More than 10% of patients with advanced CKD have a rare pathogenic genetic variant that significantly contributes to their disease (1). Ideally, early genetic testing would lead to a specific diagnosis of the underlying cause of CKD which would ultimately prevent or delay progression to kidney failure. Adult-onset conditions for which genetic testing is available in nephrology are wide ranging and include cystic kidney diseases, type IV collagen nephropathy (Alport syndrome), congenital abnormalities of the kidney and urinary tract, nephrotic syndrome including FSGS, tubulopathies including autosomal dominant tubulo-interstitial kidney disease, channelopathies including Bartter and Gitelman syndromes, and nephronophthisis among others (2). Using clinical clues to select patients for sequencing can increase the probability of discovering a pathogenic variant (2). Using commercial laboratories to provide sequencing, they report identifying pathogenic variants in nine of 19 CKD patients. An additional two patients were cleared for kidney donation because they did not have a familial pathogenic variant. The authors suggest that their experience demonstrates the feasibility of nephrology genetic testing without specific genetics infrastructure, although they admit there were administrative hurdles in obtaining preauthorization for funding and that a genetic counselor was funded by a hospital initiative.

Young age at disease onset and clinical clues suggestive of a genetic kidney disease increase the pretest probability of discovering a pathogenic variant (2). Although pediatric nephrologists recognize genetics as a valuable diagnostic tool, it is a paradigm shift to suggest that adult nephrologists can also successfully utilize genetic testing to assist in diagnosis. Features in keeping with a monogenic cause of kidney disease, such as numerous kidney cysts as in autosomal dominant polycystic kidney disease (ADPKD), eye or ear abnormalities in Fabry disease or Alport syndrome, skin findings in tuberous sclerosis, or persistent electrolyte abnormalities in Bartter or Gitelman syndrome are important clinical clues. However, even for those with the best clinical acumen, a genetic test can help seal a diagnosis. A positive family history of any kidney abnormality also increases the likelihood of a monogenic cause of kidney disease, but its absence does not exclude it, because many diseases are inherited in autosomal recessive or X-linked patterns without a clear family history. Our understanding of the CKD risk associated with carrier status for many pathogenic variants is also incomplete. For example, the CKD risk associated with heterozygous pathogenic variants in X-linked COLA4A5 is underappreciated in women (4). Moreover, many patients are unaware of their family’s history of kidney disease due to incomplete history, adoption, nonpaternity, lack of access to care, or relatives who die before the kidney condition is identified (5).

Expert opinion-based indications for clinical genetic testing in ADPKD seek to clarify unclear cases when a concrete diagnosis is desired: suspected cases with no apparent family history, cases with equivocal imaging findings or atypical features, and cases requiring diagnosis before numerous cysts are present (kidney donation or preimplantation genetic testing) (6). Importantly, in contrast to selecting individuals with a classic phenotype and clear family history, these criteria lower the likelihood of having a positive test but increase the likelihood of genetic testing altering a diagnosis. Patients with ADPKD selected because of a classic phenotype and positive family history typically yield positive genetic test results in >80% of cases. Thus, the gold standard should not be the percentage of tests that report pathogenic variants, but the number of tests that alter clinical decision making. However, what determines whether a test alters a patient’s decisions is difficult to define. Randomized controlled trials of whether genetic testing can delay CKD, kidney failure, or death are likely infeasible. Is providing a concrete diagnosis, especially in the context of high clinical suspicion, a sufficient indication to obtain genetic testing? Is it reasonable to test for a familial variant in an asymptomatic state? Unfortunately, the indications for genetic testing in kidney disease are likely to remain opinion-based and unclear. Moreover, the costs associated with genetic testing may further exacerbate disparities of health outcomes in the disadvantaged.

Ordering genetic testing is burdensome and requires assessment of cost coverage, selecting the genetic test and testing service provider, completing requisitions, arranging sample acquisition and shipping, and obtaining both genetic testing and research consent. Similar processes receive substantial funding in the context of clinical trials and are not generally supported by clinical reimbursement. Selecting the most
appropriate genetic test and properly interpreting its results is not straightforward. Exome sequencing, where the coding regions of all genes are sequenced, is becoming more common but creates significant opportunity for secondary or incidental findings, and substantially increases the complexity of interpretation. Gene panels include a curated list of genes, such as COLA4A3/COLA4A4/COLA4A5, eight genes associated with nephrotic syndrome, or >100 genes associated with kidney disease. Gene panels can be constructed by examining only candidate genes out of whole-exome data or by biochemically probing and sequencing only genes of interest. There are pros and cons to both approaches. Sequencing \(PKD1\) is particularly challenging due to genomic complexity and is limited in exome sequencing (7). Finally, it must be emphasized that individually rare genetic variants are cumulatively quite common. Genetic testing reports provide the allele frequency of identified variants in population databases and bioinformatic predictions of pathogenicity. However, the penetrance of many potentially pathogenic rare variants is incomplete. Confirmation bias can make it easy to assign pathogenicity to a rare variant in a candidate gene that appears to correspond with a clinical phenotype. A nonexpert may have difficulty assessing and integrating the results of genetic testing into the clinical scenario.

Genetic counseling is essential to educate patients about the ramifications on future children, family members, employment, and life, disability, drug, and critical illness insurance. Legislation, such as Canada’s Genetic Non-Discrimination Act or the US Genetic Information Nondiscrimination Act, attempts to protect individuals from discrimination because of genetic testing results. Regardless, providing a diagnosis to a patient in an otherwise asymptomatic state, especially in the absence of a positive family history, can have significant ramifications.

Overall, the technicalities of genetic testing remain a challenge and there is significant condition-to-condition, country-to-country, and even center-to-center variation. Commercial genetic testing providers seek to “lower the bar” to access genetic testing by streamlining sample collection, shipping, consent, interpretation, and genetic counseling. However, commercial genetic testing providers have a conflict of interest given that they generate revenue by providing the service. Direct-to-consumer genetic testing is even less regulated and fraught with even greater challenges.

The future for genetic testing in clinical nephrology is bright, but what will be the best way to implement it? Lundquist et al. suggest that genetic testing can be successfully integrated into general nephrology practice (3). One solution would be to improve genetics teaching in nephrology fellowship training and continuing medical education for practicing nephrologists to increase the number of nephrologists who are comfortable ordering it. Another model would create centers of excellence in nephrology genetics to provide an assessment of genetic contributors to kidney disease before returning the patient’s care to their primary nephrologist. The future will most likely include a mix of the two solutions, but clear agreement between patients and their families, nephrologists, genetic counselors, and health care systems on indications, processes, interpretation, and counseling is required before widespread application of nephrology genetics to clinical care.

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Author Contributions
M. Lanktree conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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