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Towards Precision Nephrology: The Opportunities and Challenges of Genomic Medicine

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Introduction

Expanded utilization of genetic testing in the clinical setting is changing how we view hereditary forms of kidney diseases. Genetic etiologies account for a substantial proportion of pediatric chronic kidney disease (CKD) cases[1], and with increased utilization of genetic testing in nephrology, we now recognize that they may be detected at appreciable frequencies amongst adult patients as well[2,3]. These findings have led some to call for genetic tests to be used as a first-line clinical diagnostic tool. Wider use of genetic testing has many potential benefits for the field of nephrology: it can help to achieve a specific diagnosis, guide treatment, and enable deeper insight onto the molecular pathogenesis of disease. However, with broader indications for genetic testing we are faced with the realities of how we make sense of large quantities of sequence data in the context of other clinical studies, return genetic results, and apply the information in a clinically meaningful way.

There are approximately 5000 known Mendelian disorders[4], which affect millions of people worldwide [5]. Though these disorders are considered rare, genetic birth defects occur in approximately 8% of live births[6]. In addition, it has been estimated that across a wide spectrum of disorders, up to 50% of individuals with rare genetic conditions are undiagnosed[7]. In the clinical setting, genetic testing is largely utilized for the detection of rare variants in individuals with suspected monogenic diseases[8]; it is also being increasingly applied in non-invasive prenatal screening[9] and for the diagnosis and individualization of therapy for various cancers[10–12]. The broader clinical utilization of genetic testing has been facilitated by the decreased costs and great technologic advancements in sequencing techniques that have occurred over the past decade with the

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advent of NGS[13]. NGS, or massively parallel sequencing, is a technological innovation that enables rapid and relatively inexpensive sequencing of multiple genes[14]; more detailed technical descriptions of NGS are reviewed elsewhere[15]. NGS thus allows for routine use genome-wide testing: whole exome sequencing (WES), the targeted capture of all coding regions of the human genome, and whole genome sequencing (WGS), which analyzes both coding and non-coding regions of the genome[16].

Traditionally, genetic workup was done using a small number of genetic and biochemical tests that required a physician to have *a priori* knowledge of the genetic etiology associated with a given clinical presentation[7]. Through single gene testing with Sanger sequencing, candidate genes were tested serially. If no variant was initially identified, additional candidate genes were then examined, making the process prolonged and resource-intensive[8,17,18]. The ability to search for variants across all genes in the genome with WES and WGS has removed much of the need for such *a priori* knowledge, and may help to diagnose disorders that are clinically misclassified, discover new disease associations, or define new genetic disorders[19,20].

The diagnostic utility of exome sequencing has been evaluated in multiple patient cohorts, and the reported yields vary considerably[21,22], reflecting the differences in the clinical characteristics of the populations studied. Broadly, the diagnostic yield of WES varies widely between different clinical indications, and appears to be higher amongst pediatric cases with specific neurological findings, such as in cases of neurodevelopmental disorders[23–27]. Importantly, WES has comparable or superior diagnostic yield versus sequential Sanger sequencing for a range of genetically heterogeneous conditions, including deafness, blindness, and mitochondrial disorders [28]. In addition, WES has been shown to identify causal variants in patients left undiagnosed by traditional methods, which suggests that using WES as a first-line test may be more cost-effective when diagnosing clinically complex cases[7]. Finally, WGS has also been effective in establishing a molecular diagnosis in multiple clinical settings[29–32], and though few studies have compared the diagnostic yields between WES and WGS, its potential advantages lie in its broader coverage of certain genomic regions as compared to WES[33].

Value of genetic testing in clinical nephrology

Establishing a molecular diagnosis

The expansion of genomic medicine in nephrology is changing paradigms of diagnosis, classification, and treatment of disease. Identification of the causal genetic variant enables more precise distinction between overlapping clinical phenotypes, which can be used to inform prognosis and management[34]. For example, genetic testing can help distinguish between Alport Syndrome (AS) and the related, milder disorder, Thin Basement Membrane Disease (TBMD). Both of these hematuric nephropathies result from mutations in *COL4A3-5*. Despite such high genetic and phenotypic overlap, the two conditions nonetheless differ markedly with respect to clinical outcomes: AS patients have more severe disease, with extra-renal features such as audiologic and ocular deficits, and progress earlier to End Stage Renal Disease (ESRD). Importantly, genotype-level knowledge can help predict phenotype: in general, biallelic *COL4A3/COL4A4* or hemizygous *COL4A5*

mutations result in AS, whereas heterozygous *COL4A3-4* mutations result in TBMD [35,36]. Thus genetic testing can provide valuable prognostic information and guide further work-up and management, such as informing the appropriate timing of transplant referrals and pursuing evaluations for visual or auditory symptoms among AS patients.

Furthermore, NGS allows better diagnosis of genetically heterogeneous conditions that carry different treatment implications, as illustrated by idiopathic nephrotic syndrome[37], a genetically heterogeneous phenotype with over 30 known causal genes[38,39]. NGS facilitates the diagnosis and informs management, as genetic forms are more likely to be steroid resistant and progress to ESRD, but recur less in renal allografts[40–42]. Similarly, NGS increases diagnostic sensitivity of genetic testing for renal ciliopathies, another genetically heterogeneous entity, and guides further evaluations for extra-renal manifestations based on the genetic form discovered, such as in cases of visual impairment and abnormal hepatic function[43,44].

Insights into disease pathogenesis

The use of NGS in clinical settings also provides us with greater insight into the disease mechanisms of various renal diseases, selected examples are listed in Table 2. NGS has contributed to the discovery of novel causal genes for a variety of clinical phenotypes, such as renal ciliopathies[45–47], congenital anomalies of the kidney and urinary tract (CAKUT) [1,48–52] and focal segmental glomerulosclerosis (FSGS)/steroid-resistant nephrotic syndrome (SRNS)[1,39,53,54]. Importantly, such discoveries provide insight into the molecular pathogenesis of disease. For example, the discovery of variants in the *DGKE* gene, which encodes an intracellular kinase expressed in endothelium, platelets and podocytes, among individuals with membranoproliferative glomerulonephritis (MPGN) and atypical hemolytic uremic syndrome (aHUS), has helped us better understand how signaling disruptions lead to endothelial damage, complement and podocyte dysregulation[55–59].

Moreover, in addition to variants within a single gene, there is an increased appreciation of how chromosomal abnormalities contribute to disease[60], particularly in children with neurodevelopmental and/or multi-organ syndromes. Such structural variation includes copy number variants (CNVs), which result from duplication and/or deletion events in one or more loci[61], and can be detected using chromosomal microarray[62,63]. These genomic imbalances have been found to contribute substantially to CAKUT[64–67], and have also been noted among pediatric CKD patients with a wide range of clinical diagnoses. Notably, recent studies show considerable genetic overlap between the CNVs found in children with nephropathy and those detected in children with neurodevelopmental disorders[68–74], with important implications in nephrology. Neurocognitive deficits have been associated with kidney disease in children and adults[75,76], and have been attributed to the burden of chronic illness[77,78]. However, the observed genetic overlap suggests that for some patients, these deficits may in fact be part of a greater multisystem disorder. Thus, broader utilization of genetic testing in nephrology has the potential to identify extra-renal manifestations that may otherwise be missed or dismissed as secondary complications, and enable physicians to provide patients with more specialized and effective care.

Finally, the majority of CKD and ESRD cases are attributed to hypertension (HTN) and type 2 diabetes mellitus (T2DM)[79,80], rather than Mendelian etiologies. While HTN- and T2DM-associated kidney disease have traditionally been thought of as acquired disorders, population-level discoveries made in the past decade with genome wide association studies (GWAS) support that there is also a genetic contribution. Findings of risk alleles for HTN[81,82] and T2DM[83,84], present at appreciable frequencies within the population suggest a complex disease model, wherein multiple common variants of smaller effect size, interact with various environmental factors to lead to the disease phenotype. Large consortia, such as the CKDGen[85–88] and KidneyGen[89–91], have been instrumental in these efforts, helping to assemble large case-control cohorts so that studies can have adequate statistical power to detect single-variant-level genetic associations. In addition, ongoing efforts to build large renal transcriptomic datasets, like EUREnOmics[92], Neptune[93,94] and GUDMAP[95], have enabled investigators to use systems biology approaches to elucidate the functional consequences of observed renal risk loci.

Challenges faced with widespread genetic testing in the clinical setting

Since NGS does not mandate *a priori* knowledge of the suspected genetic condition, it is relatively easy for a clinician to order. However, before recommending NGS as a stand-alone test, key challenges regarding the interpretation of genetic data that we must consider (see table 1). First, to process and technically validate the enormous amount of sequence data generated by NGS[13,33] is time- and labor-intensive[14,18,96,97]. Second, variant interpretation relies on careful review of large clinical variant databases and the associated primary literature. These resources can contain erroneous or ambiguous information, leading to inaccurate classification of variants as “pathogenic”; therefore, they must be used with caution[98,99]. Finally, which criteria should be used to define findings are clinically relevant and potentially disease-causing is a matter of ongoing debate[100,101].

Though best practice guidelines exist for clinical variant interpretation[102,103], they have not yet been implemented broadly, hindering reproducibility in genetic interpretation. Therefore, we rely on population genetics as an objective criterion to help guide variant interpretation, as it accounts for the background rate of human genetic variation[104]. Healthy individuals carry many rare functional variants[105], and many variants predicted to be deleterious by in-silico algorithms have been observed at appreciable frequencies in healthy controls. Thus, rarity or in-silico predictions alone are insufficient evidence for pathogenicity. Accordingly, as large, diverse population control datasets have become available, many variants previously reported to be pathogenic have been observed at frequencies incompatible with causality[106].

In addition, the utility of population genetic data to guide variant interpretation relies on having large, ethnically diverse population control databases. Yet many of the world’s populations are not well-represented in control databases. This lack of ethnic diversity in reference databases leads to the potential for underestimations of allele frequencies and considering variants common within a certain ethnic subpopulation as “rare”[107]. Such underrepresentation has contributed to the misclassification of benign variants as pathogenic, and in the large increase in variants designated of unknown significance when interpreting

minority genomes. In the clinical setting, variants of unknown significance (VUS) are of little value to the referring physician, as what relevance, if any, they have to a patient's condition and management is unclear. Therefore, as reference database include more diverse populations and evidence of variants continues to expand, such variants will need to be reviewed, and many will likely need to be reclassified[14,33,98].

Another challenge that arises from NGS-based genome-wide testing are findings unrelated to the primary indication for testing. The clinical value of reporting secondary findings has been highly debated[108–116]. In 2013, the American College of Medical Genetics and Genomics (ACMG) issued recommendations for reporting secondary findings when exome sequencing is performed for any clinical purpose in children or adults[101]. In addition to reporting variants in genes pertaining to the primary indication for testing, they recommended that laboratories assess variants in 56 genes deemed to be highly medically actionable, and return their findings to the referring clinician as well. This list was recently expanded to include 59 actionable genes[117]. Variants in these genes are implicated in various heritable, highly penetrant diseases for which medical interventions or prevention opportunities exist. As it is estimated that 1–3% of individuals may have an actionable variant in one of these genes, returning these findings may have clinical utility on a population-wide scale[96,118–120].

The clinical interpretation of other secondary findings beyond the ACMG actionable genes poses additional challenges for clinicians. It is unknown how nephrologists will make sense of potentially ambiguous genomic information, and how such information may affect clinical practices. For example, how should a clinician make sense of a variant associated with a known renal phenotype that is found in an individual with a different renal manifestation, (e.g., a variant in the *SLC5A2* gene, found in those with Familial Renal Glycosuria, in an individual with FSGS and no glycosuria), or the discovery of a variant associated with a disorder with no known renal manifestations? Such findings will require reassessment of reported evidence for pathogenicity for the variant, as well as evaluation of the patient for features consistent with the candidate genetic findings. It remains unclear whether such findings should be considered missed secondary diagnoses, phenotypic extensions, or risk modifiers, and whether additional surveillance is warranted.

Ethical, legal and social issues relating to the return of genetic results

The process of interpreting genetic results has many challenges. However, returning genetic results to individuals is also a complex matter, with many stakeholders involved in the matter. They include patients, their families and communities, geneticists and counselors, clinicians and other providers, researchers and clinical laboratories. Currently, no standardized method for returning genetic results exists, reflecting this plethora of viewpoints and the many unsettled debates still exist regarding which results should be returned[100,121–123].

Whether or not to return individual genetic research results, incidental, or secondary findings to study participants has been highly debated in the literature. Today, most agree that valid, medically important and actionable results should be reported to study participants[124]

because there are potential treatment and prevention implications. In addition, though not fully comprehensive, legislation exists through the 2009 Genetic Information Nondiscrimination Act (GINA) to protect employers and health insurance carriers from discriminating against individuals based on their genetic results[116]. However, controversy still exists with regards to which actionable results should be disclosed: solely those related to the main purpose of the initial test, or secondary findings identified during the course of the investigation as well? The ACMG recommendation to deliberately seek out additional variants in a subset of genes they deemed beneficial has also brought about more debate around issues of informed consent, patient autonomy[110,115,125–127], and the return of results for adult-onset conditions to pediatric patients[128,129].

At this time, various organizations have issued guidelines[130] for the return of genetic results, where most agree that study participants and parents of participating minors should have the option to refuse all research-level genetic test findings. This includes results related to the study purpose and unintended secondary findings, except when the results are of high clinical significance to the minor during childhood. Moreover, when studies prevent participants from “opting out” of the receipt of genetic results, it should be explicitly described during the informed consent process[124]. These guidelines are effective in the context of obtaining consent for prospective genetic studies; however, there is no consensus for what to do with actionable results discovered in participants who consented for a genetic test many years ago. Many in the genetics community believe there is an ethical obligation to still notify these individuals of such findings, with some groups choosing to re-consent individuals previously sequenced in order to address potential future discoveries made upon resequencing.

Future directions

In order to determine which patients may benefit from expanded indications for genetic testing, more studies are needed to explore how genetic working impacts patient outcomes, the disease course, and health-care utilization. As the indications for genetic testing continue to expand, more education is required for patients, communities, and clinicians, regarding topics such as genomic medicine, informed consent, the potential benefits and implications of genetic results, the current limitations in sequence interpretation, and the need for variant re-analysis and reclassifications of prior findings. The return of genetic results likewise merits deeper, multidisciplinary study. Examination of patients’ and providers’ attitudes towards broader indications for genetic testing, experiences receiving genetic results, barriers faced in the return of results, and how these results may impact an individual’s clinical course or a clinician’s medical decision-making, will help to guide development of best practices for this process.

Finally, there is a need for greater inclusion of racial and ethnic minorities in genetic studies. In the U.S., marginalized patient populations are disproportionately made up of Latino and African American communities. These communities also bear a disproportionate burden of renal disease[131]. The inclusion of more ethnically diverse cohorts are needed to generalize findings, better characterize newly discovered rare variants, and prevent the potential for worsening health disparities by creating a “genomic divide”[132] between those with access

to genetic testing and those without. Study of the obstacles that hinder participation of communities in genomic research, such as poverty, education, health literacy, and health care access[133], will help to achieve this.

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Table 1**Next-Gen Nephrology: Opportunities and Challenges**

Step	Key questions	Helpful strategies
Refer patient for genetic testing	<ul style="list-style-type: none"> For which patients is genetic testing indicated? How to ensure all patients have equal access to genetic testing? 	<ul style="list-style-type: none"> Large sequencing studies in diverse CKD patient cohorts to ascertain indications for genetic testing in nephrology Culturally sensitive outreach initiatives to facilitate access for minority and underserved populations
Clinical sequence interpretation	<ul style="list-style-type: none"> How to identify diagnostic variants amidst the vast amount of sequence data generated by genome-wide testing? 	<ul style="list-style-type: none"> Creation of disease-specific variant interpretation guidelines for different hereditary nephropathies Use of diverse control population genetic databases to help filter a patient's sequence data Clinical database review and correction of misclassified variants
Return of results	<ul style="list-style-type: none"> Which results warrant return? How should they be returned to the patient? 	<ul style="list-style-type: none"> Consensus guidelines regarding which results merit return, given the clinical context Patient education and pre- and post-test counseling to ensure informed consent and empower individuals' decision-making
Apply genetic findings to provide personalized care	<ul style="list-style-type: none"> What is clinical significance of the genetic findings, and the indicated workup and management? How to protect patients from genetic discrimination and other misuse of genetic data? 	<ul style="list-style-type: none"> Long-term studies of the impact of genetic findings on clinical outcomes to enable creation of best practice guidelines for workup and treatment EHR tools to help physicians utilize genetic findings in everyday clinical care Further legislative efforts to protect the autonomy and privacy of patients undergoing genetic testing

Table 2

Examples of notable genomic studies in nephrology

Scope of Sequencing	Importance	Disease Category Assessed	Reference
Targeted NGS Panel	This study used targeted NGS to detect a single-gene cause in 29.5% of familial SRNS cases, establishing its value as part of the diagnostic evaluation for idiopathic nephrotic syndrome.	SNRS	39
	This study identified causal variants in 6.3% of 650 families with CAKUT, establishing the utility of targeted sequencing as a diagnostic screen for a genetically heterogeneous clinical phenotype.	CAKUT	52
	Using a targeted panel, this study found 80% of 101 patients with hematuric nephropathy had a disease-causing mutation in the <i>COL4A3-5</i> genes, highlighting its value as a clinical screening tool.	AS/TBMD	36
	This study identified 36 disease-causing mutations in a cohort of 192 patients diagnosed with nephronophthisis-associated ciliopathy, using a cost-effective approach via array-based PCR amplification followed by targeted sequencing.	Renal ciliopathies	47
Exome sequencing	Using WES this study identified disease-causing variants in 26.2% of 187 pediatric patients with SRNS, demonstrating its effectiveness as a diagnostic tool in the early identification of genetic forms of SRNS.	SNRS	40
	This study used WES in a cohort of 62 families with CAKUT, and found pathogenic SNVs in 4.8% of cases and pathogenic CNVs in 6.5% of cases, demonstrating its ability to establish a molecular diagnosis in CAKUT.	CAKUT	50
	Using exome sequencing, this study implicated mutations in <i>DGKE</i> in familial aHUS, highlighting the dual capacity of WES for genetic diagnosis and discovery.	aHUS	55
Chromosomal Microarray	Using microarrays, this study detected large pathogenic CNVs among 10.5% of 522 patients with renal hypoplasia/dysplasia, showing the importance of chromosomal imbalances to renal parenchymal anomalies.	CAKUT	67
	With chromosomal microarrays, pathogenic CNVs were detected in 7.4% of 31 children with all-cause CKD, showing that a substantial proportion of children with CKD have a genomic imbalance.	All-cause pediatric CKD	66
	With chromosomal microarrays, this study detected CNVs in 10.1% of 178 children with broad phenotypes of CAKUT, finding high rates of pathogenic CNVs in phenotypes not previously thought to be enriched for them.	CAKUT	64
	This study showed that pediatric CKD cases with known genomic disorders had impaired neurocognitive function relative to noncarriers, despite controlling for CKD severity, suggesting a common, genetic pathogenesis for renal disease and neuropsychiatric disorders.	All-cause pediatric CKD	71