirming and extending the phenotypic spectrum of this gene past established cardiac and neurological phenotypes.

Whilst there are many genes that are considered to be candidate genes owing to understanding of their role in human development and physiology, there are not infrequently challenges in clarifying if genetic variation in these genes indeed relates to anticipated or expected heritable phenotypes. In regard to the kidney, this was the case for *ROBO1* but has also been the case for *LAMA5,* owing to its role with basement membranes. More compelling evidence has now established that biallelic pathogenic variants in *LAMA5* have a causative relationship across a spectrum of glomerular phenotypes from nonsyndromic nephrotic syndromes [6] to syndromic complex kidney phenotypes [7]. Other genes in which pathogenic variants have been associated with proteinuric kidney disorders are biallelic variants in *DAAM2* associated with steroid-resistant nephrotic syndrome [8] and de novo heterozygous variants in *TRIM8* with focal segmental glomerulosclerosis with extrarenal epilepsy and neurodevelopmental disease [9]. Many of these newly identified genes associated with proteinuric kidney disorders have emerged from large cohorts, existing knowledge of gene interaction networks and improved exploration of de novo heterozygous pathogenic variants.

Additional genes linked to the primary cilium are also exhibiting broader intrarenal and extrarenal phenotype spectra. Biallelic variants in *TTC21B* have been shown to result in a mixed glomerular and tubulointerstitial kidney disease [10], whilst biallelic *TULP3* variants linked together disease entities with hepatic, kidney and cardiac components all of which include fibrotic and/or fibrocystic disorders [11]. The identification of genes such as these is shedding new light on kidney ciliopathies, not only in terms of which nephron components might be affected, but also in terms of syndromic forms and underlying disease pathways such as DNA damage, repair and fibrosis.

An area of intense renewed interest in recent years for gene discovery has been cystic kidney disease. The relatively recent identification of *GANAB*, *DNAJB11* and *ALG9* as genes in which pathogenic heterozygous variants are associated with cystic kidney phenotypes has driven hope that an increasing proportion of patients with cystic kidney disorders such as autosomal dominant polycystic kidney disease (ADPKD) or atypical ADPKD may be able to attain a genetic diagnosis. Most recently, *ALG5* has been reported and appears to exhibit a condition spanning ADPKD and autosomal dominant tubulointerstitial kidney disease (ADTKD) [12], not dissimilar to what has become apparent with *DNAJB11* [13▪]. This further delineation of mixed phenotypes is further challenging ontology to extend past what has been previously dogmatically held to be true with monogenic kidney disorders aligning clearly within relatively neat and clean groupings exhibiting overlap by exception.

It is into this setting that perhaps a most interesting finding has been reported. Where previously biallelic pathogenic variants in *IFT140* were known to associate with autosomal recessive syndromic kidney ciliopathies, specifically Mainzer–Saldino syndrome [14] and Jeune asphyxiating thoracic dystrophy [15], it has now been reported that heterozygous pathogenic variants in *IFT140* are associated with ADPKD [16▪▪]. Where initially this may seem incongruent as the obligate carrier parents of affected patients with *IFT140*-related autosomal recessive ciliopathy have not otherwise been reported to harbour kidney cystic or ADPKD phenotypes. The subtlety, however, is in the nature of the pathogenic variants involved, with the recessive ciliopathy appearing to relate to missense variants whereas in dominant ADPKD, this related to truncating loss-of-function variants. There is some further chance and indeed opportunity that additional gene–phenotype relationships will emerge as understanding of variant type and de novo variants are explored at scale [17▪] with disentanglement of traditional concepts of inheritance, penetrance and variant effects.

NEW INDICATIONS FOR GENOMIC TESTING

Just as new monogenic causes are being uncovered, the potential clinical indications for genomic testing in CKD is also being further revealed. Specifically, this most recently has pertained to potential indications around prognostication, diagnostic utility in instances of unexplained CKD or kidney failure and identification of unappreciated phenocopy disorders.

In a cohort of ADTKD families, 29 of 45 achieved a genetic diagnosis in genes known to be associated with that condition. However a further 9 of 45 harboured diagnostic variants in other monogenic

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kidney disease genes not traditionally associated with ADTKD [18]. Whether these represent phenocopy phenomena, instances of incomplete phenotyping or atypical presentations is not clear but this may be clarified in coming years as large ADTKD cohorts are now being reported [19,20], which are already proposing new clinical, genetic and score-based prognostications for relevant outcomes like age at incident kidney failure.

A key feature in this space is the aggregation and analysis of large and well characterized cohorts of specific monogenic kidney disorders to illuminate prognostication factors. Just as prognostication approaches incorporating genetic factors have been identified and validated in ADPKD [21–23], these are now gaining more context [24▪] and being further added to for atypical ADPKD [13▪] whilst also emerging for ADTKD [19,20,25]. Whilst a modest minority of cases have a monogenic cause, similar cohort findings have been reported for C3 glomerulopathy [26], which aids in a pragmatic genetic approach for such conditions with mixed or complex aetiological underpinnings. Together, this emerging evidence is increasingly indicating that a genetic or genomic result for an individual can have prognostic applications, and this may be a relative or potentially absolute indication for genomic testing in some instances of CKD.

One area of substantial interest is whether or not broad genomic testing might have a diagnostic role in instances of otherwise unexplained CKD or kidney failure. At least two prospective studies are currently underway examining this question [27,28]. Whilst awaiting those prospective studies to report, new information from retrospective studies is adding evidence to this space. In a kidney transplant cohort with kidney failure before 50 years of age, exome analysis with a broad kidney gene panel unveiled new genetic diagnoses and indicated that genomic testing may have a role as a first-tier diagnostic approach [29▪▪]. Others identified that diagnosable phenocopy disorders may be more common, representing up to one in five genetic diagnoses in suspected hereditary kidney disease and that an approach rigidly applying very strictly targeted gene panels rather than broader or cascade panels does not identify such instances [30▪]. For complex phenotypes such as urinary stone disease, the evidence for broadened gene panels is further reflecting this concept that application of a very targeted gene panel approach will fail to identify a genetic diagnosis that is present and directly related to the patient phenotype in 10–20% of instances [31].

Moving from broad to more specific, new evidence is also emerging around including the potential screening of CKD patients for very rare monogenic kidney diseases such as Fabry disease. Whilst overall prevalence has been confirmed to be very low (<0.5%) amongst those with CKD [32–35], there are still cases who appear to only have been identified via cohort-screening approaches. This is all the more pointed as targeted therapies for Fabry disease are available and in clinical use. Whilst Fabry disease specifically is able to be screened for using nongenomic blood testing, this often has degraded diagnostic performance amongst women as it is an X-linked disorder. Application of gene panels that are potentially of a broader nature, may identify opportunity for very tangible clinical utility from application of broader gene panels and their application in otherwise unexplained CKD or kidney failure.

NEW INSIGHTS INTO UTILITY OF GENOMIC SEQUENCING IN CHRONIC KIDNEY DISEASE

Now that diagnostic utility is well established for genomics in suspected heritable forms of CKD, greater focus is now turning to better understanding clinical utility. Testing at scale has indicated that less than 10 genes account for the majority of overall diagnoses made [36▪] even though there is variability in terms of genetic diagnosis rates between phenotypes or panels [37–39]. Utility in disentangling atypical or complex phenotypes is also being demonstrated [40▪]. The large cohort studies such as these come from multiple jurisdictions or countries and yet affirm each other's findings is important, as this heightens confidence in broad applicability and translation.

One especial point of clinical utility that has been proposed for genomic testing in CKD is the potential to replace or act synergistically with kidney biopsy in some situations. Analyses of genomic testing concurrently [41] and after [42▪] kidney biopsy for CKD has been revealing. It appears that there may be some instances where kidney biopsy can be deferred or even avoided, but this is largely restricted to scenarios of a particular or suspected heritable monogenic kidney disorder. In the majority of instances, benefit is instead derived from adding information to a histopathological diagnosis, which adds new understanding or depth for approximately half of those attaining a genetic diagnosis after kidney biopsy. Of even greater interest is that genomic testing in conjunction with or after kidney biopsy translates to changed treatment for one in four patients attaining a genetic diagnosis.

The role of diagnostic genomics in living related kidney donor assessment has also been long

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proposed as an area for measurable clinical utility. New evidence is demonstrating that this benefit is realizable [43▪] and moreover that the proposed approach of commencing the diagnostic genomic testing cascade with a phenotypically affected relative, usually the proposed kidney transplant recipient [44,45], is appropriate and effective.

Another area of potential clinical utility is in reproductive planning, particularly preimplantation genetic testing. Recent reported experience and evidence [46▪▪] is strongly encouraging in terms of outcomes and indicated that patient interest is growing as evidenced by increasing referrals. In practical terms, discussions around family and reproductive planning should be actively considered and undertaken as part of the nephrological care of patients affected by suspected or proven heritable CKD, with consideration of genomic testing if or where indicated, to facilitate informed decision-making or advanced reproductive technologies.

Reaffirmation of proposed key factors indicating higher likelihood of an identifiable monogenic cause in CKD and thus a diagnostic outcome from genomic testing is clarifying clinical utility. Such factors include the presence of a family history of kidney disease [47], younger age of onset [48], extrarenal features, and phenotype-specific factors [49]. This is critical to frame clinical utility and to guide future implementation and education.

TOWARDS IMPLEMENTATION

The frontier currently being traversed is to translate evidence into practice with genomic testing being integrated into contemporary nephrology practice. At a whole-of-system level, the transformative nature of clinical genomics is being realized [50▪▪,51,52]. Concurrently, these benefits are being realized at a grass root level in terms of establishment of kidney genetic clinics and multidisciplinary services in new jurisdictions [53–57] complementing and building upon learnings from earlier efforts [58,59]. For more common heritable kidney disorders such as ADPKD, alternate genomic testing mainstreaming models, which are more integrated into existing nephrology models of care [60] are showing great promise for a future second wave of genomic mainstreaming in nephrology supported by novel pathways to return genetic results [61▪].

Two examples highlighting intuitive and effective implementation of genomics in CKD have been in the space of Alport syndrome and the *COL4A3-COL4A5* spectrum of kidney disorders, and the national approach espoused in Australia. Firstly, regular international condition-focused workshops [62] have brought together clinicians, researchers, scientists and consumers whilst population prevalence estimates have been refined [63] and rarer subtypes characterized [64] resulting in revised and condition-specific variant diagnostic standards [65▪] and broader guidelines around genetic testing through to management [66]. Secondly, Australia has progressed from a first multidisciplinary kidney genetics clinic in 2013 [58] to a nationwide network of 18 such clinics underpinned by understanding of nephrologist attitudes and practices around genomic testing in CKD [67], local clinical impact [68] and health economic impact [69▪] of such implementation such that nationwide reimbursement for genomic testing in suspected heritable CKD was implemented on 1 July 2022 via the Australian Government's Medicare Benefits Schedule within a universal healthcare model of healthcare. These two examples show both from disease-focused and country-focused perspectives that advancement and implementation of genomics in CKD is possible and effective with patients and families as ultimate beneficiaries.

It is also an opportune time to look towards future potential diagnostic genomic pathways and innovations that show promise for clinical implementation in the medium term. These include digital health approaches to case identification [70], transcriptomic or RNA sequencing [71,72], which can reclassify variants otherwise not considered as being disease-related [73], and globally calibrated and verified gene–phenotype curation for monogenic CKD, such as ClinGen [74] and PanelApp [75] within the Gene Curation Coalition [76▪]. Already key global consensus policy recommendations including from the European Renal Association (ERA) and European Rare Kidney Disease Reference Network (ERKNet) [77▪] and Kidney Diseases: Improving Global Outcomes (KDIGO) [78▪] are helping to consolidate and bring together experiences and learnings across countries and regions to guide ongoing implementation of genomics in CKD.

CONCLUSION

In conclusion, those patients with CKD who will benefit from genomic testing are becoming clearer and thus are more likely to benefit today than at any time previously. The discovery of new causative genes in company with new indications for genomic testing and new evidence for clinical utility are adding depth and a frame of action for established factors for both delivering diagnostic genomics in a contemporary nephrology context as well as identifying those CKD patients with greater likelihood of harbouring a genetic cause for CKD. The learnings from future and further implementation over the

coming years will likely refine this further whilst adding further depth and breadth to our understanding of which patients in which circumstances and with which genomic technologies we can deliver a patient-centric model of precision nephrology.

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Conflicts of interest

There are no conflicts of interest.

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