

University of Groningen

Genetics in chronic kidney disease

KDIGO Conference Participants

Published in:
Kidney International

DOI:
[10.1016/j.kint.2022.03.019](https://doi.org/10.1016/j.kint.2022.03.019)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
KDIGO Conference Participants (2022). Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International*, 101(6), 1126-1141. <https://doi.org/10.1016/j.kint.2022.03.019>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

KDIGO Conference Participants¹

Numerous genes for monogenic kidney diseases with classical patterns of inheritance, as well as genes for complex kidney diseases that manifest in combination with environmental factors, have been discovered. Genetic findings are increasingly used to inform clinical management of nephropathies, and have led to improved diagnostics, disease surveillance, choice of therapy, and family counseling. All of these steps rely on accurate interpretation of genetic data, which can be outpaced by current rates of data collection. In March of 2021, Kidney Diseases: Improving Global Outcomes (KDIGO) held a Controversies Conference on “Genetics in Chronic Kidney Disease (CKD)” to review the current state of understanding of monogenic and complex (polygenic) kidney diseases, processes for applying genetic findings in clinical medicine, and use of genomics for defining and stratifying CKD. Given the important contribution of genetic variants to CKD, practitioners with CKD patients are advised to “think genetic,” which specifically involves obtaining a family history, collecting detailed information on age of CKD onset, performing clinical examination for extrarenal symptoms, and considering genetic testing. To improve the use of genetics in nephrology, meeting participants advised developing an advanced training or subspecialty track for nephrologists, crafting guidelines for testing and treatment, and educating patients, students, and practitioners. Key areas of future research, including clinical interpretation of genome variation, electronic phenotyping, global representation, kidney-specific molecular data, polygenic scores, translational epidemiology, and open data resources, were also identified.

Kidney International (2022) **101**, 1126–1141; <https://doi.org/10.1016/j.kint.2022.03.019>

KEYWORDS: genetic kidney disease; genetic testing; genome-wide association studies; monogenic; polygenic; single-nucleotide polymorphism
Copyright © 2022, Kidney Disease: Improving Global Outcomes (KDIGO). Published by Elsevier Inc. on behalf of the International Society of Nephrology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Correspondence: Anna Köttgen, Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Hugstetter Str. 49, 79106 Freiburg, Germany. E-mail: anna.koettgen@uniklinik-freiburg.de; or Ali G. Gharavi, Division of Nephrology, Department of Medicine, Columbia University Irving Medical Center, Russ Berrie Pavilion, 1150 St Nicholas Avenue, New York, New York 10032, USA. E-mail: ag2239@cumc.columbia.edu

¹The KDIGO Conference Participants are listed in the [Appendix](#).

Received 13 January 2022; revised 16 March 2022; accepted 29 March 2022; published online 20 April 2022

Chronic kidney disease (CKD) affects approximately 10% of the global adult population.¹ Multiple genetic and environmental risk factors contribute to kidney diseases, making identification of the underlying pathophysiologic mechanisms difficult. However, the advent of high-throughput genotyping and massively parallel sequencing, combined with the availability of large datasets of genomic and health information, has led to rapid advances in our understanding of the genetic basis of kidney function and disease.

To date, more than 600 genes have been implicated in monogenic kidney diseases,² and known single-gene disorders account for up to 50% of nondiabetic CKD in pediatric cohorts, and 30% in adult cohorts.^{3–10} In addition, genetic variation plays an important role for kidney function in the normal range,^{11–16} and common genetic variants account for approximately 20% of the estimated genetic heritability of estimated glomerular filtration rate (eGFR).¹³ Common genetic variants also have been shown to contribute to disorders, such as IgA nephropathy,^{17,18} membranous nephropathy,^{19,20} and nephrotic syndrome.^{21–23} Hence, the pathogenesis model for many kidney diseases has expanded to include multiple genetic and environmental factors that together contribute to the pathology, commonly referred to as “complex disease.”

Genetic findings increasingly are used to inform clinical management of many nephropathies, enabling more precise diagnostics, targeted disease surveillance, and better-informed choices for therapy and family counseling.²⁴ Clinical management relies on accurate interpretation of genomic data, a labor-intensive process that can be outpaced by the speed of discovery.²⁵ To realize the promises of genomic medicine for kidney disease, many technical, logistical, ethical, and scientific questions must be addressed.²⁴ In March of 2021, Kidney Diseases: Improving Global Outcomes (KDIGO) held a Controversies Conference on the topic of “Genetics in CKD” to review the current state of understanding of monogenic and complex kidney diseases, processes for applying genetic findings in clinical medicine, and use of genomics for defining and stratifying CKD. Participants identified areas of consensus, gaps in knowledge, and priorities for research (Table 1). The conference agenda, discussion questions, and plenary session presentations are available on the KDIGO website: <https://kdigo.org/conferences/genetics-in-ckd/>.

Definitions and epidemiology of genetic kidney diseases

The familial aggregation and substantial heritability of CKD are well described across the world. Recent large-scale analyses of electronic medical records estimated observational

Table 1 | Summary points from the Genetics in CKD Controversies Conference**Consensus**

- Monogenic and complex kidney diseases exist on a continuum, but dichotomous categories are useful for practical distinction.
- There is no upper age-limit for monogenic CKD.
- Actionable genes in kidney diseases refers to genes in which the identification of pathogenic variants can lead to specific clinical actions for treatment or prevention, following recommendations based on evidence.
- There is a need for development of a reference kidney disease gene list and standardization of gene/variant reporting for kidney diseases.
- A larger workforce with expertise in kidney genetics, genomics, and computational research is needed.
- Education of the workforce is necessary for successful implementation of genetic testing in clinical nephrology.
- More studies are needed that include diverse populations worldwide to ensure equitable and generalizable implementation of genetic testing, obtain evidence of causality, establish global prevalence, and facilitate variant discovery.
- Interdisciplinary expert boards (including nephrologists, clinical geneticists, molecular biologists, genetic counselors) should be assembled to discuss potential genetic diagnostic findings and counsel primary and secondary care centers.
- Genomics should be integrated into clinical trials on kidney diseases.
- Estimates of the prevalence of monogenic CKD are important, but they are currently imprecise due to selection bias.

Ongoing controversies**Definitions/terminology**

- Two-part names (clinical condition PLUS gene name) are preferred for more-precise disease terminology.
- The term CKD of unknown etiology is not clear and is in need of consensus.
- There is no clear consensus on which VUS are to be reported in the framework of diagnostic testing.

Processes for improving data capture and analysis

- Improve phenotyping, including methods for electronic phenotyping.
- Improve the quality of genomic studies, including analytical and computational methods.
- Improve data access while protecting the privacy of research participants.
- Create processes for transferring genetic information obtained through clinical testing to research.
- Study health-economic impacts of genetic testing in nephrology.
- Establish a process for periodic reanalysis of unsolved cases with kidney disease.
- Implement high-throughput techniques for *in silico* and *in vitro* variant characterization.
- Identify and characterize rare variants, structural variants, and functional variants using functional genomic, epigenetic, and other multi-omic approaches.
- Employ new approaches to identify more homogeneous CKD phenotypes and subclassifications for genetic studies, such as using nontraditional omics biomarkers, electronic health record data, imaging, or machine learning.
- Assemble larger cohorts with genetically defined kidney disease for both research and clinical trials; collaborate internationally if possible.
- Reduce measurement errors in eGFR, and misclassification in the resulting CKD definition; for example, reassess coefficients based on race, sex, and chronological age in eGFR equations.
- Conduct large-scale genetic studies on specific kidney sub-phenotypes, such as CKD progression, acute kidney injury, cause-specific disease severity, and manifestations.
- Integrate genetic studies with biomarker and multi-omic profiling to leverage findings and increase power for both variant and pathway identification.
- Generate comprehensive molecular maps of kidney tissue/cells as well as *in vitro* and animal models to enable mechanistic studies of genes identified in GWAS of kidney traits.
- Encourage broad data sharing (FAIR principles; findable, accessible, interoperable, reusable) and transparent protocols for data generation, quality control, and analyses.
- Use federated networks to standardize key data elements across platforms and countries.
- Use portals (cloud-based) to "safely" share individual data and allow for democratization and a broader scale of integrative *in silico* analyses.
- Extend discovery analyses to nonadditive genetic models (e.g., recessive) and include nonautosomal regions (e.g., chromosome X, mitochondrial).
- Improve imputation reference panels.
- Apply and develop approaches specific to admixed populations.
- Conduct Mendelian randomization analysis to elucidate causal mechanisms.

Priorities for Implementation

- Increase genetic and genomic resources in underrepresented populations with kidney disease.
- Investigate the use of polygenic scores in clinical settings.
- Develop guidelines for nephrologist to establish core competencies in genetics, develop evaluations to test them, and identify the educational gaps of general nephrologists (some need to be country-specific).
- Develop and test the impact of dissemination tools to spread the basic knowledge required for all nephrologists.
- Measure the quality of existing or to-be-established genetic subspecialty training for nephrologists as well as training in nephrology for genetic counselors and molecular geneticists (variant interpretation side).
- Develop guidelines for the referral of nephrology patients to genetic counseling/genetic testing/reproductive counseling.
- Analyze the impact of genetic testing on clinical outcomes of nephrology patients.
- Analyze the cost-effectiveness and longitudinal clinical utility of genetic testing.
- Analyze the impact of centers of expertise on quality of care and patient outcomes.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GWAS, genome-wide association studies; VUS, variants of uncertain significance.

Table 2 | Characteristics of monogenic versus complex genetic diseases

	Monogenic (Mendelian)	Polygenic (complex)
Allele/variant frequency	Rare	Can be common
Effect size of major driving gene	Large	Small
Penetrance	High	Low
Role of environment	Limited	Strong
Inheritance model	Mendelian	None apparent

heritability of CKD to be in the range of 25%–44%, with higher estimates for patients of African ancestry.²⁶ These estimates are generally consistent with traditional family-based heritability studies of CKD and glomerular filtration rate.^{27–29} The relatively high heritability of CKD is likely attributable to both monogenic causes as well as complex or polygenic factors.

Monogenic (also termed “Mendelian”) CKD generally refers to diseases caused by rare, pathogenic variants in a single gene (Table 2); the genotype-to-phenotype relationship is strong, and environmental factors have limited influence. Oligogenic disorders are determined by rare variants in a few genes. Complex or polygenic diseases lack simple patterns of inheritance (e.g., dominant, recessive, or sex-linked) and instead are influenced by the aggregate effect of many common genetic variants in multiple genomic regions, as well as environmental factors.³⁰ Such aggregate effects of common variants (or single-nucleotide polymorphisms [SNPs]) can be quantified by SNP-based heritability, which has been estimated for various types of kidney disorders to range from 14% for renal cancer among individuals of European ancestry to 43% for membranous nephropathy among individuals of East Asian ancestry. The proportions of variance explained by known loci of these diseases are smaller, ranging from <1% for urinary albumin-to-creatinine ratio to 32% for membranous nephropathy among individuals of East Asian ancestry (Figure 1).^{13,14,17,19,31} However, common genetic factors also may influence the age of onset, severity, rate of progression, and associated extrarenal complications of monogenic diseases, which often have variable expression.^{32,33} In addition to CKD attributed to specific etiologies, genetic studies also use phenotypic readouts, such as measures of kidney function or damage (e.g., eGFR, albuminuria), kidney histology classification, and molecular injury markers to define CKD (Table 3).^{34,35}

Monogenic variants account for approximately 30%–50% of cases of CKD stages G3b–G5 in children,^{3–5,36,37} and 10%–30% in adults.^{3–10} Diagnostic yields vary between 12% and 65% among studies, with selection bias likely contributing to the variability. However, prevalence estimations for genetic diseases are likely to change over time as genetics-first approaches to diagnosis (in which sequence data are obtained first, followed by characterization of associated phenotypes) become more common.³⁸ Many common variants associated with specific kidney function measures or complex kidney diseases have been identified through

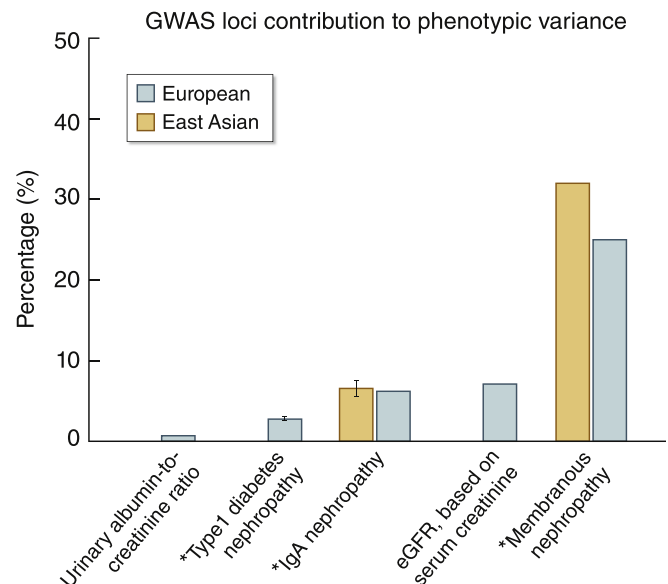


Figure 1 | Common variant contributions to kidney diseases and traits.^{13,14,17,19,31} *For binary outcomes, the proportions of phenotypic variance explained by loci from genome-wide association studies (GWAS) were estimated from Nagelkerke’s or McKelvey & Zavoina’s pseudo R². eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; SNP, single-nucleotide polymorphism.

genome-wide association studies (GWAS) and exome- or genome-sequencing studies of large population samples—usually of European or East Asian ancestry (Figure 2).^{13,14,17,19,31,39–41} The largest number of loci—genomic regions containing associated SNPs—were discovered for the continuous kidney function measure eGFR, with studies based on data from >1 million individuals reporting more than 250 such loci.^{12–14,17,19,22,23,31,40,42–66}

Although the distinction of monogenic versus polygenic diseases provides a useful practical framework, genetic risk variants for kidney diseases occur on a spectrum from rare variants with large effects to common variants with small effects, and many diseases do not fit neatly into either category. For example, apolipoprotein L1 (*APOLI*)–associated kidney risk variants are common among some populations of African ancestry and impart a relatively high risk under a recessive mode of inheritance, but these variants are not considered monogenic. The magnitude of the risk associated with *APOLI* variants varies significantly for different forms of nephropathy. For example, Black South Africans with untreated human immunodeficiency virus (HIV) and 2 *APOLI* risk alleles have been reported to have a more than 80-fold increased risk of developing HIV-associated nephropathy, but the magnitude of the risk conferred by the same risk alleles ranged between 1.2 and 2 for CKD or nondiabetic kidney failure (Figure 3).^{67–85} Similarly, the combination of 2 common variants in the *HLA-DR* and *PLA2R1* loci imparts a high risk of the complex disease membranous nephropathy, defying the common variant/small effect paradigm.²⁰

Table 3 | Disease definitions for genetic studies based on kidney function, kidney histology, and molecular markers: advantages and disadvantages

Advantages	Disadvantages
Kidney function markers (e.g., eGFR, albuminuria)	
<ul style="list-style-type: none"> • Readily attainable and standardized information in low- and high-income settings • Deployed routinely in clinical care and interventional trials • Allows the identification of genetic determinants of kidney function and factors impacting the progression of kidney disease • Relatively inexpensive • Repeated measures often readily available to assess trajectory 	<ul style="list-style-type: none"> • Descriptive nature of disease categorization • Agnostic to underlying kidney pathology and pathophysiology and disease heterogeneity • Urinary albumin excretion is underutilized • Current markers identify genetic variants related to marker metabolism but not filtration
Kidney histology	
<ul style="list-style-type: none"> • Allows for classification based on structural patterns of damage • Standardized classification scheme for most glomerular diseases • Current reference standard for clinical management with established clinical workflow • Histology classifications may reflect a more homogeneous pathophysiology than kidney-function markers 	<ul style="list-style-type: none"> • Often aggregates a diverse set of underlying disease-initiating events under a common histological damage pattern (e.g., FSGS), thereby potentially introducing functional and genetic heterogeneity • Limited accessibility in resource-constrained settings
Nontraditional molecular markers (e.g., markers quantified with high-throughput omics technologies)	
<ul style="list-style-type: none"> • Can segregate kidney-disease populations into more-homogenous subgroups and thereby facilitate the identification of underlying disease causes and drivers • Enables systems genetics analysis of kidney disease • Comprehensive multi-omics profiling possible (e.g., metabolomics, proteomics, exposomics) 	<ul style="list-style-type: none"> • Emerging technologies with limited accessibility in resource-constrained settings need to establish cost-effective readouts readily attainable in low- and middle-income countries • Access to large biobanks required for disease subtyping • Some marker levels may vary by kidney function

eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis.

Considerations for genetic testing

A positive family history, early age of onset, and presence of extrarenal symptoms are associated with a higher probability of monogenic disease. In addition, the clinical diagnosis is highly predictive of diagnostic yield and will guide the choice of genetic tests, motivating a thorough clinical workup prior to genetic testing. For example, glomerular and tubulointerstitial disorders are associated with a higher diagnostic yield than diabetic kidney disease. In general, because of the genetic heterogeneity of most forms of nephropathy, genetic testing with phenotype-driven gene panels, or exome or genome sequencing, is more efficient than sequential single-gene analyses.

Genetic testing is usually performed subsequent to a clinical workup, but in some situations, early genetic testing may be advantageous. For example, prospective kidney donors related to a recipient with a known genetic condition should be tested early during the donor-evaluation process. Other situations in which early genetic testing should be considered are listed in [Table 4](#). For healthy children and adults, currently, no data support predictive or presymptomatic genetic testing, even if a family history is present. Nevertheless, once a pathogenic variant is identified in a proband, cascade testing of family members and genetic counseling in mutation carriers are the standard practices in clinical genetics.

Most countries do not have guidelines to help determine which nephrology patients should be referred to genetic testing and counseling. Nephrology communities would therefore

benefit from developing guidelines based on best evidence and practices in clinical genetics. Overall, guidance should take into account the potential benefit of a genetic diagnosis for specific patients and their families (e.g., treatment changes, family planning, ending a diagnostic odyssey) and balance the risk of false-positive results that could engender unnecessary clinical workup for patients and their families. A position paper by the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Working Group for Inherited Kidney Diseases (WGKD) and the Molecular Diagnostics Taskforce of the European Rare Kidney Disease Reference Network (ERKNet) has been recently issued to delineate indications for genetic testing in CKDs.⁸⁶

Defining actionable genes in kidney diseases. Actionable genes in kidney diseases refer to genes that, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated if the risk were known.⁸⁷ A set of 73 actionable genes have been proposed by the American College of Medical Genetics and Genomics (ACMG), many of which are associated with phenotypes relevant to nephrology (*PALB2*, *GLA*, *HNFI1A*, *MEN1*, *MAX*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *VHL*, *TMEM127*, *TSC1*, *TSC2*, *WT1*). Although these genes were selected based on the possibility that targeting them may prevent overall morbidity and/or mortality, one can conceive of additional, kidney-specific actionable genes, nominated based on availability of interventions, that could prevent renal morbidity ([Figure 4](#)).

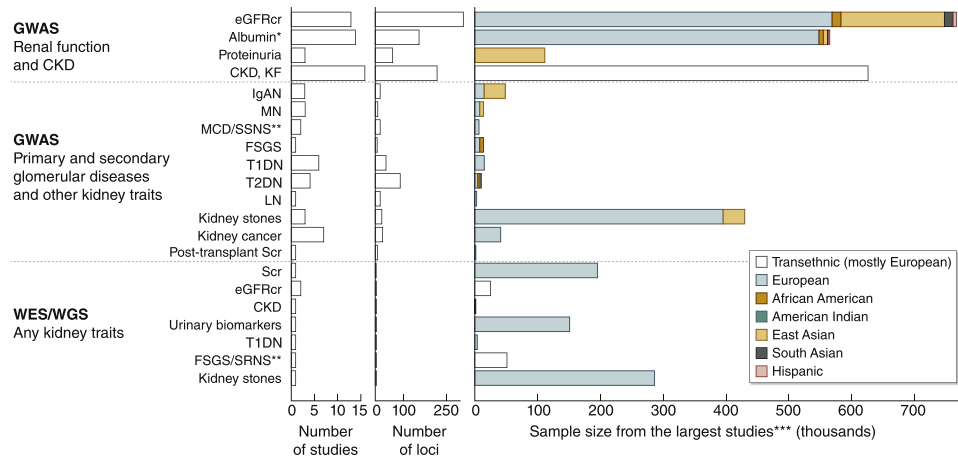


Figure 2 | Genome-wide association studies (GWAS), exome- or genome-sequencing studies of kidney function markers and kidney diseases. ^{13,14,17,19,31,39-41} *The largest study focused on urinary albumin-to-creatinine ratio. Several included serum albumin studies. **Pediatric population. ***For case-control studies, the total sample sizes were plotted. CKD, chronic kidney disease; eGFRcr, estimated glomerular filtration rate from serum creatinine; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; KF, kidney failure; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; Scr, serum creatinine; SRNS and SSNS, steroid-resistant and steroid-sensitive nephrotic syndrome; T1DN and T2DN, type 1 and type 2 diabetic nephropathy; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Examples include the following: early initiation of general renoprotective therapies (e.g., renin-angiotensin blockade for carriers of pathogenic variants in type IV collagen genes); initiation of targeted therapies (e.g., enzyme therapy for Fabry disease or CoQ10 supplementation for nephrotic syndrome due to CoQ10 deficiency); avoidance of treatment that would be futile and perhaps even deleterious (e.g., prolonged immunosuppressive therapies for genetic podocytopathies); and surveillance for recurrence of disease after kidney transplantation (e.g., atypical hemolytic uremic syndrome/thrombotic microangiopathy [aHUS/TMA],

primary hyperoxaluria). ClinGen, an international initiative to define robust disease-gene associations and curate pathogenic variants,⁸⁷ now has a kidney expert work group that is developing a stable list of nephropathy-associated genes and variants. This group is also expected to provide guidance for actionability for kidney genes and nominate them for the ACMG list. Awareness of the ClinGen Initiative should be promoted in the kidney community, along with messaging regarding the importance of variant submission to public databases such as ClinVar and the value of creating interdisciplinary expert boards to discuss controversial

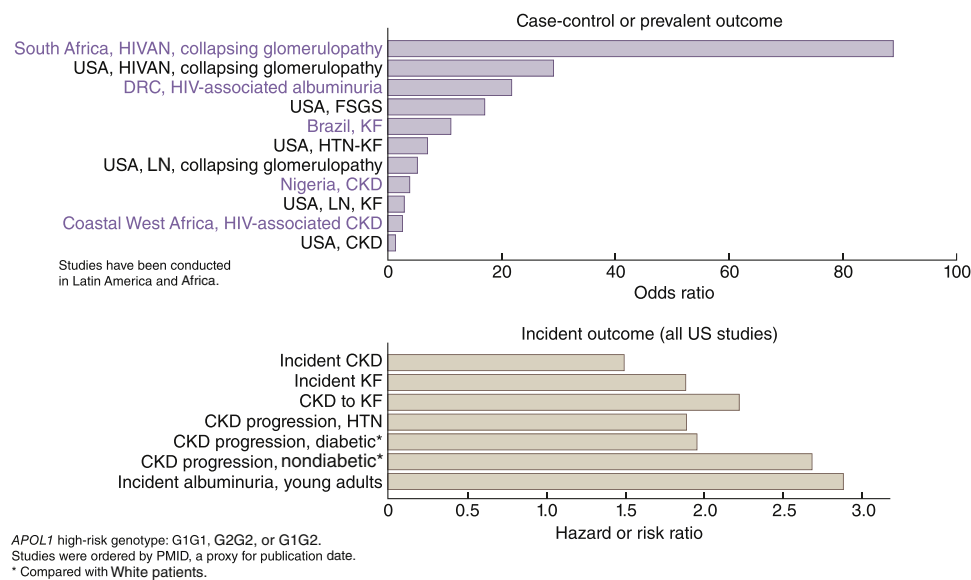


Figure 3 | Associations of APOL1 high-risk genotype and various kidney diseases or their progression. ⁶⁷⁻⁸³ APOL1 high-risk genotype: G1G1, G2G2, or G1G2. Studies were ordered by PubMed identifier (PMID), a proxy for publication date. *Compared with White patients. APOL1, apolipoprotein L1; CKD, chronic kidney disease; DRC, Democratic Republic of Congo; FSGS, focal segmental glomerulosclerosis; HIVAN, human immunodeficiency virus-associated nephropathy; HTN, hypertension; KF, kidney failure; LN, lupus nephritis.

Table 4 | Potential indications for genetic testing for monogenic forms of CKD

- The clinical work indicates the possibility of a genetic disease, such as—
 - high prevalence of monogenic subtypes within the clinical category (e.g., congenital/cystic nephropathies or steroid-resistant nephrotic syndrome)
 - positive family history of kidney disease
 - early age of onset (pediatric CKD)
 - syndromic/multisystem features
 - consanguinity
 - possibility of identifying a condition amenable to targeted treatment (e.g., enzyme replacement therapy for Fabry disease)
- The individual is an at-risk relative of a patient with a known monogenic disease, especially when the individual is a potential kidney donor
- As an alternative to kidney biopsy in patients at high risk of biopsy-related complications, especially when there is a high pre-test probability of finding a genetic variant based on family or clinical history
- CKD or kidney failure of unknown etiology when kidney biopsy would not be informative due to advanced disease, and other features suggestive of hereditary disease are present
- Information to guide continuation of immunosuppressive therapy (e.g., in steroid-resistant or partially responsive nephrotic syndrome)
- Genetic testing can provide prognostic information (e.g., ADPKD or Alport Syndrome, age at kidney failure)
- Diagnosis of diseases with risk of recurrence in kidney allografts (e.g., aHUS/TMA, primary hyperoxaluria)

ADPKD, autosomal dominant polycystic kidney disease; aHUS, atypical hemolytic uremic syndrome; CKD, chronic kidney disease; TMA, thrombotic microangiopathy.

variants of uncertain significance (VUS) and discussing the most complex cases. Additional efforts to harmonize gene and gene-panel curation, such as the Genomics England panel app (<https://panelapp.genomicsengland.co.uk>) are listed in [Supplementary Table S1](#).

In addition to rare pathogenic variants, common genetic variants or polygenic scores may become appropriate for clinical reporting if they are shown to alter patient management, indicate need for surveillance for progression or associated comorbidities, or inform familial screening.⁸⁸ In complex diseases, the current best candidates for reporting include *APOL1* risk alleles,^{89,90} genetic risk score for membranous nephropathy based on *PLA2R1*, *NFKB1*, *IRF4*, and *HLA* risk alleles,¹⁹ extremes of a polygenic risk score for eGFR,⁹¹ and pharmacogenetic variants that are informative about risk of adverse events, pharmacokinetics, and pharmacodynamics for specific drugs, some of which may be especially relevant to CKD patients (for example, azathioprine, tacrolimus, warfarin, clopidogrel, simvastatin, voriconazole, and allopurinol). However, we currently lack evidence for actionability for polygenic scores—that is, evidence that reporting can improve clinical outcomes.

APOL1 presents a special case in clinical nephrology because biallelic inheritance of 2 common variants in this gene, which present at high frequency in some populations of African ancestry, increases risk for several kidney disorders.^{89,90} Potential benefits for *APOL1* screening include improved risk stratification and opportunities for education. However, only a minority of patients with *APOL1* risk genotypes develop nephropathy, and currently no data support early intervention in asymptomatic individuals to reduce future risk of disease. Potential drawbacks to screening include potential for anxiety, stigma, or apathy, and the lack of evidence-based interventions.^{92,93} Combined, these drawbacks could lead to misunderstanding among patients, mistrust of the medical system, and perceived or real racial bias, given that *APOL1* risk variants are found predominantly in those with African ancestry. On the other hand, the failure to offer a test that could be most informative in a specific ancestry group also could be perceived as bias. For transplant patients, *APOL1* screening could prevent harm to living donors and satisfy recipients' right to know, but screening could also reduce rates of living donation, waste deceased donor kidneys, and exacerbate organ shortage. The *APOL1* Long-term Kidney Transplantation

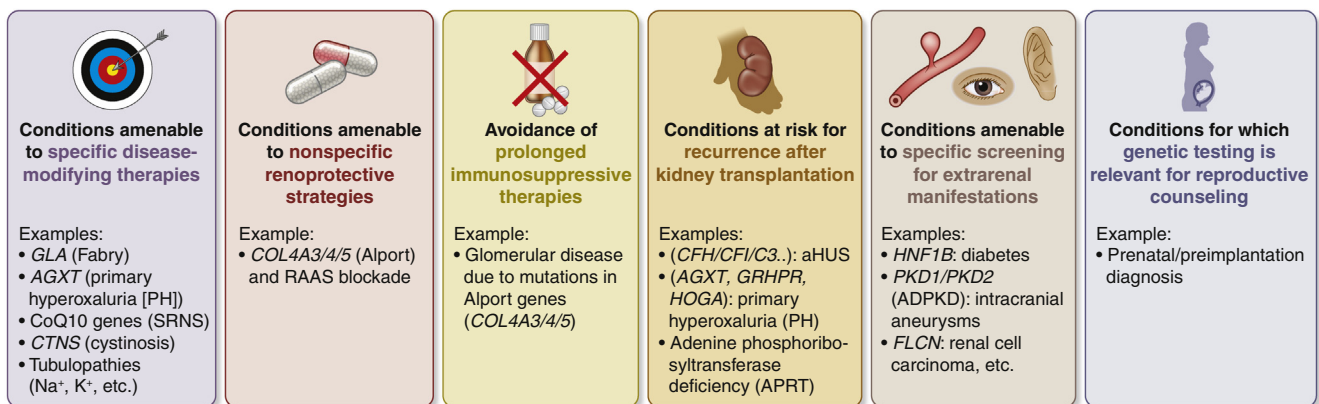


Figure 4 | Actionable genes in kidney diseases. Actionability refers to the potential for genetic test results to lead to specific clinical actions for prevention or treatment of a condition, supported by recommendations based on evidence. ADPKD, autosomal dominant polycystic kidney disease; aHUS, atypical hemolytic uremic syndrome; RAAS, renin–angiotensin–aldosterone system; SRNS, steroid-resistant nephrotic syndrome.

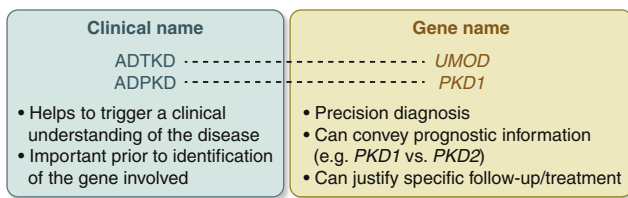


Figure 5 | Unified disease terminology. Two-part (“dyadic”) naming comprises both the clinical condition and the gene name. An example is autosomal dominant tubulointerstitial kidney disease (ADTKD), with ADTKD followed by reference to the underlying genetic defect, as in ADTKD-UMOD. ADPKD, autosomal dominant polycystic kidney disease.

Outcomes Network (APOLLO) study, which is in progress and expected to end in 2023, is prospectively evaluating the impact of *APOL1* risk alleles on donor and recipient outcomes.⁹⁴ Moreover, the initiation of genotype-driven clinical trials may change the approach to diagnostic testing for *APOL1* and other genetic disorders. These considerations emphasize the importance of further research into the usefulness of *APOL1* testing.

Reporting and terminology standards

Differences in how diagnostic laboratories evaluate and report variants pose a significant challenge in molecular diagnosis. Therefore, standardization of evaluation and reporting among different laboratories and countries is an agreed-on key priority. The determination regarding pathogenicity is a semi-quantitative process that takes into account variant allele frequency, predicted impact on protein function, and prior reports of occurrence with disease. The ACMG and the Association for Molecular Pathology (AMP) published standards and guidelines for the interpretation of sequence variants.⁹⁵ These guidelines are reviewed periodically and refined by the ClinGen Initiative to reduce discrepancies in variant interpretation among laboratories and clinicians.

The ACMG criteria classify variants into 1 of 5 tiers, with tiers 4 and 5 (i.e., likely pathogenic and pathogenic) classified as diagnostic variants.⁹⁵ All variant classes can be later upgraded or downgraded based on novel information or interpretation, perhaps necessitating periodic review of clinical genetic reports. However, the abundance of class 3 VUS has created a particular challenge and urgency for improving evaluation and reporting. The definition and relevance of VUS may be unclear to physicians or patients, causing incorrect assignment of diagnoses and/or psychological distress to patients and families. This situation necessitates proper communication with patients to inform and educate them about the possibility of VUS, in which case familial segregation analysis might be recommended. Additionally, VUS should be reported only after interdisciplinary contact between the clinician and geneticist has occurred.⁹⁶ Future reinterpretation of variants can be facilitated by diagnostic reports that provide detailed description of ACMG classification criteria that were applied at the time of reporting. Although no guidelines exist currently, incidental carrier

status for autosomal recessive inheritance is not routinely reported in standard diagnostic reports. Guidelines for systematic reporting of these variants should be developed. Heterozygosity associated with a mild phenotype is increasingly recognized in human genetics, for example, for *COL4A3/COL4A4* variants.⁹⁷

Unified disease terminology. The consensus among conference participants was that establishing a unified disease terminology that takes into account genetic disease nomenclature is an important goal for the community. In support of unified, precise disease terminology, a suggested approach is 2-part (“dyadic”) naming, comprising both the clinical condition and the gene name (Figure 5), although some controversy regarding this approach remains.^{98,99} An important example is adoption of 2-part naming in autosomal dominant tubulointerstitial kidney disease (ADTKD), in which ADTKD is followed by reference to the underlying genetic defect, such as in ADTKD-UMOD and ADTKD-MUC1.¹⁰⁰ Two-part names provide flexibility, in that some users (patients/clinicians) can use the first part only (ADTKD), and others (patients/clinicians/researchers) can use the whole name (ADTKD-UMOD). When clinical presentation is unspecific, or very heterogeneous, use of the gene name followed by “kidney disease” (e.g., *PAX2*-kidney disease) is encouraged. Potential limits to this approach include the possibility of classifying a patient with a benign prognosis as having a potentially progressive disorder, as well as the challenge of adding a second or gene name to conditions already described in International Classification of Disease codes. In this regard, participants of this KDIGO Controversies Conference did not reach consensus regarding renaming of traditional disease terms, such as Alport Syndrome.

Genomic discovery and implications for chronic kidney diseases

As demonstrated by the first GWAS for eGFR, common genetic variants that are associated with complex kidney traits usually have small effects and therefore require very large sample sizes for discovery.¹⁰¹ Accordingly, success has been limited in identifying common kidney disease susceptibility variants in individual observational studies of adult^{102–105} and pediatric^{106–108} CKD. Conference participants therefore recognized the importance of collaborative consortia, such as the Chronic Kidney Disease Genetics Consortium (CKDGen),^{11,109} Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium,^{66,110} International Genetics & Translational Research in Transplantation Network (iGeneTRaiN),¹¹¹ and Continental Origins and Genetic Epidemiology Network (COGENT) Kidney Consortium,^{112,113} that aggregate and harmonize genetic and phenotypic data across multiple studies for combined genetic discovery. In addition to enlarging sample size and providing a platform for replication studies, expanding consortia to international sites can enable studies of more ancestrally and geographically diverse populations. For more specific but less

frequent primary kidney disorders, such as IgA nephropathy, membranous nephropathy, and steroid-sensitive nephrotic syndrome, aggregating multiple international case-control cohorts is even more important to assure adequate power. Additionally, more diverse ancestral composition of analyzed cohorts facilitates fine-mapping of GWAS loci, enables discovery of ancestry-specific effects, and assures broader generalizability of genetic findings.

The identification of causal genes and variants underlying GWAS associations and definition of their pleiotropic effects are recognized as important challenges in the field. Examples such as *UMOD*, the locus with the strongest common variant association with CKD,⁶⁶ support the existence of a spectrum of risk variants, from monogenic to complex. No examples currently exist of successful translation of insights from GWAS in CKD to new therapies, but the discovery of the *MYH9* locus,^{114,115} followed by the identification of *APOL1* as the causal gene,⁶⁹ refinement of nephrotoxic mechanisms of *APOL1* risk variants,⁸⁹ and an ongoing phase IIa study of a small molecule *APOL1* inhibitors (ClinicalTrials.gov identifier NCT04340362) represent promising steps toward that end.

Conference participants recognized the emerging importance of electronic health record (EHR)-based genetic research for linking genetic information with a wide range of laboratory parameters and medical conditions. EHR-linkage is possible in various settings, ranging from existing biobanks in research settings, hospitals, or healthcare systems to entire countries, such as Iceland, Estonia, and Finland. Examples of EHR-linked biobanks, institutions, healthcare systems, and country-wide efforts are UK Biobank,¹¹⁶ Million Veteran Program (MVP),¹¹⁷ HUNT Biobank,¹¹⁸ deCODE,¹¹⁹ FinnGen,⁶⁰ BioBank Japan (BBJ),¹²⁰ Vanderbilt University biobank (BioVU),¹²¹ Michigan Genomics Initiative (MGI),¹²² Electronic Medical Records and Genomics (eMERGE) Network,¹²³ and the National Institutes of Health *All of Us* Research Program.¹²⁴ The development of standardized, scalable, and portable computable phenotypes is time consuming and represents many challenges,¹²⁵ but it can empower future genetic studies by automated identification of kidney-disease patients in large EHR databases.^{26,126} Notably, just as important as accurately defining those with a disease is defining those without to serve as healthy controls in genetic studies, which is often harder. We envision that computable phenotyping can be used to find patients with or without CKD, hypertension, kidney stones, and glomerular disease, as well as patients who have received a kidney biopsy or kidney transplant. In nephrology, computable phenotyping is underway,^{26,127–129} with CKD phenotyping perhaps best positioned for widespread implementation, given the availability of new algorithms based on International Classification of Diseases codes and laboratory values that are routinely measured in clinical practice.^{26,126}

In addition to genomic discovery, EHR-linked genetic research may allow for recontacting of patients with a specific genotype for detailed clinical and molecular studies. Linking

of EHR and genetic data also can be used to investigate pleiotropic associations of genetic variants originally discovered for a specific condition (e.g., *APOL1* or *UMOD*) with additional traits captured in medical records using phenome-wide association approaches.^{14,26,42,130} Such studies can be further complemented with Mendelian randomization methods to clarify associations between genetic variants, biomarkers, and phenotypes.¹³¹

Despite the large size of consortia and EHR-linked studies, certain groups of patients are still underrepresented in genetic research. For instance, the paucity of pediatric patients with genetic information has limited both longitudinal phenotype analyses from childhood to adulthood and the ability to identify genetic drivers of kidney diseases or traits of childhood. Also, there is urgent need to expand ancestral diversity of participants in genetic studies, specifically aiming to increase the representation of non-European populations.¹³² Additional challenges include harmonizing data for rare kidney conditions that necessitate aggregating cases from across several biobanks and EHRs; identifying ancestry-matched controls for case-control analyses; handling of missing data; and harmonizing genotypes in the presence of different types of available genetic data.^{133,134}

Partnerships between academic labs and industry allow efficient exchange of ideas and resources to promote investigation of disease mechanisms, biomarkers, and therapeutic targets. Such partnerships can enable academic labs, biobanks, and institutions and healthcare systems to conduct large-scale multi-omic studies that would not be feasible with only support from internal funds or extramural grants, and facilitate follow-up studies to “functionalize” key genes or genetic variants. Successful partnerships must achieve a balance between companies’ incentive to invest and academics’ freedom in research and publishing. Key principles and processes, such as intellectual property, publications, and data sharing and access, also must be aligned. These partnerships have been particularly valuable for generating functional genomic data from primary kidney tissues and allow for rapid implementation of new methods.^{135–138} Generation of additional such data from primary kidney tissue and cell types should continue to be a research priority because the kidney is underrepresented in many existing public databases, including the Encyclopedia of DNA Elements (ENCODE),¹³⁹ Roadmap Epigenomics,¹⁴⁰ and the Genotype-Tissue Expression (GTEx) project.¹⁴¹ The Kidney Precision Medicine Project (KPMP)¹⁴² and similar new initiatives aim to address some of these important gaps by generating and harmonizing new multidimensional molecular data for human kidney tissue in health and disease.

Polygenic scores. Polygenic scores (PGSs) are based on the results of GWAS and aggregate the effects of trait- or disease-associated variants across the genome. PGSs capture a greater proportion of genetic variance compared to individual SNPs and potentially may be useful to risk-stratify populations, enhance screening, and ultimately inform

diagnosis, prognosis, and/or treatment. PGSs have been shown to modify the penetrance of monogenic variants for hypercholesterolemia, hereditary breast and colon cancer, and obesity,^{32,33} although this effect has not yet been examined for kidney diseases. PGSs for kidney disease can be constructed using a smaller set of genome-wide significant SNPs only, such as a 147-SNP score for eGFR (odds ratio of ~2 for individuals in the highest 10% of the score)¹³ or a 5-SNP score for membranous nephropathy (odds ratio of >20 for those in the highest 10% of the score),¹⁹ or by using genome-wide scores with hundreds of thousands of variants, such as the UK Biobank score for CKD.⁹¹ Currently, most scores are derived from European populations and do not include rare or population-specific variation, potentially creating a new health disparity between individuals of European descent and others.¹³² Given that scores are constructed from GWAS for complex traits and diseases, they may reflect heterogeneous mechanisms and therefore may not necessarily point to targeted interventions.

Conference participants agreed that before applying PGSs in clinical nephrology, more research is needed to derive the most accurate and cosmopolitan scores for kidney disease. Also necessary are the following: proof of clinical utility in surveillance, diagnosis, prognosis, or treatment of kidney disease; a better understanding of dependence on the clinical context, including disease stage, ancestry, sex, or demographics¹⁴³; and cost-effectiveness and added value beyond standard clinical risk factors. PGS computation needs to be robust, open-source, and able to be incorporated into points of care. Quality standards for PGSs have recently been defined by ClinGen,^{144–146} providing a framework for evaluating clinical translation and utility.

Achieving implementation in clinical medicine

Clinical knowledge. Often, insufficient experience and knowledge are major barriers for implementing genetic evaluation in nephrology practice. To ensure equitable access to genetic testing, all nephrologists should have a sufficient knowledge base for discerning which patients would benefit from genetic testing, and at minimum, be able to collect personal and family histories. Although optimally all nephrologists would be able to recommend screening for at-risk family members if applicable, would conceptually understand types of genetic tests, including their risks and benefits, and would remain aware of local regulations around genetic testing, those who lack experience in these domains should collaborate with a clinical geneticist and/or a genetic counselor. In addition, reporting of positive genetic results to patients necessitates individual and family counseling and referrals. Hence, a multidisciplinary approach is key for successfully implementing use of genetics in the clinic.

Conference participants recognized workforce education as a critical need. Genetics is currently not part of the nephrology fellowship curriculum in the US,¹⁴⁷ and

indeed, fellows report lacking competency in genetic renal disease.¹⁴⁸ Similarly, in Australia, less than half of nephrologists feel confident in using results of genomic testing in clinical practice.¹⁴⁹ No genetics core competency guidelines are in place for nephrologists, nor are guidelines for evaluating competencies for clinical genetic consent and return of results. Based on published data and information,¹⁵⁰ a compiled list of core competencies expected from nephrologists at different levels of expertise can be found in [Supplementary Table S2](#). These gaps can be remedied by including more robust genetics curricula in medical school, residency, and fellowship training. Education for current practicing nephrologists can be achieved via workshops at national and international societies, continuing medical education, review papers in nephrology journals, and introduction of clinical genetic questions to relicensing tests.¹⁵¹ One can also envision an advanced training or subspecialty track in genetic nephrology, similar to transplant, oncology, or glomerular diseases subspecialization. [Supplementary Table S1](#) provides an overview of clinical genetics web resources to aid nephrologists.

Clinical practice. Centers of expertise are sites where patients can receive comprehensive, coordinated care from a multidisciplinary team that includes a relatively small number of nephrologists with a high skill set for genetic diagnosis ([Figure 6](#)). These centers also play an important role in training and research. Centers of expertise, or reference, are concentrated in Europe, with ERKNet constituting a consortium of more than 30 centers in 12 countries, supported by the European Union. In most regions of the globe, including the US, no centralized accreditation mechanisms are in place for developing centers of expertise or reference. The establishment of such centers can facilitate standardized variant interpretation, identify “actionable” genes associated with kidney diseases, train the future generation of physicians with dual expertise in genetics and nephrology, develop guidelines for referral and testing of patients with kidney diseases, disseminate implementation knowledge, and develop collaborative research projects and clinical trials for rare disorders.

Cost and access. Often, genetic testing is not affordable for either patients or healthcare systems. In regions with cost coverage or reimbursement, access can still be unequal, as genetic testing is based on clinical presentation, and obtaining coverage is often easier in children than in adults. Many countries do have genetic protection acts, laws, or regulations to ensure equitable access to genetic testing without fear of discrimination. However, legislation alone is not always sufficient for allaying patient concerns about the potential for prejudice.

Logistically, remote sample collection and telemedicine have potential for increasing access to genetic counseling. However, adequate physical evaluation and identification of

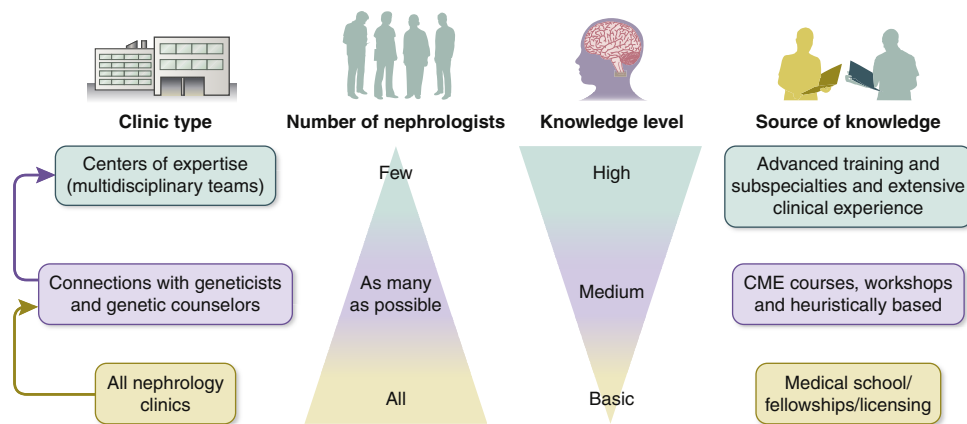


Figure 6 | Proposed organization for implementing genetics in nephrology. Within a health system, multiple center types, provider specialties, and education strategies are needed for optimal implementation of genetics in nephrology. A 3-tiered organization model includes the following: (i) a basic, common level of knowledge in genetics among all nephrologists; (ii) clinical connections between nephrologists and geneticists and genetic counselors; and (iii) centers of expertise where nephrologists with genetic expertise collaborate with geneticists and genetic counselors. CME, continuing medical education.

extrarenal manifestations can be more complicated or impossible with telemedicine. In addition, although the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has accelerated the deployment of telemedicine across many health systems, not all patients and physicians are comfortable with remote, video-based communications.

For most genetic conditions, we lack large-scale cost-effectiveness analyses to demonstrate the benefits of genetic testing. Recent data suggest that genetic testing has a high diagnostic yield in patients with CKD of unknown etiology and may reduce costly diagnostic workups, hopefully increasing the coverage of genetic testing for those patients.^{3,8} Also important is the demonstration of the clinical value of genetic testing beyond diagnosis, such as its impact

on long-term outcomes and health economics. A comparison of the cost-effectiveness of genetic testing in nephrology across different healthcare coverage systems could provide key insights and an evidence base for expanding testing.

Patient voice. Patient engagement is vital for successful treatment and advances in research. To advocate for their own genetic testing, patients need to have an awareness of and education regarding genetics and kidney disease and the relative benefits and risks of genetic testing.¹⁵² The complex ethical, psychosocial, and familial implications for genetic testing, including presymptomatic testing, can make decision-making challenging and require an understanding of patient values, goals, and priorities.¹⁵³ To engage and activate patients and patient communities, educational content needs to be

Table 5 | Recommended practices for value-based measures of implementation and quality assurance of clinical genetics in nephrology

Measure nephrologist adoption of genetic testing and appropriate referral to genetic testing
Measure nephrologist utilization of genetic results (to determine if appropriate changes in diagnosis and care have occurred)
Define disease-specific outcomes that can be measured
<ul style="list-style-type: none"> • Development of kidney failure • Rate of kidney disease progression • Change in treatment • Access to genetically stratified clinical trials • Donor risk evaluation, or deceased-donor organ evaluation • Recipient risk evaluation (e.g., improved matching, customized immunosuppression, etc.) • Utilization of information for family planning • Patient-reported outcome (quality of life, etc.) • Hospitalization, cardiovascular outcomes, mortality • Diagnosis of at-risk family members
Define and measure potential harmful impacts of genetic testing (e.g., wrongful impact on change of treatment)
Define audits/assessments for centers that offer genetic testing in nephrology as quality-assurance activity
Potentially apply USPSTF and EGAPP methods to analyze the implementation of genetic testing for kidney diseases

USPSTF, United States Preventive Services Task Force; EGAPP, Evaluation of Genomic Applications in Practice and Prevention.

accessible and sensitive to patients in terms of culture, language, and literacy, as well as be shared across multiple platforms.¹⁵⁴

The topics of race and ancestry have been widely debated in genetics, as well as nephrology.^{155–158} In specific terms, race is a social, categorical construct, whereas ancestry is based on inherited genetic variants without categorization. In principle, genetics research is agnostic to race,¹⁵⁷ and identifying disease-causing variants could obviate reliance on race or ancestry as a proxy for probability of carrying a risk allele.^{132,158}

Within nephrology, patient-reported outcome measures can provide doctors, investigators, and policymakers with important insights into patient symptoms and experiences that cannot be identified through laboratory or imaging studies alone.¹⁵⁹ Research communities that engage with patients and include the patient voice can better advocate for more research and development in rare kidney diseases.

Research in implementation. Evidence-based frameworks for evaluating quality of care in genetic testing have been put forth by ACMG,¹⁶⁰ ERKNet, and others.^{161,162} These frameworks cover different methods for evaluating the analytic and clinical validity, as well as the clinical utility, of genetic tests. Nephrology outcomes used in clinical trials have included those that are disease-specific or represent more general longer-term outcomes, such as kidney failure, cardiovascular death, or mortality, which require large datasets. Yet this space is evolving, as demonstrated by development of novel trial designs using Bayesian methodology, inclusion of patient-reported outcomes, and additional economic evaluation of genetic risk. Steps for expanding measures to best inform value-based implementation and quality assurance of clinical genetics in nephrology are listed in [Table 5](#). This large and critical space underpins clinical translation and mainstreaming, with much research and work anticipated in the coming years.

Conclusions

This KDIGO Controversies Conference on Genetics in Chronic Kidney Disease discussed many technical, logistical, ethical, and/or research questions related to the definition and epidemiology of monogenic and complex kidney diseases, applications of genetic findings in clinical medicine, and utilization of genomics for defining and stratifying CKD. Identified areas of consensus and future research priorities provide a roadmap toward realizing the promises of genomic medicine for nephrology.

APPENDIX

KDIGO Conference Participants

Anna Köttgen¹, Emilie Cornec-Le Gall², Jan Halbritter^{3,4}, Krzysztof Kiryluk⁵, Andrew J. Mallett^{6,7,8,9}, Rulan S. Parekh^{10,11,12}, Hila Milo Rasouly⁵, Matthew G. Sampson^{13,14,15}, Adrienne Tin¹⁶, Corinne Antignac^{17,18}, Elisabet Ars¹⁹, Carsten Bergmann^{20,21}, Anthony J. Bleyer²², Detlef Bockenhauer^{23,24}, Olivier Devuyst^{25,26,27}, Jose C. Florez^{28,29,30}, Kevin J. Fowler³¹, Nora Franceschini³², Masafumi Fukagawa³³, Daniel P. Gale^{24,34}, Rasheed A. Gbadegesin³⁵, David B.

Goldstein^{36,37}, Morgan E. Grams³⁸, Anna Greka^{14,15}, Oliver Gross³⁹, Lisa M. Guay-Woodford⁴⁰, Peter C. Harris⁴¹, Julia Hoefele⁴², Adriana M. Hung⁴³, Nine V.A.M. Knoers⁴⁴, Jeffrey B. Kopp⁴⁵, Matthias Kretzler^{46,47}, Matthew B. Lanktree^{48,49}, Beata S. Lipska-Ziętkiewicz⁵⁰, Kathleen Nicholls⁵¹, Kandai Nozu⁵², Akinlolu Ojo⁵³, Afshin Parsa^{54,55}, Cristian Pattaro⁵⁶, York Pei⁵⁷, Martin R. Pollak⁵⁸, Eugene P. Rhee⁵⁹, Simone Sanna-Cherchi⁶⁰, Judy Savage⁶¹, John A. Sayer^{62,63,64}, Francesco Scolari^{65,66}, John R. Sedor^{67,68,69}, Xueling Sim⁷⁰, Stefan Somlo^{71,72}, Katalin Susztak^{73,74}, Bamidele O. Tayo⁷⁵, Roser Torra⁷⁶, Albertien M. van Eerde⁷⁷, André Weinstock⁷⁸, Cheryl A. Winkler⁷⁹, Matthias Wuttke¹, Hong Zhang^{80,81}, Jennifer M. King⁸², Michael Cheung⁸³, Michel Jadoul⁸⁴, Wolfgang C. Winkelmayer⁸⁵ and Ali G. Gharavi⁵

¹Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany; ²Univ Brest, INSERM UMR 1078, GGB, CHU Brest, Brest, France; ³Division of Nephrology, Department of Internal Medicine, University Hospital Leipzig, Leipzig, Germany; ⁴Department of Nephrology and Medical Intensive Care, Charité—Universitätsmedizin Berlin, Berlin, Germany; ⁵Division of Nephrology and Center for Precision Medicine and Genomics, Department of Medicine, Columbia University Irving Medical Center, New York, New York, USA; ⁶Institute for Molecular Bioscience (IMB), The University of Queensland, Brisbane, Queensland, Australia; ⁷Department of Nephrology, Townsville University Hospital, Townsville, Queensland, Australia; ⁸College of Medicine, James Cook University, Townsville, Queensland, Australia; ⁹KidGen Collaborative, Australian Genomics Health Alliance, Melbourne, Victoria, Australia; ¹⁰Division of Nephrology, Department of Pediatrics and Medicine, Hospital for Sick Children, University Health Network, University of Toronto, Toronto, Ontario, Canada; ¹¹Division of Nephrology, Women's College Hospital, Toronto, Ontario, Canada; ¹²Dalla Lana School of Public Health, and Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; ¹³Division of Nephrology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA; ¹⁴Kidney Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA; ¹⁵Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; ¹⁶Division of Nephrology, University of Mississippi Medical Center, Jackson, Mississippi, USA; ¹⁷Laboratory of Hereditary Kidney Disease, Imagine Institute, INSERM U1163, Université de Paris, Paris, France; ¹⁸Department of Genetics, Necker Hospital, APHP, Paris, France; ¹⁹Molecular Biology Laboratory, Fundació Puigvert, Instituto de Investigaciones Biomédicas Sant Pau (IIB-Sant Pau), Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain; ²⁰Medizinische Genetik Mainz, Limbach Genetics, Mainz, Germany; ²¹Department of Nephrology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany; ²²Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; ²³Renal Unit, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK; ²⁴Department of Renal Medicine, University College London, London, UK; ²⁵Division of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ²⁶Institut de Recherche Expérimentale et Clinique, UCLouvain, Brussels, Belgium; ²⁷Department of Physiology, Mechanisms of Inherited Kidney Disorders Group, University of Zurich, Zurich, Switzerland; ²⁸Programs in Metabolism and Medical & Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA; ²⁹Diabetes Unit and Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; ³⁰Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA; ³¹The Voice of the Patient, Inc., Elmhurst, Illinois, USA; ³²Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina, USA; ³³Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; ³⁴Rare Renal Disease Registry, UK Renal Registry, Bristol, UK; ³⁵Department of Pediatrics, Division of Nephrology, Duke University Medical Center, Durham, North Carolina, USA; ³⁶Institute for Genomic Medicine, Columbia University, New York, New York, USA; ³⁷Department of Genetics and Development, Columbia University, New York, New York, USA; ³⁸Department of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; ³⁹Clinic for Nephrology and Rheumatology, University Medical Center Göttingen, Göttingen, Germany; ⁴⁰Center for Translational Science, Children's National Health System, Washington, DC, USA; ⁴¹Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; ⁴²Institute of Human Genetics, Klinikum rechts der Isar, Technical University of Munich, School of Medicine, Munich, Germany; ⁴³VA Tennessee Valley Healthcare System, Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt Center for Kidney Disease, Vanderbilt Precision Nephrology Program, Vanderbilt University Medical Center, Nashville, Tennessee, USA; ⁴⁴Department of Genetics, University Medical Center Groningen, Groningen, The Netherlands; ⁴⁵Kidney Disease Section, National Institute of Diabetes and Digestive and

Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, Maryland, USA; ⁴⁶Department of Internal Medicine, Division of Nephrology, University of Michigan, Ann Arbor, Michigan, USA; ⁴⁷Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA; ⁴⁸Division of Nephrology, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada; ⁴⁹Department of Medicine, McMaster University, Hamilton, Ontario, Canada; ⁵⁰Rare Diseases Centre and Clinical Genetics Unit, Department of Biology and Medical Genetics, Medical University of Gdansk, Gdansk, Poland; ⁵¹Department of Nephrology, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia; ⁵²Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan; ⁵³University of Kansas School of Medicine, Kansas City, Kansas, USA; ⁵⁴Division of Kidney, Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA; ⁵⁵Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA; ⁵⁶Eurac Research, Institute for Biomedicine (affiliated with the University of Lübeck), Bolzano, Italy; ⁵⁷Division of Nephrology, University Health Network, Toronto, Ontario, Canada; ⁵⁸Division of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; ⁵⁹Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; ⁶⁰Division of Nephrology, Department of Medicine, Columbia University, New York, New York, USA; ⁶¹Department of Medicine, Melbourne and Northern Health, The University of Melbourne, Parkville, Victoria, Australia; ⁶²Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK; ⁶³The Newcastle upon Tyne NHS Hospitals Foundation Trust, Newcastle upon Tyne, UK; ⁶⁴NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne, UK; ⁶⁵Division of Nephrology, ASST Spedali Civili di Brescia, Brescia, Italy; ⁶⁶Department of Medical and Surgical Specialties, University of Brescia, Brescia, Italy; ⁶⁷Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA; ⁶⁸Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA; ⁶⁹Department of Physiology and Biophysics, Case Western Reserve University, Cleveland, Ohio, USA; ⁷⁰Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore; ⁷¹Department of Internal Medicine, Yale University, New Haven, Connecticut, USA; ⁷²Department of Genetics, Yale University, New Haven, Connecticut, USA; ⁷³Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; ⁷⁴Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; ⁷⁵Department of Public Health Sciences, Loyola University Chicago, Maywood, Illinois, USA; ⁷⁶Inherited Kidney Disorders, Nephrology Department, Fundació Puigvert, IIB-Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁷⁷Department of Genetics, University Medical Center Utrecht, Utrecht, The Netherlands; ⁷⁸Alport Syndrome Foundation, Phoenix, Arizona, USA; ⁷⁹Basic Research Laboratory, Molecular Genetic Epidemiology Section, Frederick National Laboratory for Cancer Research, National Cancer Institute, Frederick, Maryland, USA; ⁸⁰Renal Division, Peking University First Hospital, Beijing, China; ⁸¹Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, China; ⁸²August Editorial, Durham, North Carolina, USA; ⁸³KDIGO, Brussels, Belgium; ⁸⁴Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium; ⁸⁵Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

Conference Co-Chairs: Anna Köttgen, Ali G. Gharavi

Steering Committee Members: Emilie Cornec-Le Gall, Jan Halbritter, Krzysztof Kiryluk, Andrew J. Mallett, Rulan S. Parekh, Hila Milo Rasouly, Matthew G. Sampson, Adrienne Tin

DISCLOSURE

AK has declared receiving research support from the German Research Foundation (DFG) Project-ID 431984000 - SFB 1453. EC-LG has declared receiving research support from Agence Nationale de la Recherche and Filière Maladies Rares Rénales. RSP has declared receiving research support from the Canadian Institutes of Health Research, National Institutes of Health (NIH), and Ontario Ministry. MGS has declared being a board member for Natera; receiving consultant fees from Janssen and Maze; and research support from the NIH. AT has declared receiving fees for speakers bureaus from the University of Virginia, Division of Nephrology Grand Round. CA has declared having a patent on the *NPHS2* gene encoding podocin (USO07388086B2) licensed to Athena Diagnostics Inc (USA). CB has declared being a board member for Medizinische Genetik Mainz and Limbach Genetics GmbH; receiving consultant fees from Alexion, Kyowa Kirin, PTC, and Sanofi; employment from Medizinische Genetik Mainz and Limbach Genetics GmbH;

fees for expert testimony from Alexion, Kyowa Kirin, PTC, and Sanofi; research support from Limbach Gruppe University of Freiburg; fees for speakers bureaus from Alexion, Kyowa Kirin, PTC, and Sanofi; fees for manuscript preparation from PTC; and fees for the development of education presentations from Alexion, Kyowa Kirin, PTC, and Sanofi. AJB has declared receiving consultant fees from Horizon and fees for speakers bureaus from Natera. DB has declared receiving consultant fees from Avrobio and fees for speakers bureaus from Advicenne and Recordati. JCF has declared receiving consultant fees from AstraZeneca; research support from NovoNordisk; and fees for speakers bureaus from AstraZeneca, Merck, and NovoNordisk. KJF has declared receiving consultant fees from Akebia, Bayer, eGenesis, Gilead, Hansa BioPharma, Natera, Palladio Biosciences, Responsum CKD, Talaris Therapeutics, Travers Therapeutics, and Veloxis. NF has declared receiving research support from the NIH. MF has declared receiving research support from Kyowa Kirin and fees for speakers bureaus from AstraZeneca and Kyowa Kirin. DPG has declared receiving consultant fees from Alexion, Atlas Venture, Judo Bio, and Reata; fees for speakers bureaus from Travers Therapeutics; and being a trustee for AlportUK. RAG has declared receiving consultant fees and research support from Reata and Travers Therapeutics. DBG has declared receiving consultant fees from AstraZeneca, Gilead Sciences, Goldfinch Bio, and Gossamer Bio; employment from Actio Biosciences; and stock from Actio Biosciences, Apostle Inc., Praxis Therapeutics, and Q-State Biosciences. AG has declared receiving consultant fees from Atlas Venture, Biogen, Blackstone, Bristol Myers Squibb, Cycleron, Goldfinch Bio, Kyn Therapeutics, Lycia Therapeutics, Maze, MPM, Novartis, Ono Pharmaceutical, Q32 Bio, and Patient Square Capital. OG has declared receiving consultant fees from Bayer AG, Boehringer Ingelheim, Codon-X Therapeutics Inc., Galapagos, Novartis, Ono Pharmaceutical Co. Ltd., Reata, Roche, and Sanofi US Services Inc./Genzyme/Regulus Therapeutics; research support from Bayer AG (Germany), Boehringer Ingelheim (Germany), German Ministry of Education and Research, and German Research Foundation; and travel expenses from AstraZeneca. LMG-W has declared receiving consultant fees from Natera and Otsuka. PCH has declared receiving consultant fees from Mitobridge, Otsuka, Regulus, and Vertex; and research support from Acceleron, Jemincare, Navitor, and Otsuka. AMH has declared being a board member for Vertex and research support from Veterans Health CSR&D Merit Grant CX001897. NVAMK has declared receiving research support from Health Holland. JBK has declared receiving research support from the NIH Intramural Research Program. MK has declared receiving consultant fees from Astellas, Janssen, and Poxel; and research support from amfAR, Angion Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Certa, the Chan Zuckerberg Initiative, Chinook, Eli Lilly, European Union Innovative Medicine Initiative, Gilead, Goldfinch Bio, Ionis Pharmaceuticals, Janssen, JDRF, Moderna, NovoNordisk, Regeneron, RenalytixAI, and Travers Therapeutics. MBL has declared receiving consultant fees from Bayer, Otsuka, Reata, and Sanofi Genzyme; and fees for speakers bureaus from Bayer, Otsuka, Reata, and Sanofi Genzyme. BSL-Z has declared receiving fees for speakers bureaus from Takeda Pharma PL and fees for the development of educational presentations from Takeda Pharma PL. KNI has declared being a board member for Amicus Australian, Sanofi Genzyme, and Takeda; receiving research support from Genzyme and Takeda; and fees for the development of educational presentations from Takeda. KNo has declared receiving fees for speakers bureaus from Daiichi Sankyo, Kyowa Kirin, and Sumitomo Dainippon Pharma. AO has declared receiving consultant fees from Vertex. YP has declared receiving consultant fees from Maze, Otsuka, Reata, and Sanofi; and fees for the development of educational presentations from Otsuka. MRP has declared being a board member for Vertex; receiving consultant fees from InxMed and Vertex, and research support from Vertex; and stock/stock options from Apo1Bio LLC. SS-C has declared receiving fees for speakers bureaus from Travers Therapeutics. JRS has declared being a board member for Kidney X Innovation Accelerator; receiving consultant fees from Boehringer Ingelheim and Maze; and research support from Calliditas, Novartis, and Vertex. SS has declared receiving consultant fees from Goldfinch Bio and Vertex. KS has declared being a board member for Jnana; receiving consultant fees from AstraZeneca, Bayer, GSK, Jnana, Maze, Otsuka, Pfizer, and Ventus; and research support from Bayer, Boehringer Ingelheim, Gilead, GSK, Jnana, Maze, NIH, Novartis, Novo Nordisk, and Regeneron. RT has declared receiving fees for speakers bureaus from Amicus, Otsuka, Sanofi, and Takeda. AMvE has declared receiving research support from the Dutch Kidney Foundation (#18OKG19) and VriendenWKZ and being on Work Groups for ERKNet (project ID No 739532) and ERA-EDTA. CAW has declared receiving federal funds from the National Cancer Institute, NIH, under contract 75N91019D00024; and support in part by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research. JMK has declared receiving fees for manuscript preparation Bayer Pharmaceuticals,

Emergent Biosciences, and Gilead Sciences. MJ declared receiving consultant fees from Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius Medical Care Asia Pacific, Mundipharma, and Vifor Fresenius Medical Care; fees for speakers bureaus from Astellas, AstraZeneca, Mundipharma, and Vifor Fresenius Medical Care; research support from Amgen; and future research support from AstraZeneca. WCW declared receiving consultant fees from Akebia/Otsuka, AstraZeneca, Bayer, Janssen, Merck, Reata, and Relypsa; future consultant fees from Boehringer Ingelheim; and research support from the NIH. AGG has declared receiving consultant fees from Actio Biosciences, Natera, Novartis, and Trave; research support from Natera and the Renal Research Institute; and fees for the development of educational presentations from Fresenius and Sanofi Genzyme. Several authors of this paper are members of the European Rare Kidney Disease Reference Network (ERKNet)—project ID No 739532. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

This conference was sponsored by KDIGO and supported in part by unrestricted educational grants from American Kidney Fund, AstraZeneca, Chinook Therapeutics, Natera, Otsuka, Reata Pharmaceuticals, and Sanofi. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

AUTHOR CONTRIBUTIONS

All Steering Committee Members contributed equally. The conference planning and the drafting and critical revision of this manuscript were performed by the Steering Committee Members, the Conference Co-Chairs, and Jennifer King, with important intellectual content contributions provided by the remaining authors.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Table S1. Online clinical genetics resources to aid nephrologists. Adapted with permission from *Annals of Internal Medicine*, Milo Rasouly H, Aggarwal V, Bier L, Goldstein DB, Gharavi AG. Cases in precision medicine: genetic testing to predict future risk for disease in a healthy patient, volume 174, issue 4, pages 540–547, Copyright © 2021 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.¹⁵¹

Table S2. Recommended competencies in genetic nephrology. Adapted from Tognetto A, Michelazzo MB, Ricciardi W, et al. Core competencies in genetics for healthcare professionals: results from a literature review and a Delphi method. *BMC Med Educ.* 2019;19:19¹⁵⁰ under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). © The Author(s) 2019.

REFERENCES

- GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2020;395:709–733.
- Rasouly HM, Groopman EE, Heyman-Kantor R, et al. The burden of candidate pathogenic variants for kidney and genitourinary disorders emerging from exome sequencing. *Ann Intern Med.* 2019;170:11–21.
- Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med.* 2019;380:142–151.
- Domingo-Gallego A, Pybus M, Bullich G, et al. Clinical utility of genetic testing in early-onset kidney disease: seven genes are the main players. *Nephrol Dial Transplant.* 2022;37:687–696.
- Bullich G, Domingo-Gallego A, Vargas I, et al. A kidney-disease gene panel allows a comprehensive genetic diagnosis of cystic and glomerular inherited kidney diseases. *Kidney Int.* 2018;94:363–371.
- Mallett A, Patel C, Salisbury A, et al. The prevalence and epidemiology of genetic renal disease amongst adults with chronic kidney disease in Australia. *Orphanet J Rare Dis.* 2014;9:98.
- Snoek R, van Jaarsveld RH, Nguyen TQ, et al. Genetics-first approach improves diagnostics of ESKD patients <50 years old. *Nephrol Dial Transplant.* 2020;37:349–357.
- Ottlewski I, Munch J, Wagner T, et al. Value of renal gene panel diagnostics in adults waiting for kidney transplantation due to undetermined end-stage renal disease. *Kidney Int.* 2019;96:222–230.
- Connaughton DM, Kennedy C, Shril S, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int.* 2019;95:914–928.
- Snoek R, van Setten J, Keating BJ, et al. NPHP1 (Nephrocystin-1) gene deletions cause adult-onset ESRD. *J Am Soc Nephrol.* 2018;29:1772–1779.
- Kottgen A, Pattaro C, Boger CA, et al. New loci associated with kidney function and chronic kidney disease. *Nat Genet.* 2010;42:376–384.
- Kanai M, Akiyama M, Takahashi A, et al. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. *Nat Genet.* 2018;50:390–400.
- Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet.* 2019;51:957–972.
- Teumer A, Li Y, Ghasemi S, et al. Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria. *Nat Commun.* 2019;10:4130.
- Okada Y, Terao C, Ikari K, et al. Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. *Nat Genet.* 2012;44:511–516.
- Morris AP, Le TH, Wu H, et al. Trans-ethnic kidney function association study reveals putative causal genes and effects on kidney-specific disease aetiologies. *Nat Commun.* 2019;10:29.
- Kirylyuk K, Li Y, Scolari F, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nat Genet.* 2014;46:1187–1196.
- Gharavi AG, Kirylyuk K, Choi M, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet.* 2011;43:321–327.
- Xie J, Liu L, Mladkova N, et al. The genetic architecture of membranous nephropathy and its potential to improve non-invasive diagnosis. *Nat Commun.* 2020;11:1600.
- Stanescu HC, Arcos-Burgos M, Medlar A, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med.* 2011;364:616–626.
- Gbadegesin RA, Adeyemo A, Webb NJ, et al. HLA-DQA1 and PLCG2 are candidate risk loci for childhood-onset steroid-sensitive nephrotic syndrome. *J Am Soc Nephrol.* 2015;26:1701–1710.
- Dufek S, Cheshire C, Levine AP, et al. Genetic identification of two novel loci associated with steroid-sensitive nephrotic syndrome. *J Am Soc Nephrol.* 2019;30:1375–1384.
- Jia X, Yamamura T, Gbadegesin R, et al. Common risk variants in NPHS1 and TNFSF15 are associated with childhood steroid-sensitive nephrotic syndrome. *Kidney Int.* 2020;98:1308–1322.
- Groopman EE, Rasouly HM, Gharavi AG. Genomic medicine for kidney disease. *Nat Rev Nephrol.* 2018;14:83–104.
- Gale DP, Mallett A, Patel C, et al. Diagnoses of uncertain significance: kidney genetics in the 21st century. *Nat Rev Nephrol.* 2020;16:616–618.
- Shang N, Khan A, Polubriaginof F, et al. Medical records-based chronic kidney disease phenotype for clinical care and “big data” observational and genetic studies. *NPJ Digit Med.* 2021;4:70.
- Fox CS, Yang Q, Cupples LA, et al. Genomewide linkage analysis to serum creatinine, GFR, and creatinine clearance in a community-based population: the Framingham Heart Study. *J Am Soc Nephrol.* 2004;15:2457–2461.
- Mottl AK, Vupputuri S, Cole SA, et al. Linkage analysis of glomerular filtration rate in American Indians. *Kidney Int.* 2008;74:1185–1191.
- Langefeld CD, Beck SR, Bowden DW, et al. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *Am J Kidney Dis.* 2004;43:796–800.
- Ghosh S, Collins FS. The geneticist’s approach to complex disease. *Annu Rev Med.* 1996;47:333–353.
- Salem RM, Todd JN, Sandholm N, et al. Genome-wide association study of diabetic kidney disease highlights biology involved in glomerular basement membrane collagen. *J Am Soc Nephrol.* 2019;30:2000–2016.
- Akbari P, Gilani A, Sosina O, et al. Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. *Science.* 2021;373:eabf8683.

33. Fahed AC, Wang M, Homburger JR, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat Commun.* 2020;11:3635.
34. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80:17–28.
35. Kidney Disease: Improving Global Outcomes. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1–150.
36. Mann N, Braun DA, Amann K, et al. Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. *J Am Soc Nephrol.* 2019;30:201–215.
37. van der Ven AT, Connaughton DM, Ityel H, et al. Whole-exome sequencing identifies causative mutations in families with congenital anomalies of the kidney and urinary tract. *J Am Soc Nephrol.* 2018;29:2348–2361.
38. Stessman HA, Bernier R, Eichler EE. A genotype-first approach to defining the subtypes of a complex disease. *Cell.* 2014;156:872–877.
39. Sandholm N, Van Zuydam N, Ahlqvist E, et al. The genetic landscape of renal complications in type 1 diabetes. *J Am Soc Nephrol.* 2017;28:557–574.
40. Verbitsky M, Krithivasan P, Batourina E, et al. Copy number variant analysis and genome-wide association study identify loci with large effect for vesicoureteral reflux. *J Am Soc Nephrol.* 2021;32:805–820.
41. Scelo G, Purdue MP, Brown KM, et al. Genome-wide association study identifies multiple risk loci for renal cell carcinoma. *Nat Commun.* 2017;8:15724.
42. Hellwege JN, Velez Edwards DR, Giri A, et al. Mapping eGFR loci to the renal transcriptome and phenotype in the VA Million Veteran Program. *Nat Commun.* 2019;10:3842.
43. Qian H, Kowalski MH, Kramer HJ, et al. Genome-wide association of kidney traits in Hispanics/Latinos using dense imputed whole-genome sequencing data: The Hispanic Community Health Study/Study of Latinos. *Circ Genom Precis Med.* 2020;13:e002891.
44. Okuda H, Okamoto K, Abe M, et al. Genome-wide association study identifies new loci for albuminuria in the Japanese population. *Clin Exp Nephrol.* 2020;24:1–9.
45. Gorski M, Tin A, Garnaas M, et al. Genome-wide association study of kidney function decline in individuals of European descent. *Kidney Int.* 2015;87:1017–1029.
46. Yun S, Han M, Kim HJ, et al. Genetic risk score raises the risk of incidence of chronic kidney disease in Korean general population-based cohort. *Clin Exp Nephrol.* 2019;23:995–1003.
47. Langefeld CD, Comeau ME, Ng MCY, et al. Genome-wide association studies suggest that APOL1-environment interactions more likely trigger kidney disease in African Americans with nondiabetic nephropathy than strong APOL1-second gene interactions. *Kidney Int.* 2018;94:599–607.
48. Parsa A, Kanetsky PA, Xiao R, et al. Genome-wide association of CKD progression: The Chronic Renal Insufficiency Cohort Study. *J Am Soc Nephrol.* 2017;28:923–934.
49. Li M, Foo JN, Wang JQ, et al. Identification of new susceptibility loci for IgA nephropathy in Han Chinese. *Nat Commun.* 2015;6:7270.
50. Genovese G, Tonna SJ, Knob AU, et al. A risk allele for focal segmental glomerulosclerosis in African Americans is located within a region containing APOL1 and MYH9. *Kidney Int.* 2010;78:698–704.
51. Iyengar SK, Sedor JR, Freedman BI, et al. Genome-wide association and trans-ethnic meta-analysis for advanced diabetic kidney disease: Family Investigation of Nephropathy and Diabetes (FIND). *PLoS Genet.* 2015;11:e1005352.
52. Taira M, Imamura M, Takahashi A, et al. A variant within the FTO confers susceptibility to diabetic nephropathy in Japanese patients with type 2 diabetes. *PLoS One.* 2018;13:e0208654.
53. Guan M, Keaton JM, Dimitrov L, et al. Genome-wide association study identifies novel loci for type 2 diabetes-attributed end-stage kidney disease in African Americans. *Hum Genomics.* 2019;13:21.
54. Chung SA, Brown EE, Williams AH, et al. Lupus nephritis susceptibility loci in women with systemic lupus erythematosus. *J Am Soc Nephrol.* 2014;25:2859–2870.
55. Howles SA, Wiberg A, Goldsworthy M, et al. Genetic variants of calcium and vitamin D metabolism in kidney stone disease. *Nat Commun.* 2019;10:5175.
56. Stafford-Smith M, Li YJ, Mathew JP, et al. Genome-wide association study of acute kidney injury after coronary bypass graft surgery identifies susceptibility loci. *Kidney Int.* 2015;88:823–832.
57. Purdue MP, Ye Y, Wang Z, et al. A genome-wide association study of renal cell carcinoma among African Americans. *Cancer Epidemiol Biomarkers Prev.* 2014;23:209–214.
58. Hernandez-Fuentes MP, Franklin C, Rebollo-Mesa I, et al. Long- and short-term outcomes in renal allografts with deceased donors: a large recipient and donor genome-wide association study. *Am J Transplant.* 2018;18:1370–1379.
59. Stapleton CP, Heinzl A, Guan W, et al. The impact of donor and recipient common clinical and genetic variation on estimated glomerular filtration rate in a European renal transplant population. *Am J Transplant.* 2019;19:2262–2273.
60. Locke AE, Steinberg KM, Chiang CWK, et al. Exome sequencing of Finnish isolates enhances rare-variant association power. *Nature.* 2019;572:323–328.
61. Nanayakkara S, Senevirathna ST, Parahitiyawa NB, et al. Whole-exome sequencing reveals genetic variants associated with chronic kidney disease characterized by tubulointerstitial damages in North Central Region, Sri Lanka. *Environ Health Prev Med.* 2015;20:354–359.
62. Weng PL, Majmundar AJ, Khan K, et al. De novo TRIM8 variants impair its protein localization to nuclear bodies and cause developmental delay, epilepsy, and focal segmental glomerulosclerosis. *Am J Hum Genet.* 2021;108:357–367.
63. Lin BM, Grinde KE, Brody JA, et al. Whole genome sequence analyses of eGFR in 23,732 people representing multiple ancestries in the NHLBI trans-omics for precision medicine (TOPMed) consortium. *EBioMedicine.* 2021;63:103157.
64. Benonisdottir S, Kristjansson RP, Oddsson A, et al. Sequence variants associating with urinary biomarkers. *Hum Mol Genet.* 2019;28:1199–1211.
65. Guo J, Rackham OJL, Sandholm N, et al. Whole-genome sequencing of Finnish type 1 diabetic siblings discordant for kidney disease reveals DNA variants associated with diabetic nephropathy. *J Am Soc Nephrol.* 2020;31:309–323.
66. Kottgen A, Glazer NL, Dehghan A, et al. Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet.* 2009;41:712–717.
67. Kasembeli AN, Duarte R, Ramsay M, et al. APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans. *J Am Soc Nephrol.* 2015;26:2882–2890.
68. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol.* 2011;22:2129–2137.
69. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic Apol1 variants with kidney disease in African Americans. *Science.* 2010;329:841–845.
70. Riella C, Siemens TA, Wang M, et al. APOL1-associated kidney disease in Brazil. *Kidney Int Rep.* 2019;4:923–929.
71. Freedman BI, Langefeld CD, Andringa KK, et al. End-stage renal disease in African Americans with lupus nephritis is associated with APOL1. *Arthritis Rheumatol.* 2014;66:390–396.
72. Larsen CP, Beggs ML, Saeed M, et al. Apolipoprotein L1 risk variants associate with systemic lupus erythematosus-associated collapsing glomerulopathy. *J Am Soc Nephrol.* 2013;24:722–725.
73. Ekulu PM, Nkoy AB, Betukumesu DK, et al. APOL1 risk genotypes are associated with early kidney damage in children in Sub-Saharan Africa. *Kidney Int Rep.* 2019;4:930–938.
74. Ekrikpo UE, Mnika K, Effa EE, et al. Association of genetic polymorphisms of TGF-beta1, HMOX1, and APOL1 with CKD in Nigerian patients with and without HIV. *Am J Kidney Dis.* 2020;76:100–108.
75. Naik RP, Irvin MR, Judd S, et al. Sickle cell trait and the risk of ESRD in Blacks. *J Am Soc Nephrol.* 2017;28:2180–2187.
76. Mukamal KJ, Tremaglio J, Friedman DJ, et al. APOL1 genotype, kidney and cardiovascular disease, and death in older adults. *Arterioscler Thromb Vasc Biol.* 2016;36:398–403.
77. Tayo BO, Kramer H, Salako BL, et al. Genetic variation in APOL1 and MYH9 genes is associated with chronic kidney disease among Nigerians. *Int Urol Nephrol.* 2013;45:485–494.
78. Foster MC, Coresh J, Fornage M, et al. APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol.* 2013;24:1484–1491.

79. Grams ME, Rebolz CM, Chen Y, et al. Race, APOL1 risk, and eGFR decline in the general population. *J Am Soc Nephrol.* 2016;27:2842–2850.
80. Chen TK, Coresh J, Daya N, et al. Race, APOL1 risk variants, and clinical outcomes among older adults: the ARIC Study. *J Am Geriatr Soc.* 2021;69:155–163.
81. Peralta CA, Bibbins-Domingo K, Vittinghoff E, et al. APOL1 genotype and race differences in incident albuminuria and renal function decline. *J Am Soc Nephrol.* 2016;27:887–893.
82. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med.* 2013;369:2183–2196.
83. Chen TK, Tin A, Peralta CA, et al. APOL1 risk variants, incident proteinuria, and subsequent eGFR decline in Blacks with hypertension-attributed CKD. *Clin J Am Soc Nephrol.* 2017;12:1771–1777.
84. Friedman DJ, Pollak MR. Genetics of kidney failure and the evolving story of APOL1. *J Clin Invest.* 2011;121:3367–3374.
85. Watanabe A, Guaragna MS, Belangero VMS, et al. APOL1 in an ethnically diverse pediatric population with nephrotic syndrome: implications in focal segmental glomerulosclerosis and other diagnoses. *Pediatr Nephrol.* 2021;36:2327–2336.
86. Knoers N, Antignac C, Bergmann C, et al. Genetic testing in the diagnosis of chronic kidney disease: recommendations for clinical practice. *Nephrol Dial Transplant.* 2022;37:239–254.
87. Rehm HL, Berg JS, Brooks LD, et al. ClinGen—the clinical genome resource. *N Engl J Med.* 2015;372:2235–2242.
88. ClinGen—Clinical Genome Resource. ClinGen complex disease PRS reporting standards. Accessed April 21, 2021. <https://clinicalgenome.org/docs/clingen-complex-disease-prs-reporting-standards/>
89. Friedman DJ, Pollak MR. APOL1 nephropathy: from genetics to clinical applications. *Clin J Am Soc Nephrol.* 2021;16:294–303.
90. Surapaneni AL, Ballew SH, Coresh J, et al. APOL1 risk alleles, cardiac markers, and risk of ESKD in African Americans: the Atherosclerosis Risk in Communities Study. *Kidney Med.* 2020;2:502–504.
91. Sinnott-Armstrong N, Tanigawa Y, Amar D, et al. Genetics of 35 blood and urine biomarkers in the UK Biobank. *Nat Genet.* 2021;53:185–194.
92. Gordon EJ, Amomiconrtegui D, Blancas I, et al. African American living donors' attitudes about APOL1 genetic testing: a mixed methods study. *Am J Kidney Dis.* 2018;72:819–833.
93. Freedman BI, Burke W, Divers J, et al. Diagnosis, education, and care of patients with APOL1-associated nephropathy: a Delphi consensus and systematic review. *J Am Soc Nephrol.* 2021;32:1765–1778.
94. Fuentes F, Kopp JB. Launching APOLLO: the role of APOL1 genetic variants in live- and deceased-donor kidney transplantation. *Kidney Int Rep.* 2020;5:252–254.
95. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405–17424.
96. Ellard S, Baple EL, Callaway A, et al. Association for Clinical Genomic Science best practices guidelines for variant classification in rare disease 2020. Accessed April 21, 2021. <https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf>
97. Furlano M, Martinez V, Pybus M, et al. Clinical and genetic features of autosomal dominant Alport Syndrome: a cohort study. *Am J Kidney Dis.* 2021;78:560–570.e1.
98. Biesecker LG, Adam MP, Alkuraya FS, et al. A dyadic approach to the delineation of diagnostic entities in clinical genomics. *Am J Hum Genet.* 2021;108:8–15.
99. Hamosh A, Amberger JS, Bocchini CA, et al. Response to Biesecker et al. *Am J Hum Genet.* 2021;108:1807–1808.
100. Eckardt KU, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—a KDIGO consensus report. *Kidney Int.* 2015;88:676–683.
101. Kottgen A, Kao WH, Hwang SJ, et al. Genome-wide association study for renal traits in the Framingham Heart and Atherosclerosis Risk in Communities Studies. *BMC Med Genet.* 2008;9:49.
102. Feldman HI, Appel LJ, Chertow GM, et al. The Chronic Renal Insufficiency Cohort (CRIC) Study: design and methods. *J Am Soc Nephrol.* 2003;14(7 Suppl 2):S148–S153.
103. Appel LJ, Middleton J, Miller ER 3rd, et al. The rationale and design of the AASK cohort study. *J Am Soc Nephrol.* 2003;14:S166–S172.
104. Klahr S. The modification of diet in renal disease study. *N Engl J Med.* 1989;320:864–866.
105. Eckardt KU, Barthlein B, Baid-Agrawal S, et al. The German Chronic Kidney Disease (GCKD) Study: design and methods. *Nephrol Dial Transplant.* 2012;27:1454–1460.
106. Furth SL, Cole SR, Moxey-Mims M, et al. Design and methods of the Chronic Kidney Disease in Children (CKiD) prospective cohort study. *Clin J Am Soc Nephrol.* 2006;1:1006–1015.
107. Querfeld U, Anarat A, Bayazit AK, et al. The Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study: objectives, design, and methodology. *Clin J Am Soc Nephrol.* 2010;5:1642–1648.
108. ESCAPE Trial Group, Wuhl E, Trivelli A, et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med.* 2009;361:1639–1650.
109. Kottgen A, Pattaro C. The CKDGen Consortium: ten years of insights into the genetic basis of kidney function. *Kidney Int.* 2020;97:236–242.
110. Psaty BM, O'Donnell CJ, Gudnason V, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet.* 2009;2:73–80.
111. Fishman CE, Mohebbasab M, van Setten J, et al. Genome-wide study updates in the International Genetics and Translational Research in Transplantation Network (iGeneTRAIN). *Front Genet.* 2019;10:1084.
112. Magi R, Horikoshi M, Sofer T, et al. Trans-ethnic meta-regression of genome-wide association studies accounting for ancestry increases power for discovery and improves fine-mapping resolution. *Hum Mol Genet.* 2017;26:3639–3650.
113. Franceschini N, Morris AP. Genetics of kidney traits in worldwide populations: the Continental Origins and Genetic Epidemiology Network (COGENT) Kidney Consortium. *Kidney Int.* 2020;98:35–41.
114. Kao WH, Klag MJ, Meoni LA, et al. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet.* 2008;40:1185–1192.
115. Kopp JB, Smith MW, Nelson GW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet.* 2008;40:1175–1184.
116. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 2015;12:e1001779.
117. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol.* 2016;70:214–223.
118. Krokstad S, Langhammer A, Hveem K, et al. Cohort profile: the HUNT Study, Norway. *Int J Epidemiol.* 2013;42:968–977.
119. Jonsson H, Sulem P, Kehr B, et al. Whole genome characterization of sequence diversity of 15,220 Icelanders. *Sci Data.* 2017;4:170115.
120. Nagai A, Hirata M, Kamatani Y, et al. Overview of the BioBank Japan Project: study design and profile. *J Epidemiol.* 2017;27:S2–S8.
121. Roden DM, Pulley JM, Basford MA, et al. Development of a large-scale de-identified DNA biobank to enable personalized medicine. *Clin Pharmacol Ther.* 2008;84:362–369.
122. Graham SE, Nielsen JB, Zawistowski M, et al. Sex-specific and pleiotropic effects underlying kidney function identified from GWAS meta-analysis. *Nat Commun.* 2019;10:1847.
123. eMERGE Consortium. Lessons learned from the eMERGE Network: balancing genomics in discovery and practice. *HGG Adv.* 2021;2:100018.
124. All of Us Research Program Investigators, Denny JC, Rutter JL, et al. The “All of Us” Research Program. *N Engl J Med.* 2019;381:668–676.
125. Shang N, Liu C, Rasmussen LV, et al. Making work visible for electronic phenotype implementation: lessons learned from the eMERGE network. *J Biomed Inform.* 2019;99:103293.
126. Norton JM, Ali K, Jurkovic CT, et al. Development and validation of a pragmatic electronic phenotype for CKD. *Clin J Am Soc Nephrol.* 2019;14:1306–1314.
127. Denburg MR, Razzaghi H, Bailey LC, et al. Using electronic health record data to rapidly identify children with glomerular disease for clinical research. *J Am Soc Nephrol.* 2019;30:2427–2435.
128. Chan L, Beers K, Yau AA, et al. Natural language processing of electronic health records is superior to billing codes to identify symptom burden in hemodialysis patients. *Kidney Int.* 2020;97:383–392.

129. Zheng NS, Feng Q, Kerchberger VE, et al. PheMap: a multi-resource knowledge base for high-throughput phenotyping within electronic health records. *J Am Med Inform Assoc.* 2020;27:1675–1687.
130. Bajaj A, Ihegword A, Qiu C, et al. Phenome-wide association analysis suggests the APOL1 linked disease spectrum primarily drives kidney-specific pathways. *Kidney Int.* 2020;97:1032–1041.
131. Tin A, Kottgen A. Mendelian randomization analysis as a tool to gain insights into causes of diseases: a primer. *J Am Soc Nephrol.* 2021;32:2400–2407.
132. Martin AR, Kanai M, Kamatani Y, et al. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet.* 2019;51:584–591.
133. Zhang Z, Hernandez K, Savage J, et al. Uniform genomic data analysis in the NCI Genomic Data Commons. *Nat Commun.* 2021;12:1226.
134. eMERGE Consortium. Harmonizing clinical sequencing and interpretation for the eMERGE III Network. *Am J Hum Genet.* 2019;105:588–605.
135. Eales JM, Jiang X, Xu X, et al. Uncovering genetic mechanisms of hypertension through multi-omic analysis of the kidney. *Nat Genet.* 2021;53:630–637.
136. Gillies CE, Putler R, Menon R, et al. An eQTL landscape of kidney tissue in human nephrotic syndrome. *Am J Hum Genet.* 2018;103:232–244.
137. Townsend RR, Guarnieri P, Argyropoulos C, et al. Rationale and design of the Transformative Research in Diabetic Nephropathy (TRIDENT) Study. *Kidney Int.* 2020;97:10–13.
138. Abedini A, Zhu YO, Chatterjee S, et al. Urinary single-cell profiling captures the cellular diversity of the kidney. *J Am Soc Nephrol.* 2021;32:614–627.
139. ENCODE Project Consortium. The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science.* 2004;306:636–640.
140. Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, et al. Integrative analysis of 111 reference human epigenomes. *Nature.* 2015;518:317–330.
141. GTEx Consortium. Erratum: Genetic effects on gene expression across human tissues. *Nature.* 2018;553:530.
142. de Boer IH, Alpers CE, Azeloglu EU, et al. Rationale and design of the Kidney Precision Medicine Project. *Kidney Int.* 2021;99:498–510.
143. Mostafavi H, Harpak A, Agarwal I, et al. Variable prediction accuracy of polygenic scores within an ancestry group. *Elife.* 2020;9:e48376.
144. Wand H, Lambert SA, Tamburro C, et al. Improving reporting standards for polygenic scores in risk prediction studies. *Nature.* 2021;591:211–219.
145. Buniello A, MacArthur JAL, Cerezo M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res.* 2019;47:D1005–D1012.
146. Lambert SA, Gil L, Jupp S, et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. *Nat Genet.* 2021;53:420–425.
147. Shaikh A, Patel N, Nair D, et al. Current paradigms and emerging opportunities in nephrology training. *Adv Chronic Kidney Dis.* 2020;27:291–296.e1.
148. Berns JS. A survey-based evaluation of self-perceived competency after nephrology fellowship training. *Clin J Am Soc Nephrol.* 2010;5:490–496.
149. Jaysinghe K, Quinlan C, Mallett AJ, et al. Attitudes and practices of Australian nephrologists toward implementation of clinical genomics. *Kidney Int Rep.* 2021;6:272–283.
150. Tognetto A, Michelazzo MB, Ricciardi W, et al. Core competencies in genetics for healthcare professionals: results from a literature review and a Delphi method. *BMC Med Educ.* 2019;19:19.
151. Milo Rasouly H, Aggarwal V, Bier L, et al. Cases in precision medicine: genetic testing to predict future risk for disease in a healthy patient. *Ann Intern Med.* 2021;174:540–547.
152. Chen J, Fowler KJ, Grams ME. Knowledge is power: patient education as a tool for patient activation. *Am J Kidney Dis.* 2020;76:163–165.
153. Logeman C, Cho Y, Sautenet B, et al. ‘A sword of Damocles’: patient and caregiver beliefs, attitudes and perspectives on presymptomatic testing for autosomal dominant polycystic kidney disease: a focus group study. *BMJ Open.* 2020;10:e038005.
154. Waterman AD, Gleason J, Lermiaux L, et al. Amplifying the patient voice: key priorities and opportunities for improved transplant and living donor advocacy and outcomes during COVID-19 and beyond. *Curr Transplant Rep.* 2020;7:301–310.
155. Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight—reconsidering the use of race correction in clinical algorithms. *N Engl J Med.* 2020;383:874–882.
156. Borrell LN, Elhawary JR, Fuentes-Afflick E, et al. Race and genetic ancestry in medicine—a time for reckoning with racism. *N Engl J Med.* 2021;384:474–480.
157. Oni-Orisan A, Mavura Y, Banda Y, et al. Embracing genetic diversity to improve Black health. *N Engl J Med.* 2021;384:1163–1167.
158. Race, Ethnicity, and Genetics Working Group. The use of racial, ethnic, and ancestral categories in human genetics research. *Am J Hum Genet.* 2005;77:519–532.
159. Nair D, Wilson FP. Patient-reported outcome measures for adults with kidney disease: current measures, ongoing initiatives, and future opportunities for incorporation into patient-centered kidney care. *Am J Kidney Dis.* 2019;74:791–802.
160. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2015;17:505–507.
161. Sun F, Bruening W, Erinoff E, Schoelles KM. Addressing Challenges in Genetic Test Evaluation. Evaluation Frameworks and Assessment of Analytic Validity. Methods Research Report (Prepared by the ECRI Institute Evidence-based Practice Center under Contract No. HHS A 290-2007-10063-I.) AHRQ Publication No. 11-EHC048-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011.
162. Giacomini M, Miller F, Browman G. Confronting the “gray zones” of technology assessment: evaluating genetic testing services for public insurance coverage in Canada. *Int J Technol Assess Health Care.* 2003;19:301–316.