Models of Care for the Implementation of Genetic Testing in Nephrology

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Summary

Genetic testing holds great potential to enhance the diagnosis and management of kidney disease, yet its integration into routine nephrology care remains limited and often delayed. Despite strong evidence supporting its clinical utility and cost effectiveness, significant barriers hinder its widespread adoption. This review examines care models designed to embed genetic testing into nephrology practice and proposes strategies to improve access for chronic kidney disease patients. Key approaches include enhancing clinical genetic services, establishing kidney genetics clinics, using technology such as virtual consultations, forming variant review boards and multidisciplinary teams, and mainstreaming genetic testing into nephrology care. For each model, the review identifies essential components for success and discusses barriers and facilitators to implementation. By focusing on practical, scalable, and patient-centered solutions, this review advocates for a paradigm shift in nephrology care. It envisions genetic testing as a standard component of kidney disease management, aiming to improve outcomes and promote equitable care for patients globally.

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INTRODUCTION

Substantial advances in the diagnostics and therapeutics of genetic kidney disease have continued to emerge over the last decade, to the point where the question is no longer *if* genetic testing is required in nephrology, but rather *how* genomic medicine should be implemented into the standard of care.[1] Data now suggest that *at least* 1 in 10 cases of chronic kidney disease (CKD) are attributable to single-gene causes,[2] with this being higher among patients who have additional genetic risk factors such as a positive family history, extrarenal features, or certain subtypes of CKD.[3,4] Coupled with the enhanced understanding of both the clinical utility and diagnostic efficacy of genetic testing, a substantial increase in the demand for genetic testing is imminent. Certainly, the high diagnostic yield of genetic testing in both pediatric and adult CKD populations should encourage the nephrology community to integrate genetic testing into the diagnostic pathway for patient with CKD. In addition, the substantial cost savings and the increasing speed at which testing can be performed stand to enhance further the feasibility of early integration of genetic testing into the diagnostic pathway. However, data consistently show delays in the integration of genetic testing into standard clinical care, and testing, when performed, is often pursued late in the diagnostic pathway.[5] This means that overall, genetic kidney disease remains under-recognized and underestimated within the general CKD population.[6] Barriers to integration are complex and multifold, including limited genetic literacy among nongenetic clinicians, lack of perceived clinical utility *even* when testing results are positive, concerns regarding results interpretation, the workload associated with ordering of testing and the interpretation of indeterminant findings, cost and resourcing concerns, and the widespread lack of access of genetic services and counseling.[6–8] Despite these barriers, genetic testing continues to extend beyond the purview of clinical geneticists and genetic counsellors, and worldwide there

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is an ever-increasing expectation for service delivery by nongenetic specialists, including nephrologists.[9] To meet this demand for genetic testing and to promote successful integration, there is an urgent need for restructuring of how we currently provide services.[10] Current practice in nephrology usually entails conducting genetic testing late in the diagnostic pathway when all other diagnostic approaches have failed to yield a diagnosis, including as an investigation of last resort.[11] Data is increasingly showing high clinical utility[10] and cost effectiveness[12] when genetic testing is offered early in the diagnostic pathway. Therefore, implementation strategies need to focus on how to shift genetic assessments to earlier in the diagnostic pathway where excess attributable health and utilization costs are minimal.[13] In line with this, the nephrology community needs to consider the current approach to testing.

At present, clinical genetic testing in nephrology practice encompasses two broad approaches: genetic testing using a phenotypic driven approach based on the suspicion of a distinct subtype of CKD (e.g., cystic kidney disease or congenital anomalies of the kidney and urinary tract) or comprehensive genetic testing approaches using genomic sequencing approaches including both exome and genome analysis. The former, phenotypic-driven approach generally employs gene panel testing and requires a high index of clinical suspicion of the subtype of CKD under investigation, prior to testing. In recent years, utilization of more comprehensive genomic testing strategies such as exome or genome analysis has gained traction, on the basis that these approaches can facilitate analysis of a broader range of genes known to be associated with genetic disease[14] in the form of virtual panels. Using either an exome or genome sequencing backbone, a bioinformatic virtual panel can be applied encompassing all genes associated with the phenotype and/or disease in question.[15] Considering that there are now over 500 single-gene causes for CKD described,[3] the added advantage of this approach is that it provides the fallback option of full exome or genome analysis, or future automated or on-demand reanalysis[16] should initial testing be negative or inconclusive (Figure 1).[6,17] Considering the heterogenous clinical presentation of CKD, with overlapping and sometimes indistinct features, comprehensive genetic testing is increasingly favored in clinical practice as the more efficient and cost-effective approach to testing.[18] The reasons to pursue genomic testing in patients with CKD is the powerful potential of a precise molecular diagnosis to optimize therapeutics, in risk prediction, and to inform decision-making for patients with genetic kidney disease. Indeed, data now show a change in management in over 90% of patients with CKD

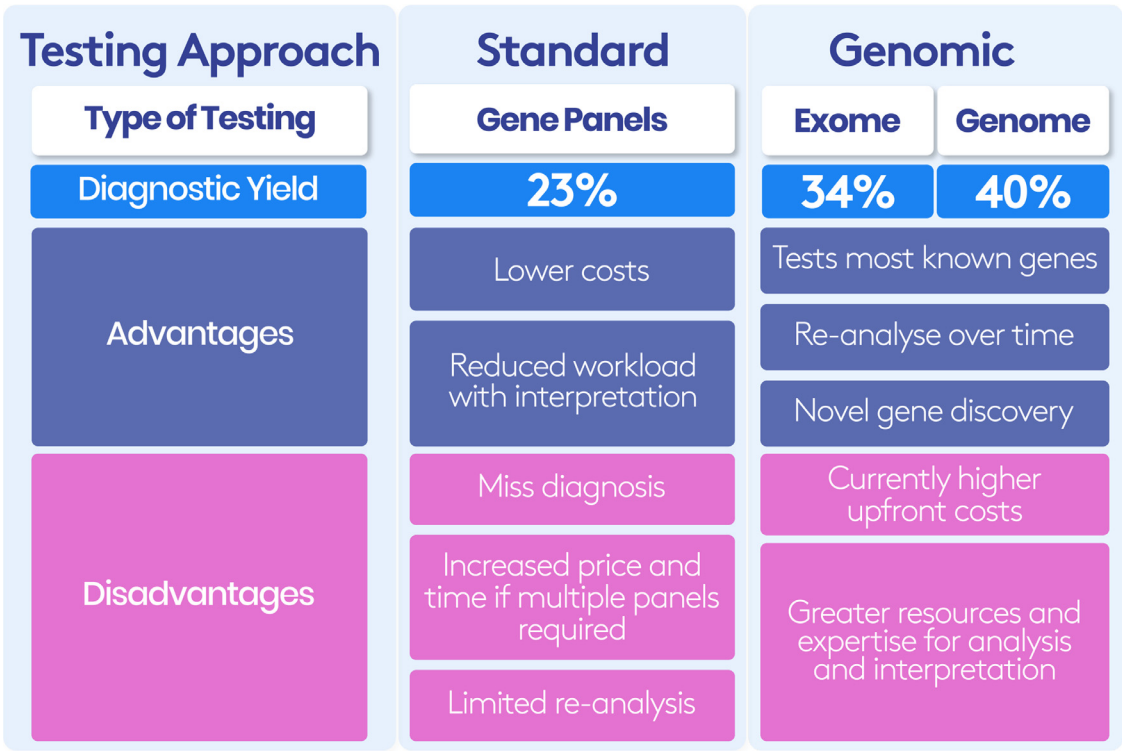

Figure 1. Current approaches to genetic testing. Standard testing includes gene panel testing either phenotypic-driven panels or comprehensive kidney disease panels. Genomic testing, so-called genome-wide sequencing, includes both exome and genome sequencing. The anticipated diagnostic yield (blue), advantages (purple), and disadvantages (pink) to testing are provided for both. Note, the reported diagnostic yield is the anticipated diagnostic yield across all cohorts of patients with genetic kidney disease and can vary across different populations and subtype of CKD.

following receipt of positive genetic testing results, with more than a third having a direct change in treatment.[10]

In this review, we examine options to enhance equitable access to genetic testing for patients with CKD and discuss strategies to promote widespread implementation of genomic medicine in nephrology practice.

MODELS OF CARE

Shift in Practice From Clinical Genetics to Nephrology-Led Genetic Services

Historically, genetic testing for CKD patients was initiated solely by clinical geneticists and genetic counselors (Figure 2). Over the past decade we have witnessed an ever-increasing demand for clinical genetic services across all disease subspecialties, including nephrology. To limit service demands, clinical genetic assessment is increasingly reserved for individuals with CKD identified as having multisystem disease or medically actionable genetic findings in a non-kidney-related organ. With the growing number of patients presenting with genetic CKD, an expansion of nephrology-initiated services for genetic testing is urgently required. One concern is that although the ordering of testing is now feasible for the non-geneticists, the interpretation of genetic variants can be complex. For example, interpretation may require the integration of more complex genetic data, including clinical and pedigree data, knowledge of genetic and genomic testing, classification of variants based on bioinformatics and computational biologics, along with a comprehensive understanding of all genetic forms of kidney disease.[19] This interpretation and integration may be outside the scope of practice for nongenetic clinicians such as nephrologists. For these reasons, additional strategies are essential to the successful integration of genomic medicine into clinical practice in nephrology.[6,20] To this end, Kidney Disease: Improving Global Outcomes (KDIGO) recently proposed a three-tiered organization framework for implementing genetic testing in nephrology, highlighting the need for increasing genetic literacy among all nephrologists; establishing working partnerships between nephrologists, geneticists, and genetic counselors; and developing centers of expertise in kidney genetics (Figure 3).

Multidisciplinary Clinics

Multidisciplinary clinics have emerged as one of the models of care to meet the increasing service demand on clinical genetics services. These specialized clinics leverage the combined expertise of both nephrologists and genetic health professionals to determine the optimal testing strategy for patients with CKD and to ensure correct interpretation of genomic testing results, with a focus on establishing a genetic diagnosis, providing genetic counseling, and making recommendations for treatment.[21] A 2021 survey of nephrologists in Australia

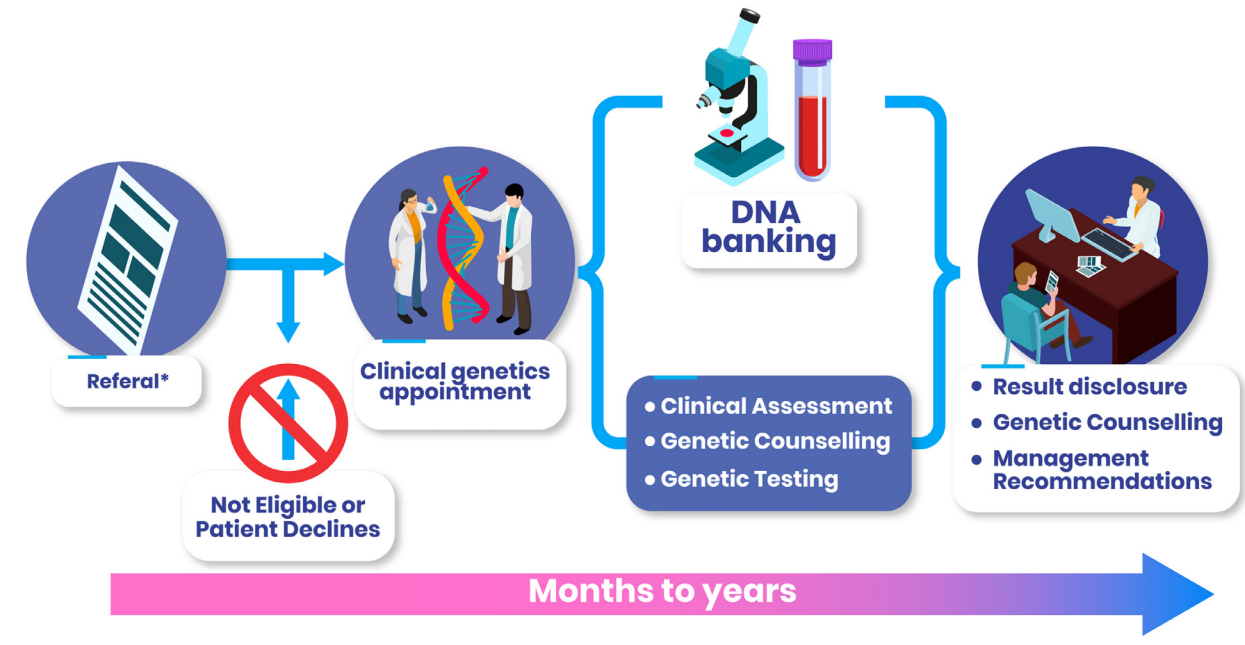

Figure 2. Standard workflow to access genetic and genomic testing services through clinical genetics consultation. The timeline from initial referral to disclosure of genetic testing results is indicated by the arrow below.

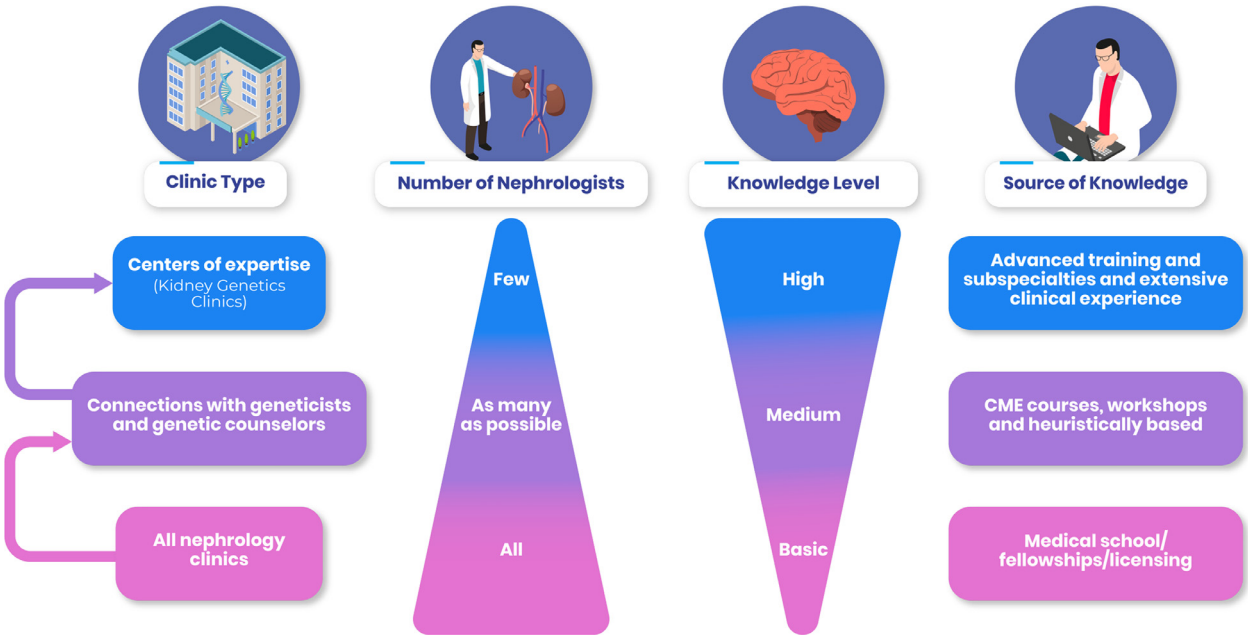

Figure 3. Proposed organization for implementing genetics in nephrology. Adapted, with full permission, from Genetics in CKD Conference Participants: A KDIGO report. *Kidney Int*. 2022;101(6):1126-1141.

indicated that 57% of nephrologists would like to access genetic testing services for their CKD patients via a multidisciplinary kidney genetic clinic.[8] Considering the increasing utilization of more comprehensive genomic testing approaches,[22] integral to these models of care is the availability of both pre- and posttest genetic counseling for patients. Counseling is essential to provide the education and pretest support necessary to make an informed decision while ensuring correct understanding of genetics results and the totality of the clinical implications. These clinics are therefore supported by clinicians (usually genetic counselors) who can provide both pre- and posttest counseling.[20] The benefits of this model are the bidirectional communication and education between nephrologists and genetic specialists and the iterative feedback established through the multidisciplinary team approach.

Nephrology-Initiated Kidney Genetics Clinics

Due to the worldwide shortage of clinicians with expertise in genetics, an emerging model of care is the nephrology led kidney genetics clinic.[23,24] In contrast to multidisciplinary clinics, these services are typically led by nephrologists who have clinical expertise in kidney genetics and genomics. In this setting nephrologists can work together with genetic counselors with a subspecialist interest in nephrology, often in close collaboration with clinical genetics (Figure 4). Data shows that many of these services are primarily a consultative service incorporating either adult and pediatric nephrologists with clinical expertise in the assessment, diagnosis, and treatment of genetic kidney disease.[5,25] The primary goals are to determine if testing is indicated, what the optimal testing strategy is, to facilitate counseling and provide posttest result interpretation. The primary focus during the assessment in these clinics is kidney disease rather than multisystem disease with pretest counseling focusing on diagnostic testing services for patients with suspected genetic kidney disease. Posttest counseling is also provided at disclosure of genetic testing results, and, if indicated, cascade testing for at-risk family members can be offered.[26] Additional services can include the longitudinal management of rarer, multisystem genetic kidney diseases, and increasingly these clinics are now also offering diagnostic evaluations of patients awaiting kidney transplant and their biologically related potential living donors.[25]

One commonly cited barrier to the establishment of kidney genetics clinics is the lack of access to genetic counselors in the field of nephrology.[27] Where there is a lack of access to genetic counseling, some groups describe success in implementing these services where the nephrologist provides counseling.[17] This process can be facilitated by the genetic counselors providing specific training to nephrologists on relevant topics, including genetic terminology, basic counseling concepts, types of results, informed consent, testing logistic, and considerations surrounding genetic discrimination.[17] Although led by a nephrologist, in some of these models a clinical geneticist is available to assist in the interpretation of genetic results, where needed.[28] This requirement largely depends on the training and expertise of the

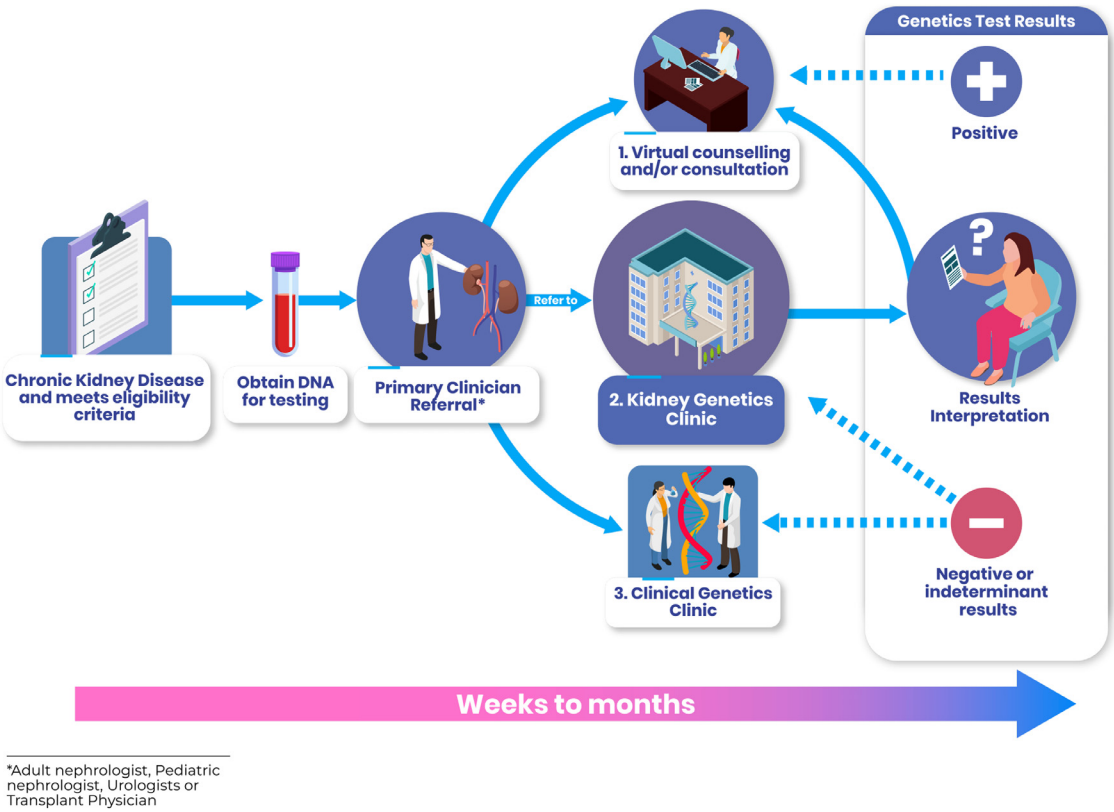

Figure 4. Workflow for a nephrology-led kidney genetics clinic that can be supported by genetic counselors in close collaboration with clinic genetics. The timeline from initial referral to disclosure of genetic testing results is indicated by the arrow below. Dashed blue arrows indicate possible options for access services in the testing of positive results for enhanced interpretation or genetic counseling or negative or indeterminate results where further evaluation of indeterminate or negative results or enhanced testing strategies are required. For these patients, assessment in a kidney genetics clinic or in a clinical genetics clinic maybe required for comprehensive evaluation.

nephrology lead and reiterates the ongoing need for organizational frameworks (Figure 4) and access to multidisciplinary teams (Figure 5) that include nephrologists, geneticists, and genetic counselors.

Combined Family Clinics

A genetic diagnosis can have a wider impact beyond the index patient, with potential implications for all biologically related family members.[29] In recognition of this impact, combined family clinics have, in some jurisdictions, been established to provide extensive review of the entire family unit. The goal of these clinics is to provide guidance on management, screening, and counseling for both the index patient and their at-risk family members.[21] These services are typically run by multidisciplinary teams that include a clinical geneticists and adult and/or pediatric nephrologists (with a special interest in kidney genetics) who come together to jointly assess families. The benefit of this approach is the ability to simultaneously counsel and perform cascade testing in at-risk family members. Cascade testing, defined as the screening of at-risk family members following confirmation of a genetic diagnosis in the index patient, has been shown to be highly effective in identifying other affected family members.[30,31] Unfortunately, data consistently show that even in at-risk family members, uptake of cascade testing is limited across all disease subtypes.[32,33] Family clinics, therefore, provide an opportunity to enhance familial communication regarding the impact of a genetic testing result and provide the opportunity for concurrent family counseling and familial variant testing.

Mainstreaming Models

Data consistently show under-referral of at-risk patients with genetic kidney disease to the specialists that currently have the capacity to initiate genetic testing.[5] Mainstreaming is defined as the process of integrating genetic and genomic testing into routine clinical care.[34] Due to the global shortage of health care professionals trained in genetics, shifting the burden of genetic testing from genetic specialists in dedicated clinics to nongenetic clinicians has the potential to rapidly enhance access to genomic services worldwide (Figure 6).[35]

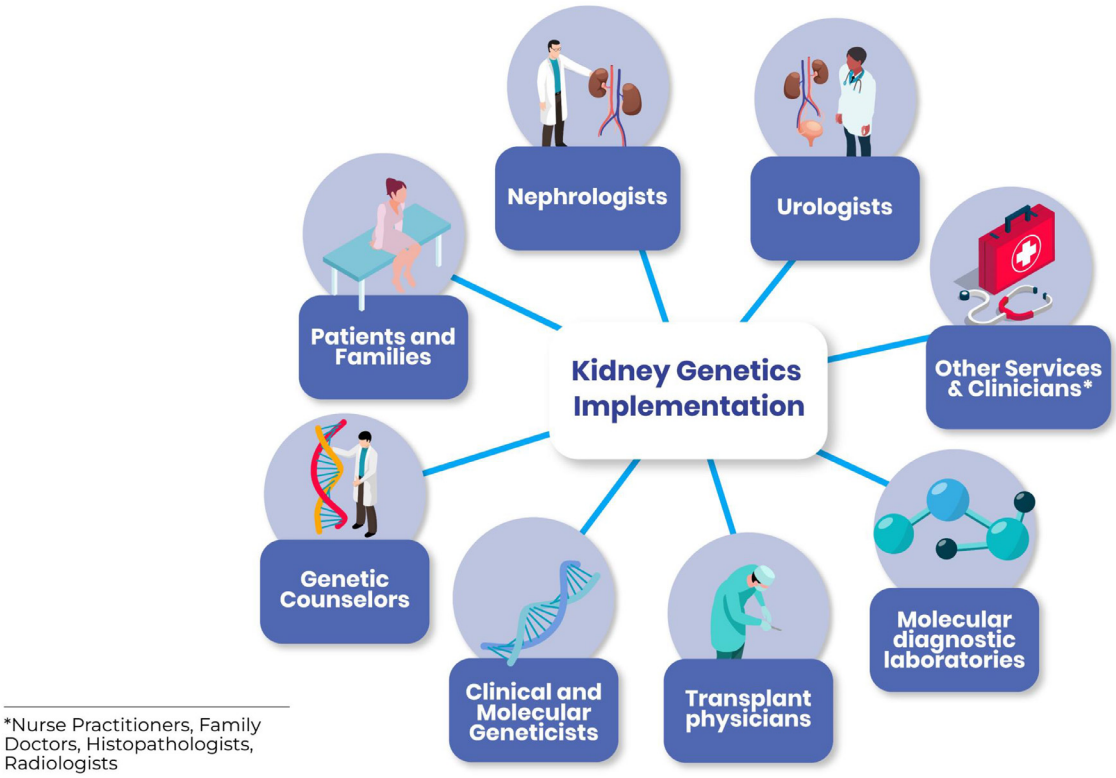

Figure 5. Multidisciplinary team input required for kidney genetics implementation.

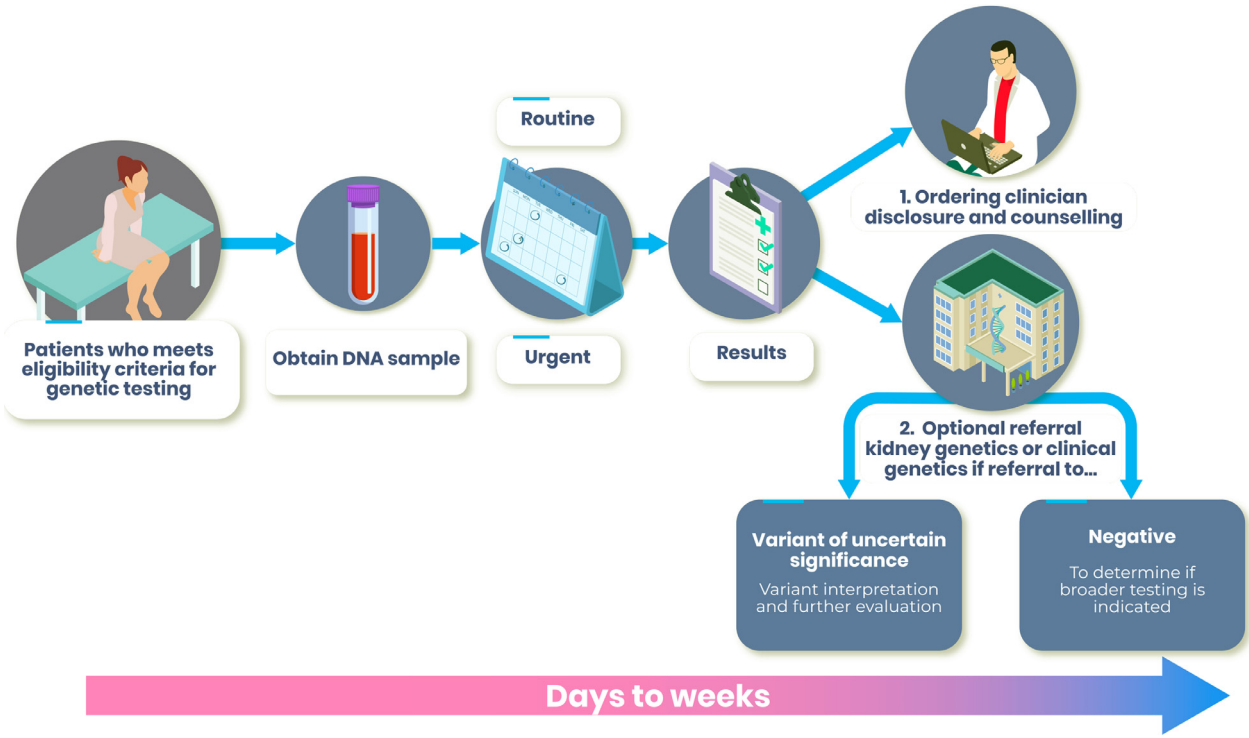

Figure 6. Mainstreaming model of care in kidney genetics. The timeline from initial referral to disclosure of genetic testing results is indicated by the arrow below.

Mainstreaming also offers the promise of enhanced and equitable access to genetic testing for patients with kidney disease.[35,36] One of the key elements in mainstreaming is shifting perceptions that the ordering clinician *must* be a genetic specialist to an ordering clinician as anyone who provides treatment and risk assessment of patients with kidney disease. This approach to genetic testing therefore hinges on the education and training of nephrologists and nephrology trainees on pre- and post-test genetic counseling, genetic testing methods (including their indications and limitations), appropriate variant interpretation, and the integration of genetic testing results into clinical care.[20] In Canada, a limited mainstreaming genetic testing pathway has been adopted in some jurisdictions for patients with autosomal dominant polycystic kidney disease. In this mainstreaming pathway the nephrologist is the primary ordering clinician with a clear testing pathway co-designed by nephrologists, medical geneticists, and genetic counselors. Using this approach, nephrologists can carry out initial counseling, consent, sample collection, and test ordering, with the interpretation and communication of results to patients completed by the clinical genetics team.[19] Implementation studies are also underway assessing nephrology-led genomic testing services for glomerular disease, with a goal to evaluate mainstreaming of genetic testing in nephrology.[23]

Kidney Genetic Networks

Equitable and sustainable implementation of genetic testing in nephrology into health care systems requires collaborative efforts across multiple sites and disciplines to ensure successful scale and spread of kidney genetic services.[37] In Australia, building on the initial establishment of multidisciplinary kidney genetics clinics, in 2016 the KidGen Collaborative was formed with the goal of providing a definitive diagnosis to patients with genetic kidney disease within a multidisciplinary renal genetic clinic setting across Australia.[38] To this end, Jayasinghe outlines a scalable, economically sustainable approach to the establishment and expansion of a national network of 20 kidney genetic clinics with direct integration of laboratory, research, and educational programs. Further, this approach supported evidence generation leading to sustainable Australian government funding for genetic testing in nephrology, which was approved and implemented iteratively between 2019 and 2022.[39] Using this nationwide approach, the KidGen Collaborative provide a blueprint for expanding clinical reach and services while using adaptive solutions to address key identified barriers such as workforce limitations, data integration issues, and patient access. The efforts of the KidGen Collaborative highlights the transformative potential of integrating genomic medicine into the diagnostic pathway for patient with CKD while providing a scalable framework for implementation in other jurisdictions and other disease specialties.

Similarly, in Europe, the Irish Kidney Gene Project is a national, collaborative network, set up initially as a research initiative, to explore the links between genetics and kidney disease. It has since evolved into a national service delivery model for kidney genetics. A key element to this approach is again the establishment of specialized genetics service and dedicated kidney genetic disease clinics, incorporating a multidisciplinary team of nephrologists, clinical geneticists, genetics counselors, nurse specialists, pathologists, researchers, and bioinformaticians, all with a common goal to diagnose, manage, and treat patients with genetic kidney disease.[40]

Clinical Research Links and Collaboration Importance

To date, clinical practice in nephrology has relied on targeted gene panel testing, with access to genome-wide sequencing, until very recently, restricted to research-based testing.[40-42] Research-based testing, although performed in select patient populations, has been a major catalyst for change by providing vital information on feasibility and utility of different genetic testing approaches in nephrology.[10,43] A key priority for implementation going forward must be to continue to support the transfer of research-based testing results into clinical practice by creating processes that support a seamless transfer of genetic information.[44] To address this, Nestor details a workflow for the return of medically actionable genetic findings to nephrology research participants. In their study, 62% of the 104 participants with positive research genetic test results were contacted, with disclosure of results ultimately occurred in 39%. Noteworthy is that in those with positive genetic results (n = 41), more than half reported a direct impact on therapeutics and management following result disclosure.[45] These findings highlight the importance of establishing and resourcing translational clinical research links to support translational efforts in kidney genetics research.

Virtual Models of Care

Marshall's stark assertion that "Health inequity is embedded in genomic medicine"[46] embodies one of the major barriers facing genomic medicine advocates worldwide. With studies now showing that at least 1 in 10 adults with chronic kidney disease has a monogenic form of disease,[2,10] enhancing access for adults with CKD is increasingly important. Major barriers such as rurality and distance to specialist referral centers disproportionately affect patients in disadvantaged communities.[47,48] Utilization of technology to improve access is increasingly being considered to overcome these barriers and to enhance equity of access to genomic

testing in more diverse geographic and patient populations. Another barrier is the concern expressed by nongenetic clinicians surrounding the need to interpret and disclose more complex genetic test results, particularly incidental genetic findings unrelated to kidney disease.[49] With the expansion of testing to more comprehensive testing platforms,[50] including both exome and genome sequencing, we anticipate larger quantities of posttest data that require correct interpretation in the context of the patient under investigation. For example, in one cohort, 8% of CKD patients had a finding in a secondary medically actionable gene following genetic testing.[49] To meet these needs, in Ontario, Canada, transformative technologies such as electronic consultations, so-called eConsults, are now being employed to meet the need for specialist advice across all disease specialists, including genetic testing result interpretation.[51] For kidney genetics, electronic consultation services such as the Ontario eConsult program can enable nongenetic clinicians to directly consult disease-specific genetic specialists, thereby alleviating some of the concern surrounding variant interpretation as a potential barrier to genetic testing.[52] With a median response time of 0.9 days for eConsult replies (ranging from <1 hour to 27 days),[53] this strategy has the potential to significantly improve timely access to specialist genetic services. Overall, data shows that eConsults reduce the need for face-to-face referral in 69% of cases.[54] In the United States, data similarly show high success of an e-Consult service established to directly address genomic-related questions. In this study, Folkerts found that an e-Consult program reduced unnecessary visits, thereby reducing the burden on clinical genetic services.[55] Considering data showing a median wait time of >10 years from time of diagnosis of CKD to confirmation of genetic kidney disease,[56] these approaches to enhance access to genomics specialists stand to enhance efficiency and reduce time to diagnosis in patients with genetic kidney disease.

Variant Review Boards

Other innovative options to overcome barriers related to result interpretation include multidisciplinary team review at dedicated nephrology genomics or variant review boards. Following the KDIGO Controversies Conference on Genetics in CKD, one of the key consensus recommendations was to establish interdisciplinary expert boards (including nephrologists, clinical geneticists, molecular biologists, and genetic counselors) to discuss genetic diagnostic findings.[57] As a result, genomic review boards (also known as variant review boards) are emerging as a strategy to enhance access to genetic testing while continuing to safeguard against misinterpretations of results. These boards usually consist of disease specialists (i.e., nephrologists), trainees, clinical and molecular geneticists, genetic counselors, pathologists, and researchers.[17] The boards leverage their collective expertise to facilitate comprehensive interpretation of genetic test results by integrating clinical and pedigree data, laboratory and imaging investigations, and histopathology. In most cases, the American College of Medical Genetics and Genomics' (ACMG) five-tier framework for variant classification is applied,[58] with additional details derived from the board members, to assist in the classification of variants of uncertain significance (VUSs) to either pathogenic or benign significance. Data show that this approach in nephrology can result in a reclassification rate of 5% following reanalysis of VUSs.[5] Interestingly, and contrary to previous reports in other disease specialties, for kidney disease patients, reports now show that a high proportion of VUSs are upgraded to either pathogenic or likely pathogenic variants, underscoring the need for comprehensive interpretation of all VUSs in patient with CKD.[59] This approach also has significant clinical implications, with 60% of the patients receiving a new diagnosis or a change in diagnosis after variant reclassification, with changes in clinical management reported for 67% of patients. It is important to note, however, that almost a third of VUSs are still downgraded to benign or likely benign variants,[59] reiterating the ongoing need for importance of structured reevaluation[60] and ensuring that VUSs are not used in clinical decision-making prior to this review.[61]

These boards can also act as a link to facilitate translation of research-based testing results into clinical practice. A recent example is the genome board established at the Hospital for Sick Children in Toronto, Canada, to address interpretation challenges that arise from research-based genome-wide sequencing such as the interpretation of secondary or incidental findings and their potential clinical actionability. This group reported on the review of 67 submissions from 13 research groups across multiple disciplines, of which 48 were requests for genetic variant review. Following evaluation, over one-third (n = 23) of the submissions resulted in clinical confirmation and recommendations for genetic counseling for patients. It should also be noted that in some cases, the genome board recommended against returning findings due to unclear clinical relevance or lack of medical guidelines for management. This approach therefore provides a scalable framework for implementing genomics consultation services in medical subspecialties such as nephrology and highlights the importance of collaboration between clinical and research domains as genomic data become increasingly utilized in health care.

Genetic and Genomic Champions

Genomic champions are health care professionals who have advanced expertise in genetics and genomics specific to their own field (e.g., nephrology). Through their

expanded scope of practice they serve to advocate for and facilitate the integration of genomic medicine in their clinical subspecialties.[62] These individuals, often working outside of clinical genetics services, can navigate barriers and bridge the gap between genetics and nephrology, playing a role in advancing genetic literacy and fostering the adoption of genomic technologies. By sharing their expertise and building collaborative networks, champions support and enable the incorporation of genomic testing into routine clinical workflows. They provide critical education in an experiential manner, enhancing the confidence and competency of non-geneticist clinicians. Additionally, they advocate for genomic medicine at decision-making tables where clinical genetics may lack representation. To maximize the impact of genomic champions, intentional strategies are needed to support them with continued training, resources, and engagement. Hospitals and institutions must implement structures that enable champions to work effectively within their expanded scope, while national and international organizations should offer formal credentialing and competency pathways. Funding and resource allocation are essential to sustain these roles, ensuring that champions can focus on promoting equitable and efficient access to genomic testing. Their efforts are pivotal in mainstreaming genomic medicine and addressing the growing demand for personalized health care solutions.

BARRIERS AND FACILITATORS

Workforce and Workload

Workforce and workload considerations in genetic testing and genomic data interpretation are critical because of the inherent complexity and labor-intensive nature of these processes. Evidence consistently shows that the analysis of genomic data carries substantial risks for both false-positive and false-negative results.[38] Diagnostic laboratories play a pivotal role in the implementation and advancement of genetic testing by ensuring accurate analysis, interpretation, and reporting of genetic variants. However, interpreting genetic and genomic test results presents ongoing challenges, particularly with VUSs.[19,58] As previously outlined, these variants pose barriers to mainstreaming genetic testing, because many nongenetic clinicians lack the necessary genetic literacy for accurate interpretation.[7] Current guidelines recommend that VUSs should not inform clinical decision-making unless they achieve a level of pathogenicity sufficient to establish causality.[25] Reclassification of VUS often requires additional analyses, such as segregation studies and functional assessments, and in some cases advanced methodologies like animal or cellular models to fully elucidate their potential role in disease pathogenesis.[19] Additionally, laboratories face increasing demands for specialized testing to identify difficult-to-detect variants, such as structural or rare noncoding variants.[50] This necessitates the development of comprehensive testing platforms and methodologies to ensure robust diagnostic capabilities.[63,64] The significant workload associated with these advancements underscores the critical need for well-resourced diagnostic laboratories and close collaboration between laboratory scientists and clinical teams. Adequate support and funding for a skilled workforce, proficient in bioinformatics and variant interpretation, are essential to meet the challenges of accurate data interpretation and incidental findings. The rapid expansion of genomic testing in clinical settings further highlights the necessity for enhanced training and upskilling of nephrologists in kidney genetics.[65] Structured service delivery models, such as those developed in Australia,[66] integrate multidisciplinary teams to ensure accurate diagnoses, effective patient management, and equitable workload distribution. Similarly, Ontario Health's Provincial Genetics Program provides comprehensive genetic services, including diagnostic testing, counseling, and clinical management, while ensuring equitable access to genetic expertise and resources for genetic testing.[67] Scaling such collaborative, multidisciplinary frameworks globally is imperative to fully realize the transformative potential of genomic medicine in nephrology, advancing both patient care and scientific discovery.

Genetic Counselor Shortage

A key concern in genetic testing is the ethical and psychosocial impact on patients, particularly when disclosing incidental or secondary findings. Managing these disclosures requires sensitivity and appropriate genetic counseling support. While our review emphasizes the importance of pre- and posttest counseling, the limited availability of genetic counselors remains a major barrier. To mitigate this, targeted training programs can equip nephrologists with the necessary skills to handle common genetic counseling scenarios, ensuring patients receive appropriate guidance.[17]

One effective strategy is the establishment of nephrologist-led kidney genetics clinics,[5,24,25] where nephrologists with specialized training in genetics play a central role in test ordering, patient counseling, and result interpretation. While not a complete substitute for genetic counselors, this model enables nephrologists to provide essential genetic services, particularly for well-defined conditions such as autosomal dominant polycystic kidney disease.[28] This approach has already been successfully implemented in certain jurisdictions, demonstrating its feasibility.

Another key solution is the use of multidisciplinary teams in which nephrologists collaborate with medical geneticists, laboratory scientists, and other specialists. Such teams facilitate case discussions and shared

decision-making, alleviating the burden on individual nephrologists and improving the accuracy of test interpretation.[21,68] Our review also highlights the role of electronic consultation services (eConsults),[51,52,56] which provide remote access to genetic specialists and have proven effective in supporting health care providers in regions with limited in-person genetic counseling services.

Leveraging digital tools for patient education and counseling represents another promising avenue. Online pretest education modules and tele-genetics services allow patients to make informed decisions without requiring face-to-face interaction with a genetic counselor.[69] This model has been successfully utilized in oncology and is increasingly being explored in nephrology.

Finally, upskilling existing health care professionals, such as nurses, physician assistants, and primary care doctors, to provide basic genetic counseling could be a practical solution, particularly in resource-limited settings. Countries that have successfully integrated genetic medicine into nephrology—such as Australia—have developed structured pathways for nephrologists to receive ongoing genetics education, which could serve as a model for other regions.

Equity in Access

Access to genetic testing varies significantly across jurisdictions due to differences in funding models. In jurisdictions were genetic testing is not covered under universal health care, testing access remains variable due to different coverage criteria from those of health insurance companies.[17] However, with growing evidence of medical necessity and decreasing costs, studies are now showing that 90% of patients had genetic testing covered by insurance, with out-of-pocket expenses ranging from $0 to $500. In other jurisdictions, such as Australia, there has been significant progress in establishing equitable models of care. For example, as of July 1, 2022, genomic testing for suspected genetic kidney disease is reimbursed nationwide under the Australian Medicare Benefits Schedule, offering universal access to testing.[66]

Unfortunately, even when financial barriers are removed, significant disparities in access can remain, with economically disadvantaged and rural communities disproportionally impacted.[46] Over two decades Bleyer outlines referral patterns for no-cost genetic testing for inherited kidney disease, showing a progressive increase in referrals for testing over time. Interestingly, 27% of all referrals (n = 176/665) were direct from patients via internet contact. Direct patient referral can in some cases be a method to overcome under-referral by the health care profession. It is noteworthy, however, that in this cohort it actually exacerbated disparities: 99% of direct patient referrals were from individuals who self-reported as white and resided in a zip code location with a mean income of $77,000, significantly higher than the US median of $49,000.[70] Indeed, one of the key priorities for implementation as outlined by KDIGO[57] is to increase genetic and genomic resources in underrepresented populations with kidney disease.[44] In addition, equitable access in minority groups often faces unique barriers such as mistrust, privacy fears, and limited culturally sensitive care.[71]

One such fear often cited as a potential barrier is actual or perceived fear of genetic discrimination. Fortunately, legal frameworks in many countries prohibit genetic discrimination in health insurance and employment,[72,73] but gaps can remain in protections for life and disability insurance. For example, in Australia, while private health insurance is not underwritten based on genetic data, life insurers can use such information, though reforms such as the proposed moratorium by the Financial Services Council may change this landscape.[74] In Canada the Genetic Non-Discrimination Act in Canada, enacted in 2017, prohibits the use of genetic test results to discriminate across health and life insurance, employment, and many other non−health care contexts.[72] Internationally, ongoing efforts are required to ensure protection of individuals' genetic privacy, to alleviate concerns surrounding participation in genetic testing and to ensure equitable access to genetic services without fear of discrimination.

Education and Training

Worldwide, the successful integration of genetic testing into nephrology largely relies on advancing education in kidney genetics, an area with significant gaps in knowledge and training.[7,8,75] A recent systematic review of nephrology trainees in the United States revealed large gaps in training: between 2004 and 2008, only 15% of trainees reported adequate exposure to genetic renal diseases, while 50% acknowledged receiving some training but not enough to feel confident in diagnosing or managing these conditions.[76] Despite this, more than 90% of trainees recognized the importance of education in kidney genetics. Similarly, a survey of 201 practicing nephrologists found that although all had treated patients with genetic kidney diseases, 37% referred fewer than five patients for genetic assessment. Over 50% of respondents cited insufficient training as a key barrier. Encouragingly, most nephrologists identified improving their genetic knowledge as a priority. These finding underscore the urgent need to capitalize on this willingness to learn and upskill by implementing targeted educational initiatives and comprehensive training programs.[75]

Patient-Led Care

Integrating genetic testing into routine clinical care necessitates a deep understanding of patient needs and

preferences. Insights from the KidGen policy implementation workshop emphasize the critical importance of educating patients and involving them at every stage of research and health care reforms.[66] This collaborative approach ensures that care models align with the real-world needs and values of individuals affected by genetic kidney diseases. For example, while clinicians often cite the psychological impact of genetic testing as a potential barrier to implementation,[7] evidence suggests otherwise.[77] Quantitative and qualitative studies reveal that most patients, when offered the choice, opt to receive genetic testing results. Furthermore, these studies indicate no significant increase in depression, anxiety, perceived stigma, or secrecy before and after testing.[78] One important point to consider, however, is that genetic counseling must differentiate between the disclosure of results directly related to the primary disease under investigation and incidental findings unrelated to the disease being evaluated. For instance, a large study involving more than 3,000 individuals who underwent exome sequencing highlighted substantial variability in patient preferences for the disclosure of secondary findings.[79] This underscores the ongoing need for robust genetic counseling and explicit, separate consent processes for both primary (disease-specific) and secondary (incidental) findings, particularly when such findings carry medically actionable results.[80]

Finally, the case of *Apolipoprotein L1* (*APOL1*) testing exemplifies the importance of culturally competent, patient-centered approaches to genetic testing in nephrology. Recessive *APOL1* risk variants, prevalent among individuals of West African descent, significantly increase the risk of kidney disease when inherited.[81] In indication-driven testing, such as for patients with established CKD, race-neutral testing is advocated as a culturally sensitive approach that ensures genetic test offerings are consistent, regardless of perceived or reported race. However, predictive testing in contexts such as living kidney donation raises complex ethical concerns.[82] For example, testing donors with two *APOL1* risk alleles may improve informed decision-making through genetic counseling, given data indicating increased risks of kidney disease in these donors.[83] At the same time, the high prevalence of two risk alleles among individuals of African ancestry without CKD (13%-15%) and the variable penetrance of these alleles introduce the potential for systemic inequities.[81] Widespread race-based testing poses significant risks and can perpetuate systemic racism and disproportionately affect certain groups. To balance clinical utility with equity, a race-neutral approach to diagnostic testing is essential, ensuring that predictive testing is both culturally competent and unbiased. Such strategies promote ethical, patient-led care models that prioritize fairness and inclusivity.[83]

DISCUSSION

This article explores the integration of genetic testing into nephrology, emphasizing its transformative potential for the diagnosis and management of CKD. It offers detailed insights into various models of care, the barriers to implementation, and strategies to overcome them. Here, we reflect on the findings, their implications, and areas requiring further attention.

Advances in Genetic Testing Integration

The shift toward earlier genetic testing in CKD diagnostics represents a critical evolution in nephrology. Evidence demonstrates that early implementation can lead to significant cost savings,[11,68] improved diagnostic yield,[3] and optimized therapeutic strategies.[10] However, despite these advantages, genetic testing remains underutilized or delayed in clinical practice.[5] Addressing this lag is pivotal for realizing the full potential of genetic testing in CKD care.

Models of Care

The models of care discussed, including multidisciplinary clinics, nephrology-initiated genetic clinics, and virtual models, highlight innovative approaches to enhance accessibility and integration. Particularly noteworthy is the emphasis on mainstreaming genetic testing into general nephrology and primary care. This model, while promising for scalability, necessitates robust training programs to equip nephrologists and primary care physicians with the skills and supports to interpret genetic data and counsel patients effectively.

Challenges in Implementation

The article underscores several challenges that are potentially hindering the widespread adoption of genetic testing in nephrology, including the following:

Limited Genetic Literacy[7,8,76]**:** A significant barrier remains the insufficient training among nephrologists and other nongenetic clinicians. Enhancing education and creating "genomic champions" could address this gap.[62]

Equity in Access: Disparities in access to genetic services, particularly in underserved populations,[46] emphasize the need for inclusive strategies. Initiatives like “culturally competent” *APOL1* testing exemplify approaches to bridging such gaps.[83]

Workforce and Resource Constraints: A shortage of genetic counselors and clinical geneticists complicates the integration process.[84,85] Models such as eConsults and variant review boards offer scalable solutions to alleviate these challenges.

Bridging Research and Clinical Practice: The discussion highlights the critical role of clinical−research linkages in advancing genetic testing. Translating findings from research into clinical practice requires systematic frameworks to ensure the seamless transfer of data and its actionable interpretation.[45] The success of programs like the KidGen Collaborative[66] and Genome Boards[1] serves as a testament to the power of interdisciplinary and national collaborations.

Ethical and Patient-Centric Considerations

Ethical challenges, such as informed consent after genetic counseling and the return of incidental findings, demand careful navigation. Embedding genetic counseling into all stages of care is essential to ensure patients are fully informed and supported. Furthermore, incorporating patient preferences and values into care models will enhance trust and uptake, underscoring the need for patient-led approaches.

Potential Risks

The expansion of genetic testing beyond specialized genetic services into nephrology and other health care disciplines presents several challenges and risks that need to be carefully addressed.[28] As highlighted in this article, mainstreaming genetic testing into nephrology practice offers the potential for earlier diagnoses and improved patient management,[28] but it also introduces concerns related to test interpretation, ethical considerations, resource allocation, and workforce readiness.[36]

One major challenge is the limited genetic literacy among nongenetic health care providers.[7,8] Many nephrologists and primary care physicians lack formal training in genetics, particularly in interpreting complex genetic variants, such as VUS.[59,61] Misinterpretation of results could lead to unnecessary patient anxiety, inappropriate changes in management, or missed diagnoses. To mitigate this, structured educational programs, genomic "champions,"[62] and collaboration with genetic specialists are essential, as outlined in our discussion of multidisciplinary teams,[21] kidney genetics clinics, and variant review boards.[68]

From a health care systems perspective, mainstreaming genetic testing also raises issues related to equity of access. While some jurisdictions have implemented reimbursed pathways for genetic testing (e.g., Australia's Medicare Benefits Schedule),[66] disparities remain in lower-resource settings where genetic testing may not be funded. Furthermore, concerns about genetic discrimination persist despite legal protections in some countries. Our discussion of *APOL1* testing in living kidney donation highlights how systemic inequities could arise if genetic testing is not integrated thoughtfully and equitably.[83]

Finally, the workforce burden is a key limitation. Increasing the number of nephrologists and other clinicians ordering genetic tests places additional strain on diagnostic laboratories, which already face challenges in variant interpretation. Our review underscores the need for variant reanalysis workflows, interdisciplinary variant review boards, and electronic consult services (eConsults) as scalable solutions to alleviate some of these pressures.

Future Directions

To promote the successful integration of genetic testing into nephrology, a multifaceted approach is needed, including the following:

- **Education and Training:** Systematic efforts to improve genetic literacy among nephrologists and other health care providers are paramount.
- **Infrastructure Development:** Investment in scalable models, such as virtual consultations and multidisciplinary clinics, can improve accessibility.
- **Equity and Inclusion:** Tailored strategies must address the disparities in access and ensure diverse populations are represented in genomic databases.
- **Policy and Funding:** Policies that support reimbursement and protect against genetic discrimination can incentivize broader adoption of genetic testing.

CONCLUSION

This article outlines a road map for integrating genetic testing into nephrology. By addressing the barriers and leveraging innovative care models, the nephrology community can ensure that genetic testing becomes a cornerstone of CKD diagnostics and management. Sustained efforts in education, collaboration, and resource allocation will be essential for the widespread implementation and equitable access to genomic medicine. This discussion encapsulates the need for a unified, global effort to integrate genomic insights into nephrology, ensuring all patients benefit from advancements in personalized medicine.

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