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Genomic medicine for kidney disease

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Abstract

Technologies such as next-generation sequencing and chromosomal microarray have advanced the understanding of the molecular pathogenesis of a variety of renal disorders. Genetic findings are increasingly used to inform the clinical management of many nephropathies, enabling targeted disease surveillance, choice of therapy, and family counselling. Genetic analysis has excellent diagnostic utility in paediatric nephrology, as illustrated by sequencing studies of patients with congenital anomalies of the kidney and urinary tract and steroid-resistant nephrotic syndrome. Although additional investigation is needed, pilot studies suggest that genetic testing can also provide similar diagnostic insight among adult patients. Reaching a genetic diagnosis first involves choosing the appropriate testing modality, as guided by the clinical presentation of the patient and the number of potential genes associated with the suspected nephropathy. Genome-wide sequencing increases diagnostic sensitivity relative to targeted panels, but holds the challenges of identifying causal variants in the vast amount of data generated and interpreting secondary findings. In order to realize the promise of genomic medicine for kidney disease, many technical, logistical, and ethical questions that accompany the implementation of genetic testing in nephrology must be addressed. The creation of evidence-based guidelines for the utilization and implementation of genetic testing in nephrology will help to translate genetic knowledge into improved clinical outcomes for patients with kidney disease.

Although individual inherited kidney diseases are rare, together they account for approximately 10% of adult end-stage renal disease (ESRD)[1–3] and at least 70% of paediatric[4,5] nephropathy. In addition to known hereditary aetiologies, compelling evidence exists for a genetic contribution across different forms of kidney disease. The `heritability` of glomerular filtration rate is estimated to be ~30–60% in the general population[6,7], and other parameters such as tubular transport of electrolytes similarly show substantial hereditability[8–10]. Moreover, 10–29% of adult patients with ESRD report a positive family history across different ethnicities and aetiologies[11– 13]. Prognosis, disease course, and appropriate management can differ markedly between hereditary and acquired forms of kidney disease, but these forms can be indistinguishable when traditional

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diagnostics alone are used[14,15]. Moreover, as early-stage disease is often clinically silent, patients might not present until they reach ESRD. Owing to such late referral and the limitations of noninvasive diagnostic tools, the cause of kidney failure is classified as unknown in more than one in ten patients with ESRD[16–18]. Thus, earlier and more specific diagnoses are needed to enable delivery of effective care[19,20].

Technologies such as `chromosomal microarray` (CMA) and `next-generation sequencing` (NGS) were first introduced as research tools in the past decade and have empowered investigation of genetic contributions to disease through assessing variation across the `genome`[21–23]. These technologies are being increasingly deployed in the clinic, reflecting a shift in the work-up of suspected hereditary disorders in clinical medicine. Traditionally, diagnosis of individuals suspected to have an inherited form of nephropathy involved multiple clinical visits and complex and/or invasive studies (such as renal biopsy or biochemical testing) to identify the most likely aetiology, which the clinician would use to select one or a few associated genes for `genetic testing`. Now, a shift towards `genomic medicine` is occurring, wherein genome-wide testing approaches are used to identify the causal aetiology of disease in a patient, and the genetic variant or variants that are identified are used to guide their clinical care[24]. As sequencing costs are rapidly declining, genome-wide testing has been advocated as a sensitive and ultimately cost-effective first-line diagnostic test[25–27]. Use of such testing could help to surmount the diagnostic challenges posed by the substantial genetic and phenotypic heterogeneity[28] of many hereditary nephropathies.

However, in order to realize the promise of genomic medicine in nephrology, many complex questions must be answered, including how to identify patients for whom genetic testing is indicated, choose the appropriate test, identify causal variants, and translate genetic findings into personalized care. Addressing these questions requires thorough investigation in large patient cohorts of diverse ages, ethnicities, and disease aetiologies. The ethical, legal, and social implications (ELSIs) that accompany genetic testing on an increasingly broad scale must also be a priority.

In this Review, we examine the opportunities and challenges that accompany the shift to genomic medicine for the diagnosis of genetic diseases of the kidney and urinary tract. We discuss the tests that are available for the work-up of suspected hereditary nephropathy and their diagnostic advantages and limitations, the patient populations for whom genetic testing is indicated, the current guidelines for interpretation of sequence data to achieve a molecular diagnosis, and the value of a `genetic diagnosis` in nephrology. We highlight the key issues that must be addressed to enable implementation of genetic findings in nephrology clinical practice and discuss how they might be surmounted.

Diagnostic genetic testing

Diagnostic genetic testing aims to identify the mutation that is causal for disease in an individual patient, but the wealth of variation within the human genome makes this task difficult. The typical human genome contains approximately 3 billion DNA nucleotides, of which ~20 million may be altered without major consequences for an individual's health[29],

and ~20,000 genes, of which nearly 4,000 have been implicated in human disease[30]. Sequence changes might occur at any of the nucleotide sites and include single-nucleotide variants (SNVs), small insertions or deletions involving <5–10 bp (indels), and structural variants. Given the abundance of rare, predicted damaging variants in a typical human genome, the risk of falsely attributing causality is high[31]. Thus, a major challenge in genetic diagnostics is to identify which variants are disease-causing mutations. Common modalities for diagnostic genetic testing include Sanger sequencing, CMA, and NGS approaches, including targeted next-generation sequencing panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS) (TABLE 1).

Sanger sequencing

Sanger sequencing has high analytical validity in detecting causal SNVs and small (<5–10 bp) insertions or deletions. Thus, this modality remains the gold standard for molecular diagnosis when a single-gene disorder is suspected and for confirmation of NGS findings[32,33]. Sanger sequencing also has utility for genomic regions refractory to NGS, such as those that are highly repetitive, homologous, or guanine–cytosine (GC)-rich. However, as Sanger sequencing is limited to single DNA fragments of <1,000 bp (REF. 34), this modality cannot detect larger structural variants and becomes increasingly costly and time-inefficient as the number of candidate genes increases, limiting its utility for genetically heterogeneous conditions[32,35].

Chromosomal microarray

Historically, testing for genomic disorders — that is, genetic diseases caused by structural variants[36] — involved karyotyping, which can detect chromosomal disorders, translocations, and other large genomic imbalances. However, many genomic disorders are caused by copy number variants (CNVs) that fall below the 1–2 Mb resolution of karyotyping[37]. CMA enables detection of both small and large CNVs[38,39].

Two major types of CMA are used in the clinical setting: array comparative genomic hybridization and single-nucleotide polymorphism arrays. Both of these techniques offer excellent genome-wide coverage and use enrichment of probes in clinically relevant regions to enable resolution at the single-exon level[23,40,41]. Owing to this high resolution, CMAs have as much as 10-fold increased diagnostic yield versus karyotyping for intellectual disability, autism, and multiple congenital anomalies[23,42,43] and are now recommended as a first-line diagnostic for these indications[23,44]. Unlike karyotyping, however, CMAs cannot detect balanced chromosomal rearrangements or low-grade mosaicism and have limited sensitivity to detect changes in certain regions, such as pseudogenes and repetitive elements. In addition, CMAs can generally resolve the boundaries of a CNV to only ~1–2 kb, hindering accurate determination of its size and of the genes affected[45,46], which are key criteria in diagnostic CNV interpretation[21,45]. Thus, findings need to be interpreted in the context of the coverage of the specific CMA platform utilized and the strength of clinical suspicion for a genomic disorder[44].

Applications

Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of paediatric nephropathy[5,47] and can present in isolation or as part of a multiorgan syndrome[48]. CMA has been shown to be an effective first-line diagnostic tool among patients with syndromic CAKUT[49,50] and may also have utility for those with nonsyndromic forms. For example, a study of 522 children with renal hypodysplasia identified CNVs that were pathogenic for a known genomic disorder in 55 of 380 (14.5%) patients with isolated genitourinary anomalies[50]. Among all studies published to date, pathogenic CNVs were identified in ~4–10% of patients with CAKUT and appear to be enriched among patients with renal parenchymal defects, explaining up to 10% of these cases[50,51–56]. These studies identified more than 40 distinct genomic disorders in children with kidney disease, with recurrent syndromes including deletions at the 17q12 (Online Mendelian Inheritance in Man (OMIM) 614527), 22q11.2 (OMIM 188400), and 16p11.2 (OMIM 611913) loci. Moreover, CMA analysis of a cohort of 419 children with all-cause chronic kidney disease (CKD) detected diagnostic CNVs in 7.4% of patients[55], a diagnostic yield comparable to that noted for the established indications of developmental delay or prenatal testing[23,43,51]. Importantly, the majority of patients studied were referred for routine evaluation to paediatric nephrology or urology clinics and had not been previously diagnosed with a syndromic form of disease, highlighting the difficulty of detecting genetic syndromes by use of traditional clinical methods.

In many cases, a diagnosis of a genomic disorder reclassifies a patient’s disease, with important implications for subsequent clinical management. Moreover, these disorders often have pleiotropic effects, including metabolic, skeletal, and neurological complications, which may initiate unnecessary and prolonged work-up in the absence of a unifying aetiology. Alternately, such manifestations may be erroneously attributed as being secondary to renal dysfunction, leading to unachievable expectations for remission after appropriate nephrological treatment. For example, children with nephropathy are at increased risk of adverse neurocognitive outcomes, but this risk has been attributed to the medical and psychosocial burden of kidney disease[57–59]. However, a study of children with CKD demonstrated that those with a genomic disorder had poorer neurocognitive performance, independent of the severity of kidney disease[60]. These findings suggest that in some patients, neurocognitive deficits result from a genomic disorder that impairs both renal and neuropsychiatric function. Thus, CMA has the potential to explain seemingly disparate clinical features, to frame therapeutic expectations, and to guide treatment approaches. Although further investigation is needed to comprehensively ascertain the prevalence of genomic disorders and indications for CMA among adult patients with kidney disease, the above findings in children strongly support its utility as a first-line tool in the diagnostic evaluation of paediatric nephropathy.

Next-generation sequencing

NGS utilizes targeted capture and massively parallel sequencing to simultaneously assess variation in selected regions of the genome, enabling rapid and cost-effective large-scale genetic investigation[32,34,61,62]. Selected regions can be multiple genes of interest

(investigated using targeted NGS panels), all protein-coding regions (investigated using WES), or both coding and non-coding regions (investigated using WGS). Each NGS approach has merits and drawbacks in the current landscape of clinical testing, and selection of the optimal modality is rapidly evolving, reflecting technical capacity, cost-effectiveness, and knowledge of the individual patient and disease. As the technical expenses of sequencing have steadily decreased, the substantial time and monetary costs required for diagnostic interpretation have become the major barriers to systematic implementation in clinical practice[32,63].

Targeted panels

NGS gene panels use targeted enrichment of selected genes to provide rapid and inexpensive sequencing at higher coverage than that achieved with WES or WGS[33,35]. Such panels have been advocated as a first-line test for the molecular diagnosis of inherited nephropathies[4]. In this approach, patients are tested for a set of genes that are commonly associated with the phenotype under consideration; for example, a patient with nephrotic syndrome would be tested using a panel containing genes that are commonly implicated in hereditary forms of this disorder[4].

As NGS panels are quickly becoming a first-line diagnostic test, it is critical that they can accurately detect whether a particular genetic variant is present in the region of interest[64,65]. Organizations such as the American College of Medical Genetics and Genomics (ACMG)[66], British Association for Clinical Genetic Science (ACGS)[67], and European Society of Human Genetics (ESHG)[68] have published technical guidelines for clinical NGS regarding `sequencing coverage and depth` as well as other quality metrics. As certain regions, such as those with high GC content (for example, the first exon of *COL4A3*, which is associated with Alport syndrome (OMIM 104200; 203780) and thin basement membrane disease (OMIM 141200)) and those with high sequence homology (for example, the *PKD1* gene, which is associated with autosomal dominant polycystic kidney disease (OMIM 173900)), are poorly covered by NGS alone, laboratories often incorporate other methods such as Sanger sequencing and long-range PCR to ensure that all targeted regions are comprehensively covered at sufficient depth[33].

As sequencing is selective, targeted panels will not yield incidental findings in genes unrelated to the primary indication for testing, reducing the potential burden of `secondary findings` that would initiate additional clinical testing for patients and physicians. If the targeted panel testing is negative, the clinician can select another panel with broader content or proceed directly to WES or WGS. This sequential procedure may be the most comprehensive and cost-effective approach at present, particularly among patients whose presentation is strongly suggestive of a specific category of genetic disease[33,35,69].

Applications—Targeted gene panels are a sensitive and cost-effective diagnostic for a wide range of kidney disorders, including nephrotic syndrome[70,71], nephrolithiasis[72,73], nephronophthisis-related ciliopathies (NPHP-RC)[74,75], and CAKUT[76,77], albeit with variable disease-specific yield in the context of testing familial and/or paediatric cases. Such targeted testing is particularly well suited to diseases that have fairly low genetic

heterogeneity. For example, mutations in three genes, *COL4A3, COL4A4*, and *COL4A5*, cause Alport syndrome (OMIM 104200; 203780; 301050) and the related milder form, thin basement membrane disease (OMIM 141200)[78,79]. Targeted NGS sequencing of these genes detected causal variants in 84 (83%) of 101 patients with a clinical diagnosis of familial haematuria[80]. Supplementation with multiplex ligation-dependent probe amplification, CMA, and Sanger sequencing enabled identification of large genetic rearrangements and causal variants in regions that were not well captured by NGS alone.

However, many kidney diseases are genetically heterogeneous, and many nephropathy-associated genes can show clinically disparate presentations, reflecting both genetic and environmental modifiers[28]. In such cases, designing a gene panel that appropriately balances sensitivity and specificity is challenging. Restricting the number of genes in the panel reduces the cost and time needed for testing; however, the panel might require frequent updates as new genes are discovered and previously implicated genes are shown to have weaker disease associations than first reported. Assessing a greater number of genes increases diagnostic sensitivity but can also increase the detection rate of variants of uncertain significance (VUS), complicating interpretation and clinical follow-up. For example, targeted sequencing of 23 known genes associated with autosomal forms of CAKUT had an ~8% diagnostic yield: 6% in 17 genes for autosomal dominant forms[76] and 2.5% in 6 genes for autosomal recessive forms[77]. An expanded sequencing panel of 208 genes associated with syndromic or isolated CAKUT, including genes implicated by functional data, identified candidate variants in 151 of 453 (33%) patients as well as 32 VUS in 69 (15%) patients[81]. Further expansion to a 330-gene panel screen detected candidate variants in 122 of 204 (60%) patients with CAKUT but also identified 120 VUS in 89 patients (44%)[82].

For patients with more ambiguous presentations, ‘Mendeliome’ panels, which target all known disease-associated genes, have been suggested as a time and cost-effective first-line test, and the studies to date report high diagnostic yield across a range of clinical indications[83–85]. Such panels also enable detection of phenotypic expansions of known genetic diseases but require periodic updates to include newly discovered disease-associated genes. Thus, the diagnostic utility and cost-effectiveness of Mendeliome panels relative to WES and WGS merits further in-depth study.

Whole-exome and whole-genome sequencing

WES and WGS provide more comprehensive testing than targeted NGS panels because they assess variation across the genome. These unbiased approaches have many advantages, including increased sensitivity for diagnosis of disorders with high genetic and/or phenotypic heterogeneity and the ability to achieve a specific diagnosis when traditional clinical methods are unsuccessful. WES and WGS also enable reanalysis of sequence data, which may include recalling variants from raw data, reannotating called variants by use of novel bioinformatics tools, and/or re-examining annotated variants in light of newly discovered gene–disease associations. Various analytical frameworks can also be used to identify novel candidate genes for follow-up study[31,86,87], and such re-examination can lead to additional diagnoses, increasing overall diagnostic yield[88–91].

Per-base coverage is generally lower with WES and WGS than with targeted panels. However, an *in silico* analysis showed that WES with standard coverage (≥10 times coverage of 90% of bases) was adequate to identify 98.6% of sites previously found to have pathogenic variants by targeted panel[92], suggesting that the sensitivity of WES is sufficient for diagnostic sequencing in most cases. Nevertheless, clinically relevant segments of the genome can be missed when using WES alone[93]. For example, the sites corresponding to ~50% of reported pathogenic variants in the *WT1* gene, which is associated with hereditary nephrotic syndrome (OMIM 256370) and Deny–Drash syndrome (OMIM 194080), were poorly covered across three leading WES capture kits[94]. Further development of sequencing technology will help to increase technical accuracy, achieve more uniform coverage, and decrease costs[61,62]. Thus, increasingly comprehensive genomic sequencing has been predicted to define the future of clinical genetic testing, with targeted panels superseded by WES, which in turn will be overtaken by WGS as a first-line diagnostic[32,35,63].

Whether WES or WGS will prove to be a superior clinical diagnostic tool in the near future is a topic of ongoing debate. As known causal variants for Mendelian disorders overwhelmingly lie in coding regions[95,96], WES has been suggested as a time-efficient and cost-efficient means for clinical diagnosis and genetic discovery[86,97,98] and has been successfully used for a variety of clinical indications. To date, the majority of diagnostic variants identified in clinical WGS investigations have been found in exonic regions[99–102]. Non-coding variants have, however, been implicated in various kidney disorders[103–107]. For example, WGS detected a deep intronic mutation in *DGKE* in two unrelated families with infantile-onset atypical haemolytic uraemic syndrome (OMIM 615008) who had been left undiagnosed by use of WES[103]. Subsequent analysis of patient RNA showed that the variant created a novel splice site that abrogated normal protein function. Intronic mutations resulting in altered splicing have likewise been noted in genetically unresolved cases of Alport syndrome[104], Schimke immune-osseous dysplasia[105] (OMIM 242900), and Gitelman syndrome[106] (OMIM 263800). Sequencing the whole genome also avoids capture bias and provides more complete per-base coverage of coding and non-coding regions[108,109], facilitating accurate detection of variants in genes with highly homologous regions, such as *PKD1* (REF. 110), and of structural variants, such as those found in several patients with Joubert syndrome[111]. Although further study is needed, WGS has been reported to detect causal variants in ~20–40% of patients left undiagnosed by WES and/or CMA[112–114].

Importantly, some types of variants remain wholly refractory to detection using current NGS technologies. For example, causal variants in the *MUC1* gene, which is associated with autosomal dominant tubulointerstitial kidney disease (ADTKD-*MUC1*; OMIM 174000) and contains a highly repetitive, GC-rich sequence, were missed by NGS-based regional capture, WES, and WGS and were identified only by long-range PCR and molecular cloning[115]. A novel assay based on mass spectrometry has been recently developed for diagnosis of ADTKD-*MUC1* (REF. 116), and with the advent of long-read sequencing, NGS-based detection of such regions may become feasible[61].

Given such increased diagnostic and analytical sensitivity, WGS has the potential to provide a single-test solution. However, with higher-performance WES capture platforms and improvements in NGS technology, the extent to which the benefits of the expanded search

space outweigh the burdens of sequencing costs, data storage, and clinical interpretation and follow-up remains unclear[117,118].

To date, investigations of the diagnostic yield of genome-wide testing in nephrology have overwhelmingly used WES. To our knowledge, the efficacy of WGS in this field remains to be comprehensively assessed. Thus, we focus below on selected studies demonstrating the utility of WES as a diagnostic tool for various forms of nephropathy.

Testing in an expanding genetic spectrum—WES has been successfully employed for a variety of conditions with high genetic heterogeneity, such as NPHP-RC and nephrotic syndrome. NPHP-RC has >90 known causal genes[119], and the advent of NGS has accelerated the discovery of additional causal genes[120]. Expansion of the genetic search space thus enables identification of mutations in noncanonical genes, increasing diagnostic yield relative to targeted panel testing. Detection rates in testing for NPHP-RC were 12% with a 13-gene panel[121], 21% with a 34-gene panel[74], and ~60–70% with WES[122,123]. Similarly, WES identified causal variants in 49 of 187 (26.2%) paediatric patients with steroid-resistant nephrotic syndrome (SRNS)[124]. Although 30 (61.2%) of the 49 patients with resolved cases had mutations in canonical genes for early-onset SRNS (*NPHS1, NPHS2*, or *WT1*), three had diagnostic variants in genes classically associated with other renal disorders, including *DGKE* (membranoproliferative glomerulonephritis and/or atypical haemolytic uraemic syndrome; OMIM 615008), *COL4A3* (Alport syndrome), and *OCRL* (Dent disease 2; OMIM 300555). These three patients all presented with primary SRNS and focal segmental glomerulosclerosis (FSGS) on renal biopsy, suggesting that the findings did not result from initial clinical misphenotyping.

Moreover, use of NGS has led to the detection of novel genes in many disorders that were previously thought to be highly genetically homogenous. For example, polycystic kidney disease (PKD) was long thought to result from mutations in only three genes, with those in *PKD1* and *PKD2* accounting for the autosomal dominant form (ADPKD; OMIM 173900, 613095) and those in *PKHD1* leading to autosomal recessive disease (ARPKD; OMIM 263200). However, ~7–10% of families with ADPKD lack mutations in *PKD1* or *PKD2* (REFS 125,126), and *PKHD1* mutations are not detected in at least 13% of patients with ARPKD[127,128]. WES of mutation-negative families implicated *GANAB* in ADPKD[129] and *DZIP1L* in ARPKD[130], broadening the genetic spectrum of PKD.

Expanding the phenotypic spectrum—Conversely, WES has demonstrated that many genetic disorders can produce a wider range of phenotypes than previously thought. These phenotypic expansions dispel the classical view that a one-to-one relationship exists between a gene and a disease and challenge traditional clinical classifications[28]. For example, mutations in *COL4A3, COL4A4*, and *COL4A5*, which are associated with Alport syndrome, have been detected among patients with a clinical diagnosis of nephrotic syndrome, expanding the range of phenotypes associated with *COL4A*-mediated nephropathy[131,132]. The variability of phenotypes among patients with mutations in *HNF1B* similarly exemplifies this point. Although *HNF1B* mutations are classically associated with renal cysts and diabetes syndrome (OMIM 137920), patients with these mutations can be nondiabetic or have other, noncystic forms of renal disease[133,134]. For example, patients

with *HNF1B*-mediated disease can present with hyperuricaemia and glomerulocystic kidney disease, such that they may be mistakenly diagnosed with ADTKD; others may present with hypomagnesaemia and hypocalciuria, causing an assumption that they have Gitelman syndrome[133]. Moreover, many of the extrarenal features of *HNF1B*-mediated disease, such as hyperuricaemia and hyperparathyroidism, can also occur as secondary complications of renal dysfunction; thus, patients might not be suspected to have a genetic form of nephropathy, especially those who are older and/or have no family history[133].

Other examples include the expansion of variants in *PAX2*, which are classically associated with CAKUT (OMIM 120330), to include hereditary FSGS (OMIM 616002)[135] and of biallelic mutations in *TTC21B* to span both cystic and glomerular disease[136,137]. Similarly, the phenotypic spectrum of *UMOD*-associated kidney disease (OMIM 609886; 162000; 603860) encompasses both tubulointerstitial nephritis and glomerulocystic disease[138], and the presentation of patients with *CLCN5* mutations, causal for Dent disease 1 (OMIM 300009), may range from tubulointerstitial disease with electrolyte imbalances[139,140] to nephrotic-range proteinuria and glomerulosclerosis on renal biopsy[141,142].

Proteinuria and glomerulosclerosis have also been reported among patients with variants in *SLC12A3*, which are associated with Gitelman syndrome, a salt-wasting distal tubulopathy (OMIM 263800)[143–145]. Similarly, mutations in *PARN* cause a telomere syndrome traditionally associated with pulmonary fibrosis and bone marrow failure (OMIM 616371), but a WES study suggests that some patients with these mutations initially present with renal tubulointerstitial fibrosis, expanding the phenotypic spectrum of *PARN*-mediated disease[146].

Resolving undiagnosed disorders—WES has transformed paediatric and neonatal care by providing a means to rapidly resolve undiagnosed cases, informing prognosis and clinical management[22,101,147]. Similarly, WES may have considerable diagnostic value for patients who present with nonspecific renal phenotypes or kidney disease of unknown aetiology (REFS 148–151). For example, one of the first clinical applications of WES was for a neonate who presented with hypokalaemic metabolic alkalosis and was thus suspected to have Bartter syndrome[148]. WES identified no candidate variants at Bartter-associated loci but rather a homozygous substitution mutation at a highly conserved residue in *SLC26A3*, and clinical follow-up confirmed the genetic diagnosis of congenital chloride diarrhoea (OMIM 214700). Putatively pathogenic variants in *SLC26A3* were found in an additional 5 of 39 (13%) patients with presumed Bartter syndrome, supporting the utility of exome-wide analysis in resolving such clinically inscrutable cases.

Subsequent studies have further highlighted this utility. For example, exome analysis of 79 children who presented with increased renal echogenicity on ultrasonography identified causal variants in 63% of these patients[122]. Notably, 36% of the patients with a genetic diagnosis were found to have a disorder other than NPHP-RC, which was the diagnosis suspected on the basis of the ultrasonography results. The researchers hypothesized that the misclassification of patients reflects the nonspecificity of increased renal echogenicity for diagnosis of NPHP-RC. Similarly, WES of 33 consanguineous families diagnosed with CAKUT detected pathogenic variants in 9 (27%) families; notably, 4 (44%) of these families had mutations in genes unassociated with CAKUT, and on clinical follow-up, they were

found to have phenotypes concordant with these alternate genetic aetiologies of disease[152]. In many patients, these unexpected diagnoses had important implications for management and therapy, including tight regulation of salt and water intake for nephrogenic diabetes insipidus type 2 (OMIM 125800)[153], cysteamine supplementation for nephropathic cystinosis (OMIM 219800)[154], and combined liver and renal transplantation for primary hyperoxaluria type 1 (OMIM 259900)[155].

Moreover, a pilot study of WES in adults with familial or undiagnosed nephropathy identified diagnostic findings in 22 of 92 (24%) patients[146]. Diagnostic yield was notably high among those with kidney disease of unknown aetiology, with 9 of 16 (56%) patients being diagnosed. These diagnoses encompassed a variety of genetic nephropathies, including autosomal and X-linked forms of Alport syndrome, Dent disease, CHARGE syndrome (OMIM 214800), and *HNF1B*-associated disease. In addition to ending the 'diagnostic odyssey', the genetic diagnoses resulting from WES impacted clinical care in many patients, including guiding choice of therapy (for example, steroid avoidance in patients with glomerulonephritis and *COL4A3–5* mutations), advising subsequent work-up and surveillance of associated extrarenal comorbidities (for example, screening for diabetes and liver function in a patient with an *HNF1B* mutation), and informing transplant prognosis and choice of donor (for example, a low risk of disease recurrence and genetic screening for candidate living related donors in a patient with Dent disease). These findings support the diagnostic utility of WES for patients with kidney disease of unknown aetiology, particularly those with familial or early-onset disease, and highlight the need for further research in this field in larger cohorts.

Indications for genetic work-up

With the widening availability and declining costs of sequencing technologies, nephrologists will increasingly incorporate clinical genetic testing into their diagnostic armamentarium. There is a risk that these new technologies will be adopted prematurely, before systematic evidence of their utility has been generated. Hence, there is a need for large, multicentre studies of diverse cohorts to develop evidence-based guidelines regarding the indications and utility of genetic testing in nephrology.

Currently, genetic testing is recommended as part of the diagnostic work-up for patients with paediatric kidney disease, especially among those with nondiagnostic presentations[156]. For adult patients, genetic testing is suggested only for those who are strongly suspected to have a known hereditary form of nephropathy. Other indications for genetic work-up include phenotypes that have a strong hereditary basis, such as CAKUT, for which CMA seems to be a valuable first-line diagnostic modality in addition to NGS-based approaches. Certain clinical situations might also merit genetic testing, such as those in which diagnostic findings would enable patients to avoid undergoing unnecessary invasive procedures (for example, renal biopsy in patients with nephronophthisis) or prevent them from receiving ineffective and costly treatment with substantial adverse effects (for example, steroid therapy in patients with hereditary aetiologies of SRNS). Genetic testing is also advised for females with clinical features and/or a history suggestive of a monogenic X-linked nephropathy, such as X-linked Alport syndrome (OMIM 301050) or Fabry disease (OMIM 301500), because

although female carriers of these diseases generally display a milder (often subclinical) phenotype than is seen in males, they can develop severe disease[157–159]. At present, clinicians are generally advised to start with a disease-specific genetic panel and if the results are negative, to proceed to a Mendeliome panel, WES, or WGS[35,66,68].

Genetic testing has also been recommended in the evaluation of potential living kidney donors, with donation contraindicated among those found to have autosomal dominant forms of inherited kidney disease such as ADPKD (OMIM 173900, 613095, 600666) or to share genetic susceptibility factors for atypical haemolytic uraemic syndrome[160]. In such cases, positive findings not only guide choice of donor but also might inform renal prognosis; for example, among patients with ADPKD owing to mutations in *PKD1* (OMIM 173900), those with loss-of-function mutations have more severe disease and progress faster to ESRD than those with missense mutations[161,162]. Carriers of autosomal recessive disorders have generally been deemed suitable kidney donors, as individuals who are heterozygous for a recessive causal `allele` are not expected to develop the disease[160]. However, reports of milder, subclinical disease phenotypes among carriers suggest that these individuals are at higher risk of developing nephropathy than previously thought and therefore may warrant nephrological surveillance. For example, hepatorenal involvement (renal echogenicity and/or liver cysts) has been noted in obligate heterozygote parents of patients with ARPKD (OMIM 263200)[163], and mild renal acidification defects and nephrolithiasis have been observed in individuals who are heterozygous for mutations in *ATP6V1B1*, which are associated with distal renal tubular acidosis with deafness (OMIM 267300)[164]. Thus, additional study is needed to assess the long-term implications of carrier status for renal function, risk of developing kidney disease, and outcomes following kidney donation.

The available epidemiological and genetic studies support the use of genetic testing in nephropathies of unknown aetiology, particularly in the setting of a compelling family history of early-onset renal failure. The 2017 US Renal Data System report notes that in ~14% of adult and ~19% of paediatric patients with incident ESRD[18], the clinical diagnosis is “other” or “unknown”, and the European Renal Association–European Dialysis and Transplant Association[17] and Australia and New Zealand Dialysis and Transplant[16] registries report similar statistics. As renal biopsy is generally contraindicated in ESRD, genetic testing is a promising diagnostic tool, and case reports demonstrate the utility of genetic findings in this patient population[165–168]. For example, in a 12-year-old boy presumed to have nonsyndromic infantile-onset retinal dystrophy, identification of Senior–Loken syndrome 5 (OMIM 609254) led to early diagnosis of unrecognized CKD, enabling preplanned initiation of dialysis, appropriate donor selection for renal transplantation, and surveillance of at-risk family members[167]. Similarly, detection of *INF2*-mediated focal segmental glomerulosclerosis (OMIM 613237)[166] and *LMX1B* glomerulopathy (OMIM 161200)[165] in patients with familial ESRD of unknown origin helped to inform transplant prognosis and choice of donor, as these diagnoses are associated with low risk of disease recurrence and indicate genetic screening for candidate living related donors. Genetic diagnosis can also lead to targeted therapy and improved post-transplantation outcomes. For example, genetic testing of a 67-year-old woman with ESRD of unknown aetiology revealed adenine phosphoribosyltransferase (APRT) deficiency (OMIM 614723)[168]; the resulting

initiation of xanthine dehydrogenase inhibitor therapy (allopurinol) prevented recurrence of crystalline nephropathy and allograft loss in this patient. Given the notable prevalence of kidney disease of unknown aetiology, even a modest diagnostic yield from genetic testing could have a large impact on clinical care.

The value of a genetic diagnosis

In addition to pinpointing the cause of disease, genetic diagnosis can inform clinical prognosis and guide patient management (TABLE 2). In general, patients and their physicians want a clear understanding of their disease, why it occurred, and how it will affect their health and medical care as well as that of their families[169]. As distinct pathophysiological processes can result in indistinguishable clinical presentations, the precise aetiology can remain unclear despite extensive history-taking and biochemical, imaging, and histopathological studies. This ‘diagnostic odyssey’ has substantial time, financial, and psychosocial costs for patients and their families and is a substantial burden on the health-care system. Thus, in addition to helping guide subsequent care, a genetic diagnosis holds substantial value through ending this process[27,69,170,171].

Importantly, translating genetic findings into improved patient care requires longitudinal studies of large cohorts of individuals with genetic diagnoses. Long-term follow-up of patients undergoing sequencing is needed to study the impact of genetic information on clinical management, health-care utilization, and outcomes. Rare disease referral networks, such as the European Reference Network for Rare Kidney Diseases[172,173], the National Institute of Health Rare Diseases Clinical Research Network[174], and the United Kingdom Kidney Research Consortium[175], will help to achieve this aim. Moreover, the knowledge generated will enable the development of best practice guidelines regarding diagnostic work-up and treatment of rare hereditary renal disorders. A genetic diagnosis can also enable referral for targeted clinical trials of therapies that might provide benefit in specific patient populations, such as microRNA inhibition for Alport syndrome[176] (OMIM 104200, 203780, 301050) and small-interfering-RNA blockade for primary hyperoxaluria type 1[177] (OMIM 259900). Disease-specific support groups can also help to direct patients to trials and other relevant clinical resources[178–180] and serve as key sources of psychosocial support for affected individuals and their families.

Finally, genetic-based stratification of clinical trials has the potential to prevent exposure to unnecessary risk of patients who are unlikely to benefit from an intervention while reducing confounders that may mask its benefit. For example, genetic testing could be used to exclude patients with hereditary forms of nephrotic syndrome, who do not tend to respond to steroid therapy[181], from a trial investigating the efficacy of a novel corticosteroid agent.

Clinical sequence interpretation

The aim of clinical sequence interpretation is to identify the genetic variant that is responsible for the phenotype of an individual patient. As the identified variant is used to guide subsequent care, it is critical that clinical sequence interpretation be highly accurate and reproducible[182]. However, the abundance of sequence variation in a typical human

genome and the vast search space provided by genome-wide testing results in a high risk of falsely ascribing causality to benign variants[183]. Although established guidelines for diagnostic interpretation exist[67,68,182], the process often remains time-consuming and highly subjective, requiring expert judgement at each step. A variety of online resources are available to aid geneticists and clinicians as they navigate the process of diagnostic sequence interpretation and application of genetic findings into clinical care (TABLE 3).

Diagnostic analysis is guided by the phenotype of the patient. Ordering clinicians are thus instructed to provide accurate and complete clinical information[182]; however, no standards currently exist for what information should be provided and/or who is qualified to give this information[184]. Moreover, even ostensibly specific clinical diagnoses may comprise a wide array of genetic and acquired disorders. For example, a diagnosis of primary FSGS could result from mutations in any one of >50 genes[124]; without further clinical information, such as age of onset, presence of extrarenal features, or pattern of inheritance, a geneticist would be hard-pressed to prioritize candidate variants during subsequent sequence interpretation. Referring clinicians should, therefore, provide detailed clinical information to the diagnostic laboratory and be prepared to discuss the patient in greater detail with the molecular geneticist in charge of sequence interpretation.

The first step in clinical sequence interpretation is to select the genes in which mutations can result in a phenotype compatible with the clinical presentation of the patient (FIG. 1). Attempts have been made to catalogue the genes that are associated with hereditary forms of nephropathy and classify them by their associated broad phenotype[1,4,185], but no systematic procedures or consensus guidelines exist regarding which genes should be evaluated for a given category of kidney disease. The choice is becoming increasingly complex owing to phenotypic expansions and is complicated because genes that are traditionally associated with nonrenal disorders can also present with nephropathy[186–188]. For example, mutations in *HNF4A* are classically implicated in maturity-onset diabetes of the young type 1 (MODY1; OMIM 125850) without renal involvement; however, the p.R76W `missense variant` has been noted in patients presenting with both Fanconi proximal tubular syndrome and MODY1 (REFS 186,187). Similarly, the identification of mutations in *FOXP1* in patients with CAKUT suggest that the phenotypic spectrum of these mutations encompasses CAKUT as well as intellectual disability (OMIM 613670)[188]. These situations require geneticists with domain expertise, who can recognize the causal connection between the mutation and the kidney phenotype. An additional challenge is the continuous need to assess the strength of gene–disease associations, as new genes continue to be rapidly identified[21] and additional research can cast doubt on those that have previously been implicated in a disease[189,190].

Interpretation at the variant level holds further complexity. Current guidelines evaluate a given variant in the context of the genetic architecture of the disease and the available literature. Lines of evidence include previous case reports, being in the same region and/or belonging to one of the functional types of variants previously noted as being causal for the disorder, having a population frequency compatible with that expected for the disease, and experimental and/or *in silico* support for a deleterious effect on protein function. Geneticists must examine the relevant observations for each of these criteria and combine them to arrive

at an overall variant-level classification of pathogenic, likely pathogenic, likely benign, benign, or VUS[182].

Finally, the genetic findings must be assessed for concordance with the clinical presentation of the patient in addition to the genetic architecture of the disease. In some cases, this process is fairly straightforward; for example, as haploinsufficiency is recognized as the genetic mechanism of *HNF1B*-mediated disease[134] and *HNF1B* is highly intolerant of loss-of-function variation, a novel nonsense variant found in a patient with cystic renal disease and early-onset diabetes can be deemed likely causal. By contrast, a novel *HNF1B* missense variant, even if predicted to be deleterious based on multiple *in silico* algorithms, would require additional evidence to support pathogenicity. Additional work-up might involve parental testing to ascertain *de novo* status in sporadic cases, examining segregation if multiple affected family members are present, evaluating the patient for other features associated with the candidate diagnosis (for example, in the case of *HNF1B*-mediated disease, diabetes, gout, hypomagnesaemia, and genital abnormalities), and/or performing functional studies to model the effect of the variant on protein function. Such work-up is critical to clarify the clinical relevance of genetic findings, especially in the context of large multigene panels or genome-wide testing, where multiple candidate variants may be found[182,184,191]. Additional genetic and/or clinical testing can, however, involve substantial time and monetary costs[192] and, in some cases, might not be feasible (for example, blood relatives may be unavailable for genetic testing, preventing variant phasing or the determination of *de novo* status).

Population-wide allele frequency data have emerged as powerful first-line tools in clinical sequence interpretation[183]. The development of large public sequence databases has shed light on the spectrum of allele frequencies across populations of diverse ancestries[29,193] and has demonstrated that a large number of previously reported variants are unlikely to be pathogenic because they are present at frequencies exceeding the prevalence of the associated disease[193–196]. For example, in the Human Gene Mutation Database, the p.Ser487Leu variant in the *EYA1* gene is noted as causal for branchio-oto-renal syndrome (BOR; OMIM 113650) on the basis of two publications[197,198]. However, this variant has been reclassified by four independent diagnostic laboratories as a VUS or likely benign[199], and noted as a VUS in two publications[76,81], because of its high prevalence in the general population. The variant is present in 197 individuals in gnomAD (a large population control database), corresponding to a global frequency of 1 in 1,500, and is present in more than 1 in 1,000 Europeans. By contrast, BOR is estimated to have a prevalence of 1 in 40,000 and is thought to be fully penetrant[200]. With frequencies 28-fold and 50-fold higher than the total prevalence of BOR, the p.Ser487Leu variant is unlikely to be causal for such a rare, highly penetrant, autosomal dominant, monogenic disorder.

Thus, a great need exists for review of clinical variant databases using newly available population genetic data. In the meantime, variant interpretation will require time-intensive and subjective curation of the primary literature in the context of often limited knowledge of the prevalence, penetrance, and expressivity of a disease. In addition, many of the variants in clinical databases may have been classified by a single diagnostic laboratory; with no further explanation and/or supporting data, such findings have limited value.

Given the many layers of complexity, the existence of persistent interlaboratory and even inter-reviewer discordance in variant classification[201–204] despite adoption of fine-grained variant interpretation guidelines[182] is unsurprising. Frameworks for semiquantitative assessment of the clinical validity of gene–disease associations[205] and semiautomated clinical variant interpretation[206,207] have been proposed and might help to increase the reproducibility and efficiency of clinical sequence interpretation. However, these approaches still rely on subjective review of genetic and experimental evidence from the primary literature, and thus, the potential for divergent interpretation remains. Creation of consensus guidelines and quantitative standards will enable more objective and automated analysis at some steps, but as clinical sequence interpretation ultimately relies on clinical judgement, some degree of subjectivity will remain.

Applying genetic findings in the clinic

A genetic diagnosis provides a valuable answer but is only a starting point. For genetic findings to have clinical utility, they must be applied in the context of clinical care. This process is as complex as that of clinical sequence interpretation, and multiple barriers must be overcome to enable the promise of genomic medicine to be achieved. Key challenges in the implementation of genetic findings into clinical nephrology include return of results, physician education, sequence reanalysis, and the consideration of ELSIs[208–210].

Return of results

Clinical genetic testing is rapidly moving towards genome-wide assessment[32,35,63]. This expanded genetic scope increases diagnostic sensitivity but also has the potential to identify variants that are unrelated to the primary indication for testing. Such secondary findings must be considered with respect to their clinical validity and actionability[211]. Clinically valid findings include those that can be used to accurately predict that a patient will have the associated condition[212]; these encompass variants in genes for highly penetrant Mendelian diseases, pharmacogenomic variants that are informative regarding drug metabolism, and risk variants that affect susceptibility for a given condition. This category also includes clinically actionable variants, the detection of which would enable a physician to implement interventions that prevent or lessen the clinical consequences of the disease for which the variant confers increased risk. Clinically actionable variants have been recommended for return by both the ACMG[213,214] and the ESHG[215].

Currently, the ACMG advises returning known and expected pathogenic variants in 59 genes to patients regardless of their age or indication[214]. These genes encompass conditions deemed to be highly penetrant and actionable and predominantly consist of those that are associated with various hereditary forms of cancer and cardiovascular disease. Sequencing studies on large, unselected adult cohorts show that approximately 1–3% of the general population has a pathogenic mutation in one of these 59 genes[216,217]. Importantly, the ACMG actionable list includes genes that are associated with conditions relevant to renal medicine, such that the broadening use of genome sequencing may lead to additional nephrology consultations. These conditions include hereditary pheochromocytoma-paraganglioma syndrome (OMIM 168000, 601650, 605373, 115310), multiple endocrine

neoplasia (OMIM 131100, 171400, 162300), Wilms tumour (OMIM 194070), Fabry disease (OMIM 301500), Von Hippel–Landau syndrome (OMIM 193300), and tuberous sclerosis complex (OMIM 191100, 613254). Moreover, the detection of actionable mutations in other ACMG genes can impact nephrologic care, such as pretransplant defibrillator implantation in kidney transplant recipients with a *KCNQ1* mutation causal for long QT syndrome (OMIM 192500) or reduction of the dosage of immunosuppressive therapy in patients with mutations in genes that are associated with hereditary cancers, such *BRCA1*.

The ACMG encourages clinical specialists to nominate gene–disease pairs that they feel meet these actionability criteria as well as selected pharmacogenomic variants for medications that are commonly prescribed and/or associated with serious adverse events. Thus, there may be an opportunity to add nephrology-specific loci to the ACMG list, such as genes for highly penetrant and medically actionable hereditary nephropathies and pharmacogenomic variants that affect metabolism of medications commonly used in the care of patients with CKD[218,219]. Formation of multicentre interdisciplinary working groups and use of evidence-based frameworks to assess disease actionability[220] would greatly facilitate this effort.

Continuous review

As new genetic knowledge emerges, classifications shift. New genetic or experimental data may reclassify a mutation that was previously deemed diagnostic as a VUS or benign variant as pathogenic. Moreover, discovery of new genes may lead to a genetic diagnosis upon review of WES or WGS data from previously unsolved cases. As physicians use genetic diagnoses to guide care, such shifts are hugely important — altered classification of a variant can result in altered management of patients and their families. Yet no explicit standards for review of clinical genetic testing data currently exist, and the practice is rare, with a 2017 study reporting that only 1 of 21 laboratories surveyed routinely engaged in the practice[221].

In addition to questions regarding the optimal frequency and analytical methodology, continuous review of sequence data involves a multitude of ELSIs, including who should be responsible for requesting reanalysis, physician liability and duty to inform versus the right of patients not to know, and the psychosocial impact of recontact on patients and their families[222,223]. Given the scientific and ethical complexity and the many stake-holders involved, continuous review is not an easy issue to address or to create policies around; nevertheless, the issue is unavoidable as sequencing is increasingly incorporated into clinical practice. Comprehensive study of the clinical utility, cost-effectiveness, and psychosocial impact of continuous review and dialogue between relevant stakeholders, including patients, physicians, and genetics professionals, will help to ascertain its advantages and drawbacks and enable creation of formal guidelines regarding its implementation.

Genetic education and counselling

Under current guidelines for clinical genome-wide testing, the ordering clinician is expected to ensure informed consent by providing patients with comprehensive pretest counselling, including discussing the limitations of the test, the potential for secondary findings, and the complexity of the genetic interpretation[68,224]. The clinician is likewise expected to return

not only the primary results but also any secondary findings if the patient has opted to receive them. Investigations to date show that the majority of patients do opt to receive secondary findings[225], which necessitates a greater breadth and depth of genetics knowledge for the interpretation of their test results. However, there is currently a shortage of clinicians with adequate knowledge in genetics, genetic counsellors, and clinical geneticists who are capable of administering such comprehensive counselling[226,227]. Although genetics is being increasingly included in medical education, reports suggest that limited time and a lack of integration of genetics with clinical topics leaves students unprepared to apply genomics in patient care[228]. For example, a survey of recently graduated nephrology fellows noted that 65% felt that they had insufficient competence regarding genetic renal diseases, despite considering them important to their current clinical practice[229]. Among practising clinicians, no requirement currently exists for nongeneticists to have any specific knowledge or competencies in genetics[230], such that more senior clinicians may also feel unprepared.

Given the complexity of interpretation of genome-wide data and the many demands on their time, expecting nephrologists to act as genetic counsellors may be unreasonable. Rather, nephrologists should be expected to have a basic familiarity with genetics as well as more detailed knowledge of genetic forms of renal disease and to be aware of the general best practices regarding genetic testing. In the future, nephrogenetics may emerge as a superspecialty, similar to transplant or interventional nephrology. Genetic counsellors specialized in nephrology should become part of multidisciplinary teams fully integrated into the clinical setting, as has been successfully implemented in oncology[231] and cardiology[232]. In the absence of a geneticist in the clinical team, patients should be referred to genetic counsellors for counselling before and after testing. Efforts to provide genetics education to physicians, foster interaction between referring physicians and clinical testing laboratories, and create clinical decision support tools will help to achieve this aim and will facilitate implementation of clinical care based on genetic findings[233,234].

Ethical, legal, and social implications

The ELSI programme was founded as an integral part of the Human Genome Project with the understanding that genetic information can affect individuals, families, and society in a way that few other medical findings can. The historical role of human genetics in the development of eugenics and associated governmental policies such as compulsory sterilization invite caution as sequencing is introduced to general clinical practice. Here, we highlight some of the key ELSIs that must be considered when implementing genomic medicine in nephrology.

Participation in genetic research

In the landscape of genomic medicine, the boundaries between bench research and bedside care have become increasingly blurred. Participating in research can directly impact the clinical care and disease course of patients with hereditary nephropathies, for example, through enrolling in clinical trials such as the EARLY PRO-TECT trial, which is assessing the safety and efficacy of angiotensin-converting-enzyme inhibition in children with Alport syndrome[235,236]. In addition, researchers have begun to integrate patients' electronic health-

care records with their genetic data to study complex phenotypes such as resistant hypertension[237], and the promise of receiving medically actionable findings is a major incentive for many participants in genetic research[238,239].

The results generated through taking part in genetic studies differ markedly, however, from those that are returned from clinical diagnostic testing. A clinical genetic test aims to provide a genetic diagnosis for a patient within a defined time period, whereas sequencing performed in the context of genetic research aims to generate generalizable knowledge useful for future patients[240]. Although the latter approach might lead to diagnostic results, the time frame for their return is generally indefinite, and owing to the lack of regulation surrounding research-level genetic sequencing, putatively causal variants should be validated in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory before they can be returned in the context of clinical care[241,242]. Some have argued for the unification of research and clinical genetic testing, including requiring all research-level sequencing to be conducted in a CLIA laboratory environment to enable genetic discoveries to be rapidly implemented in patient care[243,244]. In the meantime, however, genetic counselling is needed to direct patients to the indicated sequencing modality given the clinical context (such as the urgency of a genetic diagnosis) and to ensure that they have appropriate expectations regarding what they may learn and in what time frame.

Minority populations

Substantial racial and ethnic disparities, which likely stem from both genetic and environmental factors, exist in kidney disease prevalence, severity, and treatment outcomes[245,246]. Importantly, knowledge of ancestry-specific alleles can have clinical utility for Mendelian nephropathies and for more common, complex forms of CKD. For example, founder mutations for autosomal recessive Alport syndrome (OMIM 203780)[247], Fanconi anaemia type C (OMIM 227645)[248], and Zellweger syndrome (OMIM 614866)[249] have been documented among Ashkenazi Jews, such that carrier screening may be beneficial in this population. With respect to more common, complex forms of CKD, the *APOL1* risk genotypes (BOX 1) substantially impact disease risk and clinical outcomes among patients of sub-Saharan African descent[250–252,287], and the sickle cell trait (*HBB* variant) may similarly confer increased CKD risk in this population[253,254].

Knowledge of population-specific allele frequencies can also help to prevent genetic misdiagnosis. Owing to a paucity of appropriate population controls, minority genomes have been frequently interpreted in the context of European sequence data, yielding an excess of reportedly pathogenic variants and VUS[255,256]. For example, in an analysis of genetic variants listed as pathogenic for hypertrophic cardiomyopathy, those with frequencies that were too high to be compatible with disease causality were significantly over-represented among healthy African Americans[256]. Importantly, these benign variants had been returned as diagnostic findings to African-American patients undergoing genetic testing for hypertrophic cardiomyopathy. Such false positive results can result in inaccurate understanding of risk status, medical mismanagement (for example, unnecessary implantation of a cardioverter–defibrillator), and substantial psychological distress for patients and their families. Thus, evaluation of sequence data in the context of a patient's

ancestry is critical to avert variant misinterpretation and the associated clinical perils. In addition, diverse population control databases are needed to address such disparities in genetic diagnostic testing among minority populations[257,258].

Genetic testing has been historically underutilized by minority populations, reflecting disparities in health-care access as well as negative perceptions regarding its application[259–261]. To ensure that the benefits of genomic nephrology are available to all patients with kidney disease, it is imperative that minority populations have equal access to participation in genetic research and to clinical genetic assessment. Ongoing efforts to identify and address existing barriers to participation, perform sequencing studies in diverse populations, and develop educational materials tailored to individuals of varied backgrounds will help to achieve these aims[262].

Resource-limited settings

In low-income and middle-income countries (LMICs), access to clinical screening and care, including genetic testing, can often be limited[263–265]. Thus, individuals with hereditary nephropathies are likely underdetected and cannot access appropriate care. Several strategies have been recommended to address these disparities[156,266]. Provision of logistical and technical support will help to build national registries, biobanks, and other infrastructure and to establish standards of care. Electronic modes of communication can enable international collaboration with global experts in rare nephropathies, helping local physicians to create and implement best practices for patients. Proposed approaches to implementing genetic testing in LMICs emphasize providing clinically useful and cost-effective services tailored to fit the needs of the given population. Strategies include targeted testing for founder variants in genes associated with medically actionable autosomal recessive nephropathies that have high prevalence in the region (for example, screening of the *MEFV* gene, associated with familial Mediterranean fever (OMIM 134610, 249100), in the southeast Mediterranean[267]) and focused NGS panels containing the genes that are most commonly mutated in the disorder (for example, a panel including *NPHS1, NPHS2*, and *WT1* for suspected hereditary early-onset nephrotic syndrome). Although WES or WGS are becoming the standard for work-up of undiagnosed disorders, the high cost and limited availability of these technologies are substantial barriers to their use in LMICs. Mendeliomes have been recommended as a means of providing broad assessment of the disease-associated genome at a feasible cost and have shown promising results as diagnostics in this context[268,269].

Organizations such as Human Heredity and Health in Africa (H3Africa) and the Mexico National Institute of Genomic Medicine (INMEGEN) have already begun to implement such strategies, which will help to make the benefits of genomic medicine available globally. The H3Africa Kidney Disease Research Network initiative centres upon a case–control study of 4,000 patients with CKD and 4,000 healthy controls across four sub-Saharan African nations[270]. The clinical diagnoses to be studied include SRNS, biopsy-proven glomerulopathy, CKD of unknown aetiology, and hereditary glomerulopathies. Patients will undergo comprehensive clinical work-up, including genetic testing, with long-term follow-up over a period of 5 years. Importantly, the H3Africa consortium is developing a new

genotyping array to ensure maximal coverage of the highly genetically diverse African genome[271]. In addition, the consortium aims to build the resources needed to support genomic nephrology in Africa through training physicians and researchers and establishing biorepositories and sequencing facilities. This initiative will provide critical data regarding the genetic architecture of kidney disease and help to build a strong foundation for genomic nephrology in the region, providing a model for subsequent global efforts.

Paediatric genetic testing

As early-onset CKD is enriched for genetic aetiologies, genetic testing has been advocated as a first-line diagnostic for paediatric nephropathy[4,156]. The discussion to date has overwhelmingly focused on the diagnostic value of genetic testing for this population; however, the ethical implications and psychosocial impact of genetic testing in minors must also be addressed. Important issues include the age at which consent for testing should be provided by the child rather than by the parents, how to balance the potential for early clinical intervention versus the right of the patient to an open future[272], how to explain the primary findings to the patient, and the potential impact of knowledge of a genetic condition on the psychoemotional development and health of the child.

With the advent of genome-wide testing, the question has also arisen of how secondary findings should be treated among paediatric patients. The majority of the genes designated by the ACMG for analysis of medically actionable secondary findings are associated with hereditary cancers and other adult-onset conditions. Thus, the value of returning such results to paediatric patients is debatable. Although this knowledge could resolve parental anxiety regarding risk status and inform family planning, it threatens the right of the patient to autonomy and confidentiality and could result in considerable psychological harm[273]. Moreover, no clear consensus guidelines currently exist regarding this topic. The American Academy of Pediatrics recommends deferring predictive testing for later-onset conditions until adulthood, whereas the ACMG advises that the decision be made on a per-family basis[274,275]. Matters become even more complex with adolescents, as they may want to decide independently of their parents or other family members and/or may not want to have their genetic findings shared with their families[276]. Longitudinal study of the medical and psychosocial impact of genetic testing on paediatric patients and their families will help to guide creation of best practice guidelines regarding these topics.

Legal protection

In 1997, the United Nations Educational, Scientific and Cultural Organization (UNESCO) Declaration on the Human Genome and Human Rights ruled that genetic information should not be used to infringe upon “human rights, fundamental freedoms, and human dignity”, establishing an international stance against `genetic discrimination` (GD). In Europe, the 1997 Convention on Human Rights and Biomedicine and the 2012 Charter of Fundamental Rights of the European Union protect individuals against GD; under the primacy of European law, these protections take precedence over any conflicting national legislation, and many European nations have also created their own anti-GD statutes[277,278]. Other nations, such as Australia, the US, and Canada, have also passed anti-GD legislation. By contrast, anti-GD protection remains scant in Latin America, Africa, and the Middle

East, with the exception of Mexico, Chile, Malawi, and Israel[278]. Anti-GD legislation is similarly sparse across Asia, despite the strong presence of genetic research and personalized medicine in many Asian nations; to date, only South Korea and Taiwan have created specific prohibitions[278,279].

Legal protection for individuals undergoing genetic testing has focused on regulating the use of genetic findings by insurers and employers, reflecting concerns that these parties will use genetic information to deny individuals employment and/or associated insurance benefits[277,280]. However, the degree of legal protection varies substantially between nations. The 2016 Council of Europe recommendation requires insurers to justify use of all "health-related personal data" and prohibits insurers from requiring individuals to undergo genetic testing for insurance purposes[281]. Similarly, in Israel, the Genetic Information Law of 2000 bars use of genetic information for employment and insurance purposes[282]. Other countries take a looser stance; in the UK, for instance, insurers may use genetic test results if approved by the government[283], and in Canada, insurers have pledged to not "use genetic test results for life insurance coverage of $250,000 or less" (REF. 284).

In the USA, the lack of a national health-care system has magnified concerns, as individuals usually obtain employment-based insurance. In an effort to protect individuals against GD, in 2008, the US government enacted the Genetic Information Nondiscrimination Act (GINA), which forbids employers and health insurers to request genetic information from individuals and/or discriminate against them on the basis of any available genetic information. These protections do not, however, extend to other types of insurance, including life and disability coverage, and have been threatened by subsequent legislative initiatives. For example, under the 2017 H.R.1313 bill, employers would be able to request that their employees undergo genetic testing and share their results as part of a workplace wellness programme. Employees who refuse could face increased yearly insurance premiums, a substantial financial penalty that some argue would effectively force individuals into participating, undermining their autonomy and privacy. Conversely, limited legal protection can also discourage individuals from choosing to participate in genomic research for fear that the data gathered would have to be shared and could be used to discriminate against them. Such fears could cause people to forgo potentially medically valuable tests and obstruct the clinical research needed to better understand and treat a variety of health conditions[285].

Conclusions

Genomic medicine aims to use genetic information about patients to inform their clinical care. CMA and NGS have revolutionized nephrology research, illuminating the molecular pathogenesis of a variety of genetic kidney diseases, and have great potential clinical utility across a wide range of indications. The remaining questions are how to fill in the substantial gaps in knowledge and how to translate what is currently known into personalized care. Strategies that may help to accomplish these aims include multicentre sequencing studies in large, diverse all-cause CKD cohorts; the establishment of expert working groups to create disease-specific standards for required pretest phenotypic information, genes assessed and variant interpretation; utilization of genetic stratification to better power clinical trials; and

the inclusion of geneticists and genetic counsellors in multidisciplinary care teams (TABLE 4).

While pursuing these efforts, it is imperative that we remain mindful of the limitations of our knowledge. Genetic testing does not give absolute answers, but rather provides a probabilistic biomarker, the meaning of which must be interpreted in the overall genomic and clinical context[286]. In many cases, the ‘one gene, one disease’ model does not apply owing to the presence of genetic and environmental modifiers. Thus, physicians and geneticists must incorporate diagnostic sequence interpretation with traditional tools such as clinical history and renal biopsy as well as with other sources of omic data, all of which can provide crucial insight into the genetic findings. Through considering each individual comprehensively in his or her own unique clinical context, genomic nephrology can deliver truly personalized care for patients with kidney disease.

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Glossary

Heritability
The proportion of interindividual variation in a given trait that is due to genetic factors.

Chromosomal microarray (CMA)
A technique to detect copy number variants by hybridizing a patient’s DNA to probes corresponding to various regions of the genome; the hybridization pattern for a given probe reflects the number of copies that the patient has of that genomic region.

Next-generation sequencing (NGS)
Simultaneous sequencing of multiple DNA segments; also known as massively parallel sequencing.

Genome
The entirety of an individual’s DNA. The genome is divided into smaller protein-coding segments called genes.

Genetic testing
The assessment of DNA sequence variation. Genetic testing can be performed at the level of a single variant, a gene, multiple genes, or the entire genome.

Genomic medicine
An emerging branch of medicine that uses information about an individual’s genome to inform their clinical care, including diagnosis, prognosis, and treatment.

Genetic diagnosis
The hereditary aetiology of a patient’s presentation, as identified by genetic testing.

Single-nucleotide variants (SNVs)
Changes of single bases (nucleotides) in a DNA sequence. SNVs can lead to an altered amino acid sequence in the encoded protein (nonsynonymous variants) or leave the sequence unchanged (synonymous variants).

Insertions or deletions
The gain or loss of bases in a DNA sequence, resulting in an altered amino acid sequence in the encoded protein.

Structural variants
Large (≥1 kb) DNA variants that include balanced (for example, inversions or reciprocal translocations) and imbalanced alterations (for example, copy number variants).

Sanger sequencing
A DNA sequencing method that uses labelled chain-terminating dideoxynucleotides to identify the nucleotides in the DNA strand being sequenced. This method generates a sequence chromatogram that can be analysed to detect genetic variants.

Targeted next-generation sequencing panels
Next-generation-sequencing-based analysis of a set of genes commonly associated with the patient's clinically suspected phenotype.

Whole-exome sequencing (WES)
Next-generation-sequencing-based analysis of the exome — the protein-coding regions of the genome that contain the majority of known causal variants for Mendelian disorders.

Whole-genome sequencing (WGS)
Next-generation-sequencing-based analysis of the whole genome, including protein-coding and non-coding regions.

Karyotyping
A technique used to detect large genomic imbalances through visual inspection of stained chromosomes using a microscope at high magnification (× 1,000).

Copy number variants (CNVs)
Structural variants that results in gain or loss of DNA at the relevant locus.

Array comparative genomic hybridization
A type of chromosomal microarray in which patient and control DNA are labelled with different coloured fluorescent dyes and cohybridized to a single DNA probe in order to directly compare copy number at that genomic region.

Single-nucleotide polymorphism arrays
A type of chromosomal microarray in which a patient's DNA is hybridized to DNA probes corresponding to single-nucleotide polymorphisms and the hybridization pattern is compared with previously analysed controls. This type of chromosomal microarray can detect a patient's genotype in addition to copy number at a given genomic region.

Balanced chromosomal rearrangements
Chromosomal rearrangements that do not cause a net loss or gain of genetic material.

Sequencing coverage and depth
In this Review, sequencing coverage denotes the percentage of bases in the DNA region targeted by sequencing that is sequenced a given number of times. Sequencing depth refers to the average number of times that a given nucleotide is read in a set of DNA sequence reads. Higher coverage and depth means that more of the targeted genomic region has been sampled a greater number of times, increasing the accuracy of the resulting data.

Secondary findings
Genetic findings that are not related to the primary indication for testing; also called incidental findings.

Multiplex ligation-dependent probe amplification
A technique in which patient DNA is hybridized to two oligonucleotide probes, corresponding to the 5′ and 3′ ends of the DNA, which are then ligated and PCR-amplified using a fluorescently labelled primer. The resulting PCR products are size-separated using capillary electrophoresis, and the fluorescent signal intensity is compared between the probe and the patient's DNA to determine copy number at that region. In addition to identifying copy number variants, this technique can detect mosaicism for a copy number variant and DNA methylation status.

Variants of uncertain significance (VUSs)
Genetic variants that have an unclear association with a given disorder owing to insufficient or conflicting evidence.

Phenotypic expansions
Phenotypic expansions occur when mutations in a gene that is classically associated with one phenotype are demonstrated to cause another clinically distinct phenotype.

Allele
Within each chromosome, the DNA sequence at a given region can vary; these variants are alleles.

Missense variant
Single-nucleotide variant that leads to the replacement of the amino acid normally encoded with another amino acid.

Haploinsufficiency
The state that arises when one copy of a gene is deleted or otherwise inactivated and the single remaining copy is insufficient to produce the amount of gene product needed to maintain normal function, leading to an abnormal (disease) phenotype.

Loss-of-function variation
DNA sequence alteration that leads to a protein with severely reduced or no function. Genetic variants that result in a prematurely truncated protein, such as nonsense variants, generally cause loss of function; however, missense variants can also have this effect.

Nonsense variant

Single-nucleotide variant that leads to the replacement of the amino acid normally encoded with a stop codon, leading to a prematurely truncated protein.

Variant phasing

Determining whether two variants in an individual's genome are both on the same copy of the gene (in cis) or on different copies of the genes (in trans) by use of parental testing. If two variants in a gene associated with a recessive disorder are in *trans*, they are more likely to be causal for the disorder, as they will impact both copies of the gene.

Allele frequency

The incidence of an allele in a population. Allele frequency is calculated by dividing the number of times that the allele is found by the total number of chromosomes. The allele frequency can be used to assess the rarity of a certain allele to help ascertain its pathogenicity during clinical sequence interpretation.

Penetrance

The proportion of individuals with a certain genetic variant who display the phenotype that is associated with this variant.

Genetic discrimination (GD)

Differential treatment of individuals on the basis of their genetic information.

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Key points

- Inherited aetiologies are responsible for ~10% of adult end-stage renal disease and >70% of paediatric hephropathy; sequencing studies of large cohorts will shed further light on genetic contributions across different forms of kidney disease
- In addition to ending the ‘diagnostic odyssey’, a genetic diagnosis can provide a deeper understanding of disease pathogenesis, inform prognosis, and guide clinical management
- Genetic testing is currently recommended for patients with early-onset nephropathy and/or other clinical features consistent with an inherited form of disease as well as for evaluation of living kidney donors
- Development of disease-specific guidelines and use of population genetic data will help to facilitate accurate clinical sequence interpretation; nevertheless, patient-level assessment results in the continued need for expert judgement
- The broadening clinical use of genetic testing in nephrology has raised questions regarding the return of results, physician education, testing across different patient subpopulations and many other practical and ethical issues
- Interdisciplinary research and dialogue will help to address unresolved challenges and inform the creation of best practice guidelines for genomic medicine in nephrology

Box 1

Genetic testing for *APOL1* risk alleles

A rapidly developing area in nephrology is the issue of genetic testing for *APOL1* risk alleles: two common coding variants that strongly influence the risk of multiple forms of nephropathy among individuals of sub-Saharan African descent. *APOL1*-mediated disease has been reported to follow a recessive model, with individuals with these two risk variants displaying a 7 to 10-fold higher risk of hypertension-associated end-stage renal disease (ESRD) and a 10 to 17-fold higher risk of focal segmental glomerulosclerosis (FSGS)-associated ESRD than those with one or no risk variants[251,287]. Subsequently, the *APOL1* risk genotypes have also been associated with increased risk of other forms of kidney disease, progression to ESRD, and allograft failure[250,252]. They might also impact risk of cardiovascular disease, although the precise nature of this association remains to be determined as both positive and protective effects have been reported[288].

Importantly, penetrance is variable; although the *APOL1* risk genotypes confer substantially higher odds of nephropathy than nonrisk genotypes, only a minority of individuals with *APOL1* risk genotypes develop kidney disease[289]. This finding suggests that *APOL1*-mediated kidney disease follows a two-hit model, whereby a secondary factor is required in addition to the risk genotype for disease development[250,252]. Such secondary factors might include environmental or genetic modifiers, including risk variants at other loci[290], and immunological triggers, such HIV infection[291,292]. Given the complexity of *APOL1*-mediated kidney disease, the clinical utility of the risk genotypes remains unclear.

The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend *APOL1* testing for candidate kidney donors but acknowledge that the evidence base is moderate, as insufficient evidence exists regarding the impact of donation on lifetime risk of nephropathy[160]. Additional investigation, including of the long-term outcomes of individuals with *APOL1* risk genotypes, allograft survival from donors with the *APOL1* risk genotypes, and the pathobiology underlying *APOL1*-mediated disease, will help guide how to best utilize *APOL1* risk variant status in nephrology[293].

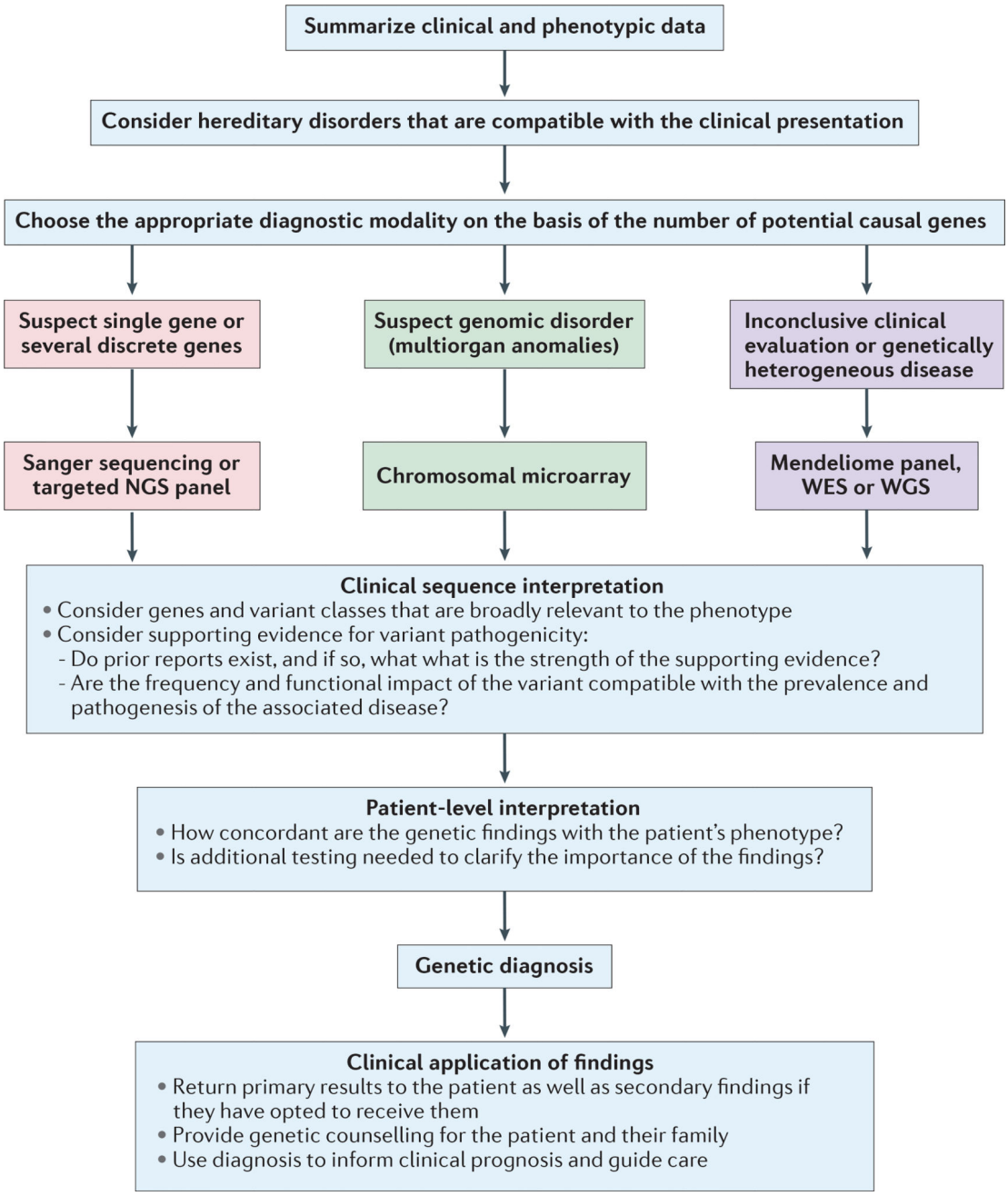

Figure 1. The genomic nephrology workflow: genetic diagnosis and clinical application

The first step in obtaining a genetic diagnosis for a patient with kidney disease is to characterize their disease phenotype by summarizing their clinical history and other relevant data (for example, findings from biochemical, imaging, and histopathological studies). This phenotype is then used to guide the choice of genetic testing modality. Among patients with genetically heterogeneous disease aetiologies, clinically ambiguous phenotypes, or null results obtained using targeted forms of genetic testing such as Sanger sequencing or targeted next-generation sequencing (NGS) panels, increasingly broad sequencing approaches can be applied, including Mendeliome panels, which can detect variants in all

known disease-causing genes; whole-exome sequencing (WES), which can detect variants in all coding regions; and whole-genome sequencing (WGS), which can detect variants in all coding and non-coding regions. Clinical sequence interpretation should be performed according to consensus guidelines[66,67,182]. This process involves identifying genes that are relevant to the phenotype of the patient, prioritizing variants on the basis of prior reports in disease cases as well as compatibility with the prevalence and genetic pathogenesis of the associated disease, and assessing the concordance between the genetic findings and the clinical phenotype. If deemed diagnostic, these primary findings, together with secondary findings if the patient has opted to receive them, can be returned and used to inform prognosis and guide personalized care, including targeted work-up and surveillance, choice of therapy, referral for clinical trials and family counselling.

Table 1

Major genetic testing modalities: indications and limitations

Modality	Scope	Indications for use	Examples	Advantages	Disadvantages
Sanger sequencing	Detection of SNVs and small indels (<10 bp) within a DNA segment of <1 kb	• Confirmation of NGS findings • Regions refractory to NGS, such as GC-rich, highly repetitive segments • Patients whose phenotype is indicative of a disorder caused by mutations in one specific gene	• Confirm frameshift *COL4A3* variant detected by NGS • Diagnostic testing for Fabry disease • Detect *CTNS* mutation (nephropathic cystinosis) in a patient with corneal cystine crystals and Fanconi syndrome	• High analytical accuracy • Easier and faster sequence interpretation compared with multigene testing enables faster turnaround time • No risk of secondary findings	• Resolution <1 kb; cannot detect larger structural variants • Increasingly time- and cost-inefficient with increasing gene length and/or number of genes tested
Chromosomal microarray	Genome-wide detection of CNVs ≥200–400 kb	Patients with phenotypes commonly resulting from genomic imbalances, such as multiple congenital anomalies	• Detect whole-gene deletion of *HNF1B* in a patient with renal hypodysplasia and autism • Detect 22q11.2 deletion (DiGeorge syndrome) in a patient with renal agenesis and neonatal hypocalcaemia	• Higher resolution enables detection of CNVs missed by karyotyping • Genome-wide CNV detection increases diagnostic sensitivity	• Cannot detect SNVs, indels, and small CNVs • Limited ability to detect balanced chromosomal rearrangements, low-grade somatic mosaicism, and CNVs in certain regions (such as pseudogenes and repetitive elements)
Targeted NGS panels	Detection of SNVs and small indels (<1 kb) within genes of interest for the clinically suspected phenotype	• Patients with phenotypes that are fairly specific for a particular disorder • Disorders with low genetic and/or phenotypic heterogeneity	• Testing *AGXT*, *HOGA1*, and *GRHPR* for primary hyperoxaluria in a patient with childhood-onset calcium oxalate urolithiasis • Testing for *COL4A3*, *COL4A4*, and *COL4A5* mutations in a patient with suspected Alport syndrome	• Can be optimized to ensure sufficient coverage of variants in targeted regions • Interrogation of genes that are related to the clinical indication facilitates interpretation and minimizes risk of secondary findings	• Testing a limited number of genes decreases diagnostic sensitivity, especially for genetically and/or phenotypically heterogeneous disorders • Challenges of panel design (gene selection and need for frequent updates) • Minimal capacity for sequence reanalysis
Whole-exome sequencing	Detection of SNVs and small indels (<1 kb)	• Patients with highly genetically heterogeneous or	• NPHP-RC[122,123] • Diagnosis of congenital chloride	• Unbiased approach increases diagnostic sensitivity	• Lower analytical sensitivity and specificity than whole-genome sequencing

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Modality	Scope	Indications for use	Examples	Advantages	Disadvantages
	within coding regions of the genome	nonspecific phenotypes • CKD of unknown aetiology • Patients left undiagnosed by targeted NGS panels	diarrhoea in an unresolved case of presumed Bartter syndrome[148] • Diagnosis of *LMX1B* glomerulopathy in familial ESRD of unknown origin[165]	• Interrogation of the coding regions that are enriched for known disease-causing mutations is a cost-effective approach to genome-wide testing • Genome-wide scope enables sequence reanalysis and discovery of novel genes	owing to limited coverage of certain regions and inability to accurately call certain types of variants (such as indels) • Approach can lead to multiple candidate variants, increasing time required for interpretation and need for follow-up testing • Burden of secondary findings in genes unrelated to the primary indication for testing
Whole-genome sequencing	Detection of SNVs and small indels (<1 kb) within coding and non-coding regions of the genome	• Patients with highly genetically heterogeneous phenotypes • Patients with nonspecific phenotypes • CKD of unknown aetiology • Patients left undiagnosed by all other genetic testing modalities	• Detection of causal intronic variants, for example, in a genetically unresolved case of Gitelman syndrome[106] • Genetic diagnosis of ADPKD (owing to high sequence homology of *PKD1*)[110] • Detection of causal balanced translocations for congenital anomalies[294,295]	Superior diagnostic and analytical sensitivity to whole-exome sequencing owing to its ability to assess SNVs, indels, and CNVs in coding and non-coding regions and more complete per-base coverage	• Difficulty of interpreting non-coding variants • Large amount of data generated results in substantial time and monetary costs, hindering return of results • Burden of secondary findings in genes unrelated to the primary indication for testing • Burden of long-term sequence data storage

ADPKD, autosomal dominant polycystic kidney disease; ADTKD-*MUC1*, autosomal dominant tubulointerstitial kidney disease due to mutations in *MUC1*; *AGXT,* alanine-glyoxylate aminotransferase; CKD, chronic kidney disease; CNV, copy number variant; COL4A, collagen type IV α-chain; *CTNS*, cytinosin, lysosomal cystine transporter; ESRD, end-stage renal disease; GC, guanine-cytosine; *GRHPR*, glyoxylate and hydroxypyruvate reductase; *HOGA1*, 4-hydroxy-2-oxoglutarate aldolase 1; *HNF1B*, HNF1 homeobox B; *LMX1B*, LIM homeobox transcription factor 1β; *MUC1*, mucin 1, cell surface associated; NGS, next-generation sequencing; NPHP-RC, nephronophthisis-related ciliopathy; *PKD1*, polycystin 1, transient receptor potential channel interacting; SNVs, single-nucleotide variants.

Table 2

Examples of the clinical utility of genetic diagnoses in nephrology

Indication	Genetic finding	Genetic diagnosis	Clinical impact	Refs
Steroid-resistant nephrotic syndrome	Homozygous Fin-major mutation in *NPHS1*	Nephrotic syndrome type 1 (OMIM 256300)	Increased risk of post-transplant disease recurrence	296,297
	COQ2 mutation	CoQ_{10} deficiency 1 (OMIM 607426)	CoQ_{10} supplementation can attenuate proteinuria and extrarenal complications such as encephalopathy	298,299
	COL4A3 or COL4A4 missense mutation	Alport syndrome (OMIM 104200; 203780) or TBMD (OMIM 141200)	• Distinguishes between autosomal (*COL4A3* or *COL4A4*) and X-linked (*COL4A5*) inheritance, informing family counselling • Missense mutations are associated with less severe disease and slower progression to ESRD than loss-of-function mutations • Avoid immunosuppression (a commonly used therapy for nephrotic syndrome)	79, 300–302
Cystic renal dysplasia	17q12 deletion	Renal cysts and diabetes syndrome (OMIM 137920)	Multisystem work-up for associated extrarenal complications, including testing for diabetes, exocrine pancreatic insufficiency, hepatic function, neurological anomalies, and/or neurocognitive impairment	133,134, 303
Nephrolithiasis	*APRT* mutation	APRT deficiency (OMIM 614723)	Xanthine dehydrogenase inhibition to prevent crystalline nephropathy and allograft loss	304,305
Episodic hypertension	*SDHD* mutation	Hereditary paraganglioma-pheochromocytoma syndrome (OMIM 168000)	• Imaging studies to screen for additional tumours • Catecholamine antagonists and/or surgical tumour resection • Knowledge of parent-of-origin effect due to maternal imprinting informs genetic counselling • Lower risk of malignancy than other genetic causes of familial paragangliomas-pheochromocytoma syndromes informs prognosis	306,307
Failure to thrive, hepatomegaly, and hyperuricemia	*G6PC* mutation	Glycogen storage disease Ia (OMIM 232200)	• Dietary therapy (frequent meals, nasogastric tube, and/or raw starch to prevent hypoglycaemia; oral bicarbonate and avoidance of fructose and glucose to prevent acidosis)	308,309

Indication	Genetic finding	Genetic diagnosis	Clinical impact	Refs
			• Surveillance for hepatic adenoma; liver transplant may be needed	

APRT, adenine phosphoribosyltransferase; *COL4A*, collagen type IV α-chain; CoQ_{10}, Coenzyme Q_{10}; *COQ2*, coenzyme Q2, polyprenyltransferase; ESRD, end-stage renal disease; G6PC, glucose-6-phosphatase catalytic subunit; *NPHS1*, nephrin; SDHD, succinate dehydrogenase complex subunit D; TBMD, thin basement membrane disease.

Table 3

Resources for diagnostic sequence interpretation and clinical application

Resource	Description	Website(s)
Summarize patient data		
PhenoTips	• Web interface for clinicians to enter patient data and map symptoms to HPO terminology • Suggests candidate OMIM disorders and associated gene panels on the basis of phenotypic information	https://phenotips.org
Linking Open Data for Rare Diseases	• Web database that helps to code rare diseases by use of Orphanet, HPO, and OMIM data; provides information on epidemiology, inheritance, and characteristic features • Users can browse by disease name, medical specialty, signs or symptoms, and organ system(s) affected	https://bioportal.bioontology.org/projects/LORD
KCCG Patient Archive	• Web interface for clinicians to securely enter and store patients' clinical and genetic data and share these with other clinicians • Stores filtered summary results of genetic testing, facilitating writing of≈clinical genetic notes and return of results	http://www.patientarchive.org
Choose genes to analyse		
OMIM	• Database of >5,000 Mendelian disorders and >15,000 genes derived from curation of the primary literature • Provides an overview of each disorder and the associated genes and selected variants that have previously been reported	https://omim.org
Orphanet	• Database of rare diseases and associated genes, coded using HPO terminology • Diagnostic criteria are included for each disease to help users to gauge the relevance to a patient's phenotype	http://www.orpha.net
PanelApp	• Database of curated gene panels for particular indications, including a variety of renal disorders • Indicates the strength of association of each gene with the relevant phenotype; those with strong evidence are recommended for clinical testing panels	https://panelapp.extge.co.uk/crowdsourcing/PanelApp
ClinGen Gene-Disease Clinical Validity Classification Framework	Framework to assess the strength of association between a gene and a disease on the basis of evidence including the number of reported patients with variants in the gene and supporting experimental data	https://www.clinicalgenome.org/working-groups/gene-curation/projects-initiatives/clinical-validity-classifications
Prioritize variants		
ExAC and gnomAD	• ExAC is a database of WES data from 60,706 individuals; its successor, gnomAD, includes WES data from 123,136 individuals and WGS data from 15,496 individuals, encompassing seven major global populations • ExAC and gnomAD exclude related individuals and/or those with severe early-onset disorders but do include those sequenced as part of various adult-onset disease cohorts; individuals were not phenotyped in detail, so their disease status is unknown	• http://exac.broadinstitute.org • http://gnomad.broadinstitute.org
1000 Genomes	• Database of WGS data from 2,504 individuals from 26 different global populations; the data are of variable quality and include some related individuals • The participants are self-declared as healthy, but additional data regarding their health status was not collected	http://grch37.ensembl.org/index.html
Database of Genomic Variants	Database of >2.5 million structural variants detected in >22,300 healthy individuals; the relatedness status of participants is not mentioned	http://dgv.tcag.ca/dgv/app/home
ClinVar	• Open-access database of inherited and somatic genetic variants detected in individuals across a broad spectrum of disorders; contributors include diagnostic laboratories, other databases and research groups • Each variant is accompanied by assertions regarding its pathogenicity (or lack thereof) for the associated disease phenotype	https://www.ncbi.nlm.nih.gov/clinvar

Resource	Description	Website(s)
	• The number of stars accompanying an entry reflects the strength of supporting evidence for the classification, which varies considerably	
Human Gene Mutation Database	Database of disease-associated genetic variants, manually curated from review of the scientific literature; access to the most comprehensive version requires a paid subscription	https://www.qiagenbioinformatics.com/products/human-gene-mutation-database
Human Genome Variation Society	Repository for various disease and gene-specific databases, many of which are organized within the LOVD framework; individual databases vary in the amount and quality of information provided regarding the variants deposited	• http://www.hgvs.org/content/databases-tools • http://www.lovd.nl
Variant Effect Predictor	Software tool that predicts the impact of a genetic variant on the encoded protein and assesses its predicted pathogenicity by use of various *in silico* algorithms	http://www.ensembl.org/Tools/VEP
Uniprot	Protein database; users can query genes to see whether a variant is located in a conserved domain or has experimental data supporting an effect on protein function	http://www.uniprot.org
Patient-level interpretation		
MyGene2	• Web portal of phenotypic and genetic data from patients with rare genetic diseases • Users can search by gene or clinical symptom and connect with researchers, clinicians, and patients who share findings in the gene and/or the relevant phenotype	https://www.mygene2.org/MyGene2
Decipher	• Database of sequence and structural variants from patients with rare genetic disorders • Users can search by variant, gene, or disease and directly compare a patient's genetic data to the variants present	https://decipher.sanger.ac.uk
Clinical application of genetic findings		
ClinicalTrials.gov	• Global database of clinical studies, including interventional and observational protocols • Patients, researchers, and clinicians can find opportunities to participate in disease-specific studies and view the results of completed studies	https://clinicaltrials.gov
GeneReviews	• Database that provides clinically relevant and medically actionable information about inherited conditions • Articles are written by domain experts and address aspects including clinical prognosis and management, genetic counselling recommendations, and patient support groups	https://www.ncbi.nlm.nih.gov/books/NBK1116
Orphanet	• Directory of expert centres, physicians, tests, ongoing research and patient organizations and an inventory of orphan drugs • Links users to clinical referral centres, patient registries, and research networks for rare renal diseases	http://www.orpha.net
EURenOmics	International consortium that applies genomic and phenotypic studies of large patient cohorts with functional studies to gain greater insight into rare renal diseases and identify potential therapeutic targets	https://www.eurenomics.eu
American Board of Genetic Counseling	Web portal that enables patients to search for genetic counsellors worldwide by medical specialty and/or location	https://www.abgc.net/about-genetic-counseling/find-a-certified-counselor.aspx

ExAC, Exome Aggregation Consortium; gnomAD, Genome Aggregation Database; HPO, Human Phenotype Ontology; KCCG, Kinghorn Centre for Clinical Genomics; LOVD, Leiden Open Variant Database; OMIM, Online Mendelian Inheritance in Man; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Table 4

Strategies for bench-to-bedside translation of genetic findings in nephrology

Insight from genetic studies	Clinical need	Knowledge required	Potential strategies to enable translation
A molecular cause can be identified across a variety of clinical presentations	Evidence-based guidelines regarding indications for genetic testing	• Prevalence of genetic forms of nephropathy among patients with kidney disease • Clinical features that predict a genetic form of nephropathy	• Multicentre sequencing studies in large, diverse all-cause kidney disease cohorts • Electronic health record tools to help alert physicians to patients with relevant indications for genetic testing
Expanding the scope of genetic testing increases diagnostic sensitivity but also increases the time and expertise needed for interpretation	Ability to select the appropriate genetic test given the clinical context and provide the phenotypic information needed for sequence interpretation	• The technical and diagnostic advantages and limitations of available genetic testing options • The phenotypic information that should be provided to the diagnostic testing laboratory	• Comprehensive study comparing diagnostic yield and cost-effectiveness between test modalities for different patient populations and clinical indications • Expert working groups to create disease-specific standards for required pretest information, genes assessed, and variant interpretation
In many cases, a one-to-one relationship does not exist between a given genetic mutation and a clinical phenotype	The ability to inform patients and families about the clinical relevance of the genetic variant detected and provide the indicated work-up	• The range of phenotypes associated with mutations in a gene • The factors resulting in genetic pleiotropy and variable expressivity • The prognostic importance of genetic findings	• Comprehensive patient phenotyping, including assessment of extrarenal and renal features • Integration of additional omics data into clinical sequence interpretation • Large cohort studies of patients with genetic forms of kidney disease that investigate the relationship between genotype and long-term clinical outcomes
Genetic findings can substantially impact clinical outcomes, such as health-care utilization, morbidity and mortality, and choice of therapy	Personalized treatment plans and targeted pharmacological agents tailored to specific genetic disorders	• The relationship between a genotype and key clinical outcomes • Disease pathogenesis at a molecular level	• Observational studies assessing the impact of genetic findings on clinical outcomes • Utilization of genetic stratification to better power clinical trials • Application of the biological insights gained from research into development of novel targeted therapeutic agents
The causality and medical actionability of genetic findings are probabilistic and evolving concepts	Appropriate counselling before and after genetic counselling	• The understanding of patients and physicians regarding genetic testing and their preferences for return of results and sequence reanalysis • The types of genetic variants that merit return as medically actionable secondary findings	• Include geneticists and genetic counsellors in multidisciplinary care teams as part of clinical genetic testing • Establish best practice guidelines for sequence reanalysis and patient recontact • Establish a multidisciplinary nephrogenetics working group to create a list of medically actionable secondary renal findings