Check for updates

Implementation and Evaluation of a National Multidisciplinary Kidney Genetics Clinic Network Over 10 Years

Kushani Jayasinghe[1,2,3,4], Erik Biros[3,5,6], Trudie Harris[3,6], Alasdair Wood[3], Rosie O'Shea[3], Lauren Hill[3], Lindsay Fowles[7], Louise Wardrop[3], Carolyn Shalhoub[8,9], Deirdre Hahn[10], Gopala Rangan[11,12], Lucy Kevin[10], Michel Tchan[11], Paul Snelling[13], Rhiannon Sandow[13], Madhivan Sundaram[14], Swasti Chaturvedi[14], Peter Trnka[15], Randall Faull[16], Nicola K. Poplawski[16,17], Vanessa Huntley[16], Denisse Garza[18], Mathew Wallis[18], Matthew Jose[18], Anna Leaver[19], Alison H. Trainer[20,21,22], Ella J. Wilkins[3,4,23,24], Sue White[23], Yoni Elbaum[23], Yael Prawer[25,26,27], Emma Krzesinski[25,26,27], Giulia Valente[19], Ingrid Winship[20], Jessica Ryan[25], John Whitlam[19], Kathy Nicholls[20], Kirsty West[20], Liz Donaldson[20], Lilian Johnstone[25,28], Miranda Lewit-Mendes[25], Peter G. Kerr[25], Simon Bodek[19], Aron Chakera[29], Mandi MacShane[29], Christine Mincham[30], Elaine Stackpoole[29,30,31], Francis Willis[30], Jacqueline Soraru[31], Nick Pachter[31], Bruce Bennetts[32,33], Thomas A. Forbes[4,24,36,37], Amali Mallawaarachchi[4,34,35], Catherine Quinlan[4,24,36,37,38], Chirag Patel[4,39], Hugh McCarthy[40,41,42], Illias Goranitis[3,43,44], Stephanie Best[3,21,45,46], Stephen Alexander[40,42], Zornitza Stark[4,24,47] and Andrew J. Mallett[3,4,5,6,48,49]

[1]Department of Nephrology, Monash Medical Centre, Melbourne, Victoria, Australia; [2]School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia; [3]Murdoch Children's Research Institute, Melbourne, Victoria, Australia; [4]The KidGen Collaborative, Australian Genomics Health Alliance, Melbourne, Victoria, Australia; [5]College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia; [6]Townsville University Hospital, Townsville, Queensland, Australia; [7]Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [8]Sydney Children's Hospital, Randwick, Sydney, New South Wales, Australia; [9]School of Clinical Medicine, UNSW Medicine and Health, Randwick Clinical Campus, Sydney, New South Wales, Australia; [10]The Children's Hospital at Westmead, Sydney, New South Wales, Australia; [11]Westmead Hospital, Sydney, New South Wales, Australia; [12]Michael Stern Laboratory for Polycystic Kidney Disease, Westmead Institute for Medical Research, The University of Sydney, Sydney, New South Wales, Australia; [13]The Royal Prince Alfred Hospital, Sydney, New South Wales, Australia; [14]Royal Darwin Hospital, Darwin, Northern Territory, Australia; [15]Queensland Children's Hospital, Brisbane, Queensland, Australia; [16]Royal Adelaide Hospital, Adelaide, South Australia, Australia; [17]Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia; [18]Royal Hobart Hospital, Hobart, Tasmania, Australia; [19]Austin Hospital, Melbourne, Victoria, Australia; [20]Royal Melbourne Hospital, Melbourne, Victoria, Australia; [21]Department of Oncology, Sir Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Victoria, Australia; [22]Department of Medicine, University of Melbourne, Victoria, Australia; [23]Royal Children's Hospital, Melbourne, Victoria, Australia; [24]Department of Paediatrics, University of Melbourne, Victoria, Australia; [25]Monash Health, Melbourne, Victoria, Australia; [26]Monash Genetics, Monash Health, Melbourne, Victoria, Australia; [27]Department of Paediatrics, Monash University, Melbourne, Victoria, Australia; [28]Department of Paediatrics, Monash University, Clayton, Victoria, Australia; [29]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; [30]Perth Children's Hospital, Perth, Western Australia, Australia; [31]Fiona Stanley Hospital Perth, Western Australia, Australia; [32]Department of Molecular Genetics, Sydney Genome Diagnostics, Western Sydney Genetics Program, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; [33]Specialty of Genomic Medicine, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia; [34]Garvan Institute of Medical Research, Sydney, New South Wales, Australia; [35]Department of Medical Genomics, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia; [36]Department of Nephrology, Royal Children's Hospital, Melbourne, Victoria, Australia; [37]Kidney Regeneration, Murdoch Children's Research Institute, Melbourne, Victoria, Australia; [38]Melbourne Genomics Health Alliance, Melbourne, Victoria, Australia; [39]Genetic Health Queensland, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [40]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; [41]Department of Nephrology, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; [42]Department of Nephrology, Sydney Children's Hospital, Randwick, Sydney, New South Wales, Australia; [43]Health Economics Unit, Centre for Health Policy, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia; [44]Australian Genomics, Melbourne, Victoria, Australia; [45]Department of Health Services Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [46]Victorian Comprehensive Cancer Centre Alliance, Melbourne,

Correspondence: Andrew J. Mallett, Department of Renal Medicine, Level 2, Townsville University Hospital, Angus Smith Drive, Douglas, Queensland 4814, Australia. E-mail: andrew.mallett@health.qld.gov.au

Victoria, Australia; [47]Victorian Clinical Genetics Services, Melbourne, Victoria, Australia; [48]Kidney Health Service, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; and [49]Institute for Molecular Bioscience and Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

Introduction: Diagnostic genomic sequencing is the emerging standard of care in nephrology. There is a growing need to scale up the implementation of genomic diagnostics nationally to improve patient outcomes.

Methods: This pragmatic study provided genomic or genetic testing to patients with suspected monogenic kidney disease through a national network of kidney genetics clinics (KGCs). We sought to evaluate the experiences of implementing genomic diagnostics across Australia and associated diagnostic outcomes between 2013 and 2022.

Results: We successfully established and expanded a nationwide network of 20 clinics as of 2022; concurrently developing laboratory, research, and education programs to scale the clinical application of genomics in nephrology. We report on an Australian cohort of 1506 kidney patients, of whom 1322 received their test results. We assessed barriers to implementation in the nephrology context, and where possible, applied real-time solutions to improve clinical processes over 10 years.

Conclusion: Developing a multidisciplinary kidney genetics model across multiple health services nationally was highly successful. This model supported optimal care of individuals with monogenic kidney disease in an economically responsible way. It has continued to evolve with technological and service developments and is now set to scale further as genomic testing for kidney patients transitions to health care system funding.

Kidney diseases are a major global health priority, and monogenic causes account for 30% to 50% of childhood nephropathy[1,2] and 10% to 30% of adult chronic kidney disease.[3,4] A timely and accurate genetic diagnosis can provide valuable prognostic and predictive information, influence clinical decision-making, including treatment strategies and kidney transplant-related considerations, and inform reproductive decisions for affected individuals and their families.[5,6] Furthermore, genomic sequencing can transform diagnostic pathways by facilitating the diagnosis of rare disorders and improving the understanding of disease mechanisms, paving the way for future therapies.

Although many studies have validated the diagnostic yield, clinical utility, and cost-effectiveness of genetic and genomic sequencing in kidney disease cohorts,[7–9] most of these investigations have occurred within research settings, focusing on specific phenotypic subgroups.[10] This context underscores the imperative to transition these findings into broader clinical implementation.[11,12] Equitable and sustainable implementation in the clinical setting requires whole-system changes[13] that overcome implementation challenges relating to workforce capacity, infrastructure, and funding, as well as the establishment of appropriate service delivery models.[14,15]

Multidisciplinary clinics are a well-recognized means of addressing such implementation challenges.

This model of care has an established track record of supporting genomic implementation in kidney medicine and other specialties such as cardiology and oncology.[16,17] For example, a 5-year review of a single KGC highlighted the benefits of including a multidisciplinary team (MDT) for kidney patients in the United Kingdom.[16] The multidisciplinary KGC (MD-KGC) model allowed for a coordinated approach between clinical genetics and nephrology, and resulted in timely diagnosis and improved clinical management of genetic kidney disease.[16] In the United States, an MD-KGC model consists of adult and pediatric nephrologists and genetic counselors and reported on only a relatively small number of patients.[17] Support for genomic testing among nephrologists, with a strong preference for a multidisciplinary model involving a nephrologist, clinical geneticist, and genetic counselor, has also contributed to establishing a network of KGCs within the Australian public health care system.[7] The first MD-KGC was established in Queensland (Australia) and provides services to pediatric and adult patients with suspected monogenic kidney disease.[18] Subsequently, the MD-KGC started its implementation in other Australian jurisdictions, including a network of 4 academic centers in Victoria (Australia).[19]

The initial focus on demonstrating the clinical benefits of a multidisciplinary approach to genomic testing in kidney disease also precipitated the need to document practical experiences from its implementation

into clinical practice.[20] Furthermore, it is vital to scale up these models beyond individual tertiary centers to serve the needs of diverse and geographically dispersed populations. Studies that explore clinical testing at a broader scale, particularly in a nephrology context, are lacking. The implementation and contextual factors at organizational, provider, and individual levels (clinician and patient) that lead to the successful integration of genomic testing in nephrology are poorly defined. Nevertheless, some barriers have been identified that hinder the effective implementation of genomic testing into the routine clinical management of genetic kidney diseases. For example, a lack of funding and awareness among clinicians and their perceived lack of preparedness have been highlighted.[16,17,21] A learning health care system has been suggested to address these challenges using continuous quality improvement strategies, which can keep up with technological advances in genetic medicine.[17]

We developed and implemented an iterative learning health care system approach to delivering kidney genomic services in Australia. Through this model, we established and used a national network of KGCs to continuously collect and aggregate sequencing data, including diagnostic and clinical outcomes. Analysis of these data informed implementation efforts to scale up genomic medicine in kidney disease at the national level. We actively collected feedback from clinical practices to inform our ongoing service model delivery. Here, we present a decade of extensive experience and proven results; our nationwide network of MD-KGCs has demonstrated significant improvements in the availability of genetic diagnosis for patients while optimizing the process for health care providers.

METHODS

Ethics

This study was approved by the Human Research Ethics Committee at Melbourne Health (HREC/16/MH/251) as part of the Australian Genomics Health Alliance: preparing Australia for Genomic Medicine program. Governance site-specific approval for the project was obtained for all participating KGCs. All participants provided written informed consent for data collection and to undergo clinically indicated genomic/genetic testing.

Context

In 2013, the first MD-KGC in Australia was established in Brisbane, Queensland, with initial outcomes subsequently reported.[18] Subsequently, a consortium of clinicians, counselors, scientists, and researchers (KidGen Collaborative) was formed to improve genetic

kidney disease outcomes.[22] These activities have occurred in the context of broader state and national genetic initiatives aimed at supporting the integration of genomics in clinical and research settings, including the Australian Genomics Health Alliance, the Melbourne Genomics Health Alliance, and the Queensland Genomics Health Alliance.[14,23-25] These initiatives have focused on building the evidence base for using genomic testing in different clinical scenarios, including kidney disease while tackling some of the data infrastructure, policy, ethics, and workforce challenges that large-scale implementation poses. Some notable developments from the Australian Genomics Health Alliance include developing a national clinical consent form and the Shariant platform, which enables evidence sharing across Australian clinical genomic testing laboratories to support and promote variant interpretation consistency.[20,26]

Genomic test funding in the clinical setting is a pressing issue. One major enabler is that the KidGen Collaborative facilitated access to funding for genomic testing for all patients with suspected monogenic kidney disease. Funding sources varied, including local hospital departments, research projects, and state-based funding until 2022. From mid-2022, and partly due to the collaborative work undertaken by KidGen, genomic testing for kidney diseases has been funded through the Australian Federal Government's national Medicare health schemes (mbsonline.gov.au), which provides Australians with subsidized health care.

Assessment of Implementation

We conducted a formative evaluation to investigate the uptake of genomic testing while establishing a national MD-KGCs network. Clinicians delivering the MD-KGC service were invited via email to give written feedback on the perceived barriers to KGC service delivery at their site during 2021 and 2022. The rationale behind this approach was rooted in the clinicians' firsthand experiences with patients, which were crucial for shaping effective implementation strategies. For instance, these clinicians identified, nominated, and presented their cases at MDT meetings. Their active engagement ensured that MD-KGC operations were continuously refined to align with the evolving needs of both patients and health care providers, thereby enhancing the effectiveness and quality of care provided.

In addition, clinicians were encouraged to nominate any solutions they had implemented to address identified barriers, fostering a collaborative effort toward improvement. Three primary periods of interest along the patient journey were before referral (before the patient was referred to MD-KGC), pretesting (includes

clinical assessments by MD-KGC and laboratory interactions), and posttesting (the return of results). We mapped the barriers and solutions to the Consolidated Framework for Implementation Research to generate findings that could be applied to other settings.[27] The Consolidated Framework for Implementation Research is a versatile framework for analyzing and enhancing innovation and intervention implementation in complex organizations. It includes the following 5 key domains: (i) intervention characteristics (complexity and adaptability), (ii) outer setting (external factors like resources and culture), (iii) inner setting (organizational factors like leadership support and staff skills), (iv) characteristics of individuals (unique factors like motivation and beliefs), and (v) process (implementation activities like planning and training).[27-29]

Participants

Participants with kidney disease were recruited from our MD-KGCs network. Two distinct groups were enrolled. The first group consisted of a retrospective cohort comprising individuals undergoing clinical genomic testing directly or after being referred to MD-KGCs between 2013 and 2019. The second group comprised a prospective cohort of patients referred to MD-KGCs between 2017 and 2022, including individuals who did not undergo genomic testing. All patients were referred to a KGC, and advice was sought for clinical genomic testing by the MDT, which included representation from at least 1 of each discipline, such as a nephrologist, geneticist, and genetic counselor. Each patient was seen at least twice in the KGC, once before genomic testing and again for the return of the results. During each clinic visit, a team of 2 or more disciplines reviewed the patient's case. Patients with existing confirmed molecular genetic diagnoses were excluded from the study. In addition, patients without a clear clinical indication for genomic testing and those determined by the MDT to have a low likelihood of an underlying monogenic basis were excluded from this study.

Genetic/Genomic Testing and Variant Analysis

DNA was isolated from blood or saliva samples, and sequencing was undertaken at clinically accredited laboratories for both cohorts, as described elsewhere.[19,30] Genomic and genetic testing in our cohort encompassed chromosomal microarray analysis, Sanger sequencing, whole exome sequencing, whole genome sequencing, and variable number of tandem repeats testing as clinically indicated. The earlier tests utilized targeted panels of genes and the newer technologies, such as whole genome sequencing and whole exome sequencing, were analyzed only for variants in a virtual panel of genes specific to the clinical phenotype using a curated list of several hundred genes associated with genetic kidney disease (PanelApp, Australia).[31] In Supplementary Table S3, we provide a comprehensive list of all the genes included in the Kidneyome Super-Panel (Version 8.53). Detected variants were classified according to American College of Medical Genetics and Genomics guidelines for clinical sequencing interpretation.[32] MDT meetings reviewed variants and phenotypic data when required to assist with interpretation at the case level before reporting.

Data Collection

Genomic and genetic test results and clinical and demographic data were collected and entered a research electronic data capture (REDCap) and data management platform[33,34] hosted at the Murdoch Children's Research Institute, Melbourne, Australia. Data capture included age at the test, testing date, KGC location, sequencing approach, and diagnostic outcomes. The suspected clinical diagnosis before genomic testing was also collected and classified according to a broad aetiologic category.

Statistical Analysis

Baseline characteristics are expressed as counts (n, %) or medians with interquartile range, as appropriate. The Chi-square or Fisher exact tests were performed to compare the proportions of clinical characteristics between respective groups. The primary outcome was the diagnostic yield based on variants classified as "pathogenic" and "likely pathogenic" according to American College of Medical Genetics and Genomics guidelines,[32] with consideration of appropriate inheritance patterns and phenotype consistency. Variants of uncertain significance (VUS)[32] were not included. Accordingly, the diagnostic yield was calculated using the formula: Diagnostic Yield = positive result (PR / [PR + NR + VUS] × 100), where PR represents positive results, and NR denotes negative results. Diagnostic yield is expressed as percent (%). Data were analyzed using the Stata/MP 16.0 statistical package (StataCorp LP, College Station, TX). Statistical significance was determined using 2-sided P-values, with a significance level set at the conventional 5% threshold.

RESULTS

Determinants of Implementation of Genomic Testing Within KGCs

As of 2022, 20 MD-KGCs have been established across all Australian state jurisdictions. Participating clinicians at these MD-KGCs identified contextual and individual provider issues that may impact future implementation programs. Barriers were identified by

geneticists and nephrologists who were working in KGCs. Most were coded to the "inner setting" and "intervention characteristics" Consolidated Framework for Implementation Research domains (Table 1). Barriers relating to the "inner setting" domain dominated both the "before referral" and "post referral-pretesting periods," with barriers falling under the structural characteristics and implementation climate, knowledge, and available resources subdomains (Table 1). The "intervention characteristics" domain dominated the "post referral-pretesting" period, with responses relating to the complexity of whole genome sequencing or whole exome sequencing technology (Table 1). Key strategies to overcome barriers during the "before referral" period included presenting new evidence of genomic testing and highlighting the clinical utility of genomic testing in kidney disease through education and engagement activities such as conferences and workshops. Concerns about testing efficiency were noted. Strategies, including variant prioritization meetings and shared gene lists, aimed to enhance consistency in analysis. However, the MD-KGC model could not address all barriers, such as funding insecurity and patient remoteness (Table 1).

In addition to establishing a publicly available nationwide network of MD-KGC, the KidGen Collaborative has also invested in many other resources to help improve equity and appropriate use of genomic testing for those with suspected monogenic kidney disease. The network has driven national consensus on gene panels for kidney genomic tests. These panels are hosted on PanelApp Australia, an openly accessible platform.[31] The network developed an education program consisting of online modules and workshops to upskill nephrologists on various aspects of genomic testing, including patient selection, test ordering, and result interpretation. In addition, the KidGen Collaborative has recently hosted 5 educational events dedicated to genetic kidney diseases, marking the 10th anniversary of the first KGC in Australasia.[18]

Demographics

In total, 1506 participants were included in the study, of whom 125 did not proceed with genomic or genetic testing, leaving 1381 participants who underwent testing. Among the tested patients, results of 59 individuals (from the prospective cohort only) were not returned by the end of the audit cut-off date, bringing the total number of patients with genetic testing results to 1322 (Figure 1). The underlying reasons for the absence of results were not explicitly examined but included those that had not yet had results reported during the study period. The demographic characteristics of participants are shown in Table 2. Almost two-thirds (849/1381) of participants were adults, and the median age at testing was 29 (interquartile range: 10–45) years. Detailed patient recruitment data across various states, stratified by years, is presented in Supplementary Table S1. It is noteworthy that during the most severe period of the COVID-19 pandemic in 2020, recruitment activities nearly ceased across all states except Western Australia, where only 4 patients were successfully recruited.

The retrospective cohort comprised 714 participants who all underwent genomic testing. The prospective cohort comprised 792 participants referred to KGCs, of whom 667 underwent genomic testing (Figure 1). Five percent (41/792) of participants within the prospective cohort were not recommended for testing by the MDT (greyed Figure 1) for the following reasons: testing would not impact the clinical management of either the participant or family members, an adequate prior diagnosis, or clinical presentation was not in keeping with monogenic kidney disease. In addition, 11% (84/792) of the prospective participants in the prospective cohort were not tested as the participant declined ($n =$ 31) or for unknown reasons ($n = 53$) (Figure 1).

Within the retrospective cohort, 48% (341/714) received a positive (pathogenic/likely pathogenic) result (PR) from genomic testing. In addition, a VUS was detected in 14% (100/714). Of the patients with a VUS identified, 30 of 100 (30%) were VUS with suspected clinical relevance (VUS×). Within the prospective cohort, 43% (288/667) received a PR. In addition, a VUS was detected in 17% (112/667) participants, and of those, 8% (9/112) had a VUS with suspected clinical relevance (Figure 1).

### Diagnostic Yield, Clinical Diagnoses, and Sequencing Method

The diagnostic yield for the national cohort between 2013 and 2022 was 45.8% (606/1322) (Table 3).

When the overall cohort is stratified according to the pretest clinical diagnosis, the diagnostic yield is highest for Alport syndrome (61.7%; 127/206) and lowest for congenital anomalies of the kidney and urinary tract (24.7%; 18/73), as shown in Table 4. The diagnostic odds ratio for Alport syndrome was 2.14, and for congenital anomalies of the kidney and urinary tract, it was 0.37 (Table 5). The evolution of sequencing methods throughout the study is presented in Table 6. In the earlier years (2013–2015), targeted panels of genes using massively parallel sequencing and Sanger sequencing were most commonly utilized. Since 2017, whole exome sequencing or whole genome sequencing-based approaches have been more widely used.

Table 1. Barriers and suggested interventions to integrate routine kidney genomic testing into clinical practice

Clinician reported barrier	CFIR construct	Description	Intervention applied in practice	Impact on the clinical setting
Before-referral period				
Delay in referrals and uptake by nephrologists not engaged with kidney genetics	Inner setting	Culture and implementation climate	Education initiatives	Earlier referrals to kidney genetics clinics
The inequity of referral for testing	Inner setting	Structural characteristics and underpinnings of inequity	Education initiatives	Increased referrals and reach of genomic testing
Variable access to testing between jurisdictions	Inner setting	Structural characteristics and readiness for implementation	Education initiatives	Equitable access to genomic testing in kidney disease
Nephrologists are unsure whom to refer to	Characteristics of individual	Knowledge and beliefs about the intervention	Education initiatives	Increased number of appropriate referrals
Nephrologists uncertain of the benefit of referral	Intervention characteristics	Evidence Strength & Quality	Education initiatives	Increased number of appropriate referrals
Poor community and consumer understanding of genomic testing	Process	Engaging	Engagement with communities and public engagement events	Increased utilization of genomic testing and application of findings
Patients and the general community are uncertain of the benefits of referral.	Intervention characteristics	Evidence strength & quality	Engagement with communities and public engagement events	Increased utilization of genomic testing and application of findings
Post referral-pretesting period				
The logistics of testing are too complicated to incorporate into clinics	Intervention characteristics	Complexity	Process simplification	Increased utilization of genomic testing
Nephrologists did not know how to order tests or prioritize patients for testing.	Inner setting	Knowledge and beliefs about the intervention, self-efficacy	Education initiatives	Increased utilization of genomic testing
Clinicians are unsure of which genes to test, which method to use	Inner setting and characteristics of individual	Access to knowledge and information	Developing standardized gene lists and recommended method	Increased utilization of genomic testing
Delay in sequencing	Process	Executing	Variant prioritization - meetings initiated	Earlier genomic testing
Variation in access to and cost of testing	Intervention characteristics	(Perceived) Cost		
No consistent clinical genetics support	Inner setting	Available resources	Engagement with clinical genetics services and national consortia; Identification of clinical geneticist champions	Increased clinical genetics department engagement
The remote location of the clinical geneticist	Inner setting	Available resources	Telehealth clinics, remote/visiting clinics	Increased access to clinical geneticists
The remote location of patients who may lack literacy	Outer setting	The patient's needs and resources		
Missed appointments to clinics reduce sustainability.	Outer setting	The patient's needs and resources		
Unable to access clinical geneticist during clinic	Inner setting	Available resources		
No secure funding for the multidisciplinary team (MDT) model of care	Inner setting	Available resources	Engagement with clinical services for the redesign of existing activities and demand; clinical champions engaged	Sustained operation of MDT models of care within existing resourcing
Variable hospital funding for tests	Outer setting	External policy and incentives		
Post-testing period				
Long turn-around-time for sequencing and analysis	Intervention characteristics	Complexity	Variant prioritization - meetings initiated	Earlier genomic testing
Delay in return of results	Inner setting	Available resources	MDT results meetings and review systems	Improved accountable delivery of results to consumers
Results difficult for nephrologists without specific training to interpret/apply	Intervention characteristics	Complexity	Targeted and sustained multimodal education supported by the National Strategic Action Plan for Kidney Disease	Perceived improving clinician confidence
Results not received by the referring doctor	Process	Executing	Upfront information for doctors	Clinical translation of genomic testing
Unclear recommendations to referrer regarding the clinical application of findings	Intervention characteristics	Complexity	Facilitated interpretation and clinician guidance in interprofessional communication	Supported referrer actioning of result outcomes
Difficulty in understanding the implications of a variant of uncertain significance	Characteristics of individual	Knowledge and beliefs about the intervention and self-efficacy		
Delay or failure of whom to clinically act on genetic findings	Characteristics of individual	Knowledge and beliefs about the intervention	Upfront information for doctors and patients	Clinical translation of genomic testing

CFIR, Consolidated Framework for Implementation Research; MDT, multidisciplinary team.
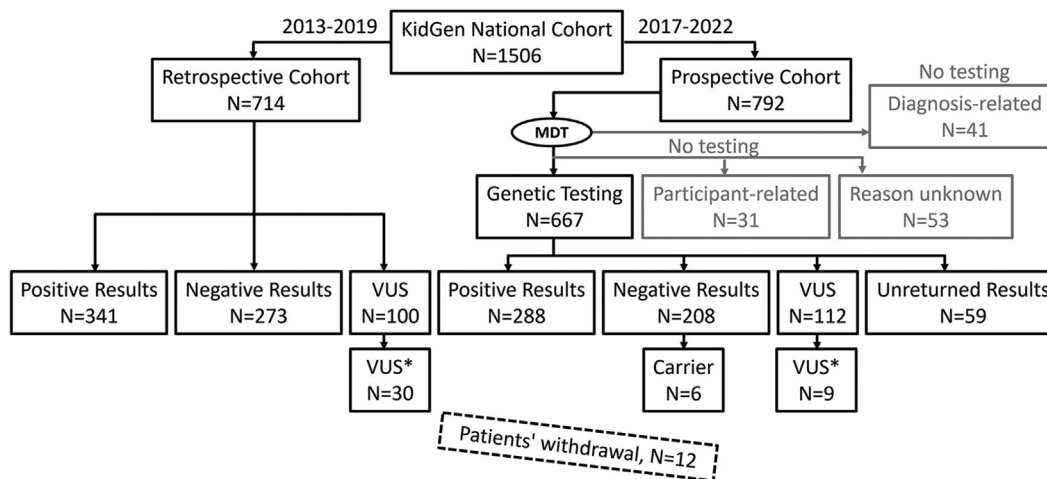
Figure 1. Recruitment of the KidGen national cohort for genomic testing. Two participant nonoverlapping retrospective and prospective cohorts were recruited between 2013 and 2022, creating the KidGen national cohort. The dashed rectangle depicts the number of patients who withdrew and were excluded from the study. Carrier, an individual with an allele predisposing to disease; MDT, multidisciplinary team; VUS, a variant of uncertain significance; VUS×, VUS with suspected clinical relevance.

Genes With Clinically Significant Variants

Pathogenic and likely pathogenic variants were identified in genes relating to cystic kidney disease, Alport syndrome, and renal tubular disorders in descending frequency, accounting for approximately two-thirds of the pathogenic and likely pathogenic variants identified (Figure 2). The most frequently affected gene in cystic kidney disease was PKD1(106 cases), followed by PKHD1 (56 cases) and HNF1B (28 cases). The SLC12A3 gene was the most frequent in tubular kidney disease (Figure 2), where we identified 18 compound heterozygotes and 12 homozygotes carrying pathogenic variants in this gene. All genes are listed in Supplementary Table S2. Variants of unknown significance (VUS or

VUS with suspected clinical relevance) identified in the cohort are presented in Supplementary Figure S1.

DISCUSSION

Our study delves into the complex process of implementing genomic testing within kidney medicine, emphasizing the successful role of a nationwide KGCs network embedded with a MDT. Focusing on real-world applicability, we explored the challenges and successes of integrating genetic testing seamlessly into clinical practice. We extended a theory-informed approach to determining barriers to implementing genomic testing in a nephrology context and, where

Table 2. Demographic characteristics of participants who underwent genomic testing

Characteristic	Retrospective cohort (2013–2019; $n = 714$)	Prospective cohort (2017–2022; $n = 667$)	All KidGen cohort ($N = 1381$)
Patient			
Adult (≥18 yr)	387 (54.20%)	462 (69.27%)	849 (61.48%)
Pediatric (<18 yr)	327 (45.80%)	205 (30.73%)	532 (38.52%)
Total	714	667	1381
Median Age (IQR)	22 (6–42) $n = 707$ (99%)	33 (17–49) $n = 594$ (89%)	29 (10–45) $n = 1301$ (94%)
Sex[a]			
Male	339 (47.48%)	327 (49.02%)	666 (48.23%)
Female	374 (52.38%)	289 (43.33%)	663 (48.01%)
Unknown	1 (0.14%)	51 (7.65%)	52 (3.76%)
Total	714	667	1381
Location			
Queensland	324 (45.38%)	164 (24.59%)	488 (35.34%)
New South Wales	226 (31.65%)	137 (20.54%)	363 (26.29%)
Victoria	121 (16.95%)	244 (36.58%)	365 (26.43%)
South Australia	28 (3.92%)	59 (8.85%)	87 (6.30%)
Western Australia	10 (1.40%)	63 (9.45%)	73 (5.29%)
Northern Territory	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tasmania	5 (0.70%)	0 (0.00%)	5 (0.36%)
Total	714	667	1381

[a]Sex has here been defined as a set of biological attributes associated with physical and physiological features.
Nominal variables are numbers with percent (%), while continuous variables are median with interquartile range (IQR).

Table 3. Diagnostic yield in the national KidGen cohort stratified by year of genomic testing

Yr	Sequencing performed number of patients	Diagnostic variants present number of patients	Diagnostic yield percent
2013	22	13	59.1
2014	78	41	52.6
2015	71	37	52.1
2016	157	68	43.3
2017	340	158	46.5
2018	295	125	42.4
2019	124	52	41.9
2020	4	2	50.0
2021	127	58	45.7
2022	60	30	50.0
Unknown	44	22	50.0
Total[a]	1322	606	45.8

NR, negative result; PR, positive result; VUS, a variant of uncertain significance.
[a]Test results were unknown for 59 patients by the end of the 2022 cut-off. DY (diagnostic yield) was calculated using the formula: DY = (PR / [PR + NR + VUS] × 100) and is expressed in percent (%).

possible, implementing real-time solutions to optimize respective processes.[35] Our theory of change for the Australian MD-KGC model stands on 3 pillars: capacity, care, and patients (Figure 3). We hypothesized that building the capacity for genomic testing would improve KGC care, where patients would benefit immediately (given an outcome), and ultimately in the long term, improve the clinical management of chronic kidney diseases in Australia. Indeed, the program has succeeded in all 3 pillars of effective change. This accomplishment is evidenced by established adult and pediatric KGCs in 7 Australian states and territories, which have been operational for almost 10 years. Importantly, this model involved collaboration between geneticists, nephrologists, and genetic

Table 4. Diagnostic yield in the national KidGen cohort stratified by clinical diagnosis

Clinical diagnosis	Sequencing performed number of patients	Positive results number of patients	Diagnostic yield percent
Alport syndrome	206	127	61.7
Tubular disease	134	74	55.2
Cystic kidney disease	506	256	50.6
Glomerular disease	50	19	38.0
Other	122	45	36.9
Complement-mediated	89	26	29.2
Nephrotic disease	142	41	28.9
CAKUT	73	18	24.7
Total[a]	1322	606	45.8

CAKUT, congenital anomalies of the kidney and urinary tract-syndromic; DY, diagnostic yield (was calculated using the formula: DY = (PR / [PR + NR + VUS] × 100) and is expressed in percent (%); NR, negative result; PR, positive result; VUS, a variant of unknown significance.
[a]Test results were unknown for 59 patients by the end of the 2022 cut-off.

Table 5. Clinical predictors of genetic diagnosis

Clinical diagnosis	Odds ratio	95% confidence interval	P-value
Alport syndrome	2.14	1.58-2.90	<0.001
Tubular disease	1.52	1.06-2.18	0.022
Cystic kidney disease	1.36	1.09-1.70	0.006
Glomerular disease	0.72	0.40-1.28	0.259
Other	0.67	0.45-0.98	0.038
Complement-mediated	0.46	0.29-0.74	0.001
Nephrotic disease	0.44	0.30-0.65	<0.001
CAKUT	0.37	0.21-0.63	<0.001

CAKUT, congenital anomalies of the kidney and urinary tract-syndromic; *P*, 2-sided *P*-value.

counselors at local sites, with support from the integrated national network, which created a practical, best-practice MDT approach to delivering genomic medicine in kidney disease. The effectiveness primarily stemmed from networking, because all KGCs were interconnected and actively exchanged ideas. This collaborative approach significantly eased the decision-making burden, particularly in handling complex cases and selecting the appropriate test based on the patient's phenotype. This collaborative network facilitated the rapid enhancement and spread of expertise, far outpacing what could be achieved in isolation. The collective clinical expertise, complemented by funding from various sources contingent on jurisdiction, was pivotal in establishing essential infrastructure to streamline the genomic testing process. The MD-KGC model, therefore, becomes the preferred service delivery model for kidney genetics in Australia among nephrologists[7] and accounts for a relatively high diagnostic yield by selecting patients who were most likely to benefit from testing. The model also improves result interpretation and subsequent clinical actioning due to the availability of clinical genetics or genetic counselors and nephrology expertise within the clinic. Smaller clinics particularly benefitted from access to the highly specialized MD-KGC expertise. However, as demand for testing increases, this model may not be sustainable, and a "mainstreaming" model of care is already beginning to emerge in other specialties and some subgroups of genetic kidney disease, such as autosomal dominant polycystic kidney disease (ADPKD).[21]

Concerning the implementation barriers identified in our clinics, we identified several challenges encountered by clinicians at local KGCs. Above all, the complexity of the entire process (outlined above) dominated as a significant barrier. Most of these concerns aligned with the "inner setting" of the Consolidated Framework for Implementation Research construct and could be addressed locally. For example, most confusion accumulated around referrals and sampling processes, selecting the right test, and using

Table 6. The use of the testing method in the national KidGen cohort stratified by a year of testing

Yr	CMA	Targeted panel	Sanger	TE	VNTR	WES	WGS	Not specified	Total
2013	0 (0.0)	6 (20.7)	7 (24.1)	4 (13.8)	0 (0.0)	4 (13.8)	1 (3.4)	7 (24.1)	29 (100.0)
2014	1 (1.2)	6 (7.2)	18 (21.7)	24 (28.9)	1 (1.2)	2 (2.4)	0 (0.0)	31 (37.3)	83 (100.0)
2015	3 (3.9)	7 (9.1)	7 (9.1)	27 (35.1)	0 (0.0)	2 (2.6)	0 (0.0)	31 (40.3)	77 (100.0)
2016	8 (4.5)	15 (8.4)	6 (3.4)	53 (29.6)	1 (0.6)	12 (6.7)	10 (5.6)	74 (41.3)	179 (100.0)
2017	6 (2.0)	9 (3.0)	14 (4.7)	78 (26.0)	2 (0.7)	67 (22.3)	24 (8.0)	100 (33.3)	300 (100.0)
2018	11 (3.7)	8 (2.7)	16 (5.4)	40 (13.6)	2 (0.7)	63 (21.4)	36 (12.2)	118 (40.1)	294 (100.0)
2019	7 (5.6)	6 (4.8)	4 (3.2)	31 (25.0)	0 (0.0)	4 (3.2)	20 (16.1)	52 (41.9)	124 (100.0)
2020	0 (0.0)	0 (0.0)	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	4 (100.0)
2021	1 (0.8)	0 (0.0)	8 (6.3)	32 (25.2)	2 (1.6)	28 (22.0)	51 (40.2)	5 (3.9)	127 (100.0)
2022	4 (4.5)	0 (0.0)	11 (12.5)	17 (19.3)	2 (2.3)	28 (31.8)	21 (23.9)	5 (5.7)	88 (100.0)
Total[a]	41 (3.1)	57 (4.4)	92 (7.0)	308 (23.6)	10 (0.8)	211 (16.2)	163 (12.5)	423 (32.4)	1305 (100.0)

CMA, chromosome microarray analysis; Not specified, sequencing type not indicated; Sanger, Sanger sequencing, also known as the "chain termination method;" Targeted panel, using massively parallel sequencing (MPS); TE, targeted clinical exome sequencing with virtual panel; VNTR, variable number tandem repeat of the mucin 1 (MUC1) gene; WES whole exome sequencing (with virtual panel); WGS, whole-genome sequencing (with virtual panel).
[a]A test was not performed, results were unreturned, or the year of testing was not specified in 201 patients.

the appropriate sequencing method. Professional development educational activities address these challenges. In the global context, our identified barriers align with those reported worldwide; however, some were less pronounced in Australia. A US study with 150 nephrologists identified high laboratory or testing
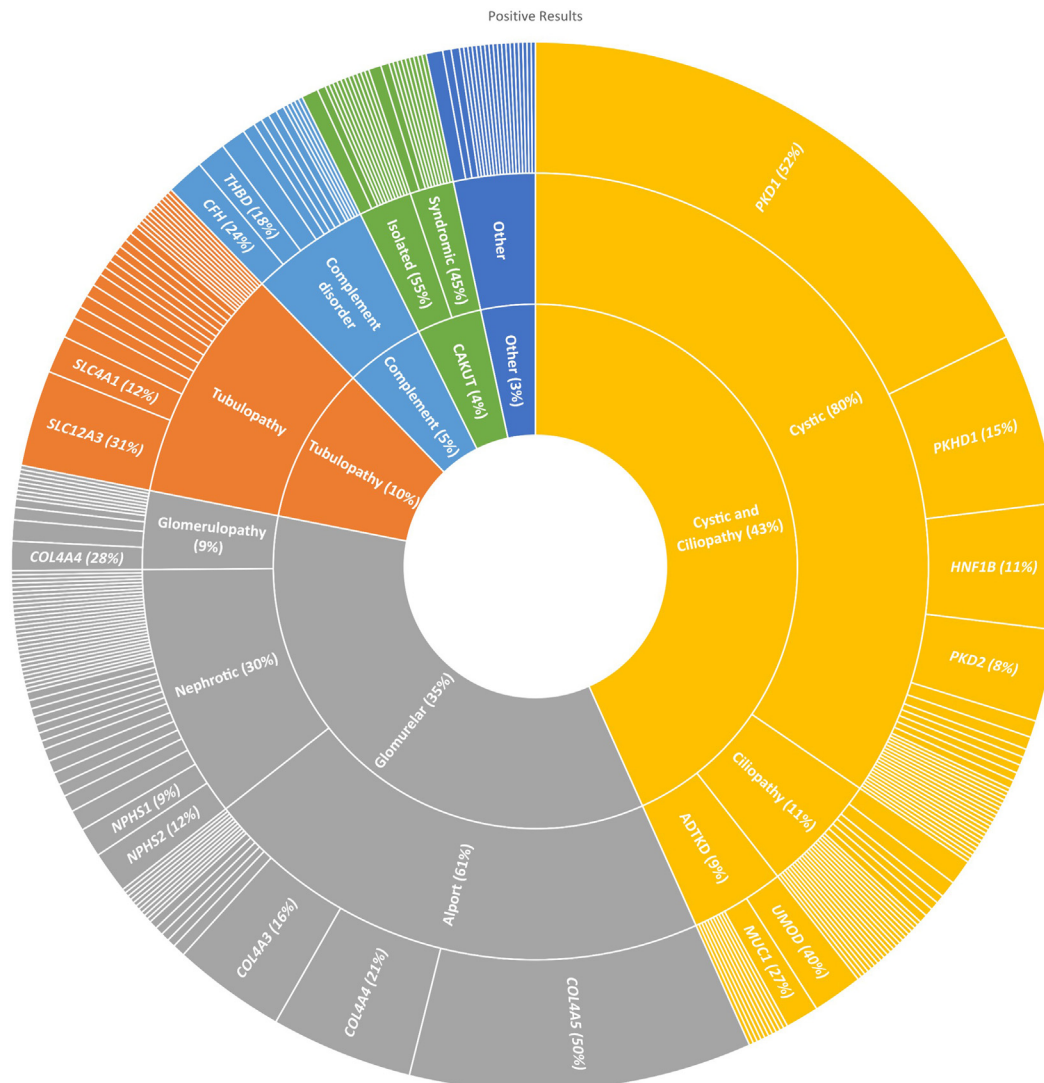
Figure 2. Genes with pathogenic/likely pathogenic variants in the national KidGen cohort. The genes are stratified by clinical diagnosis, with the width of the cut-outs indicating the number of times each gene appears. All genes are listed in Supplementary Table S2.
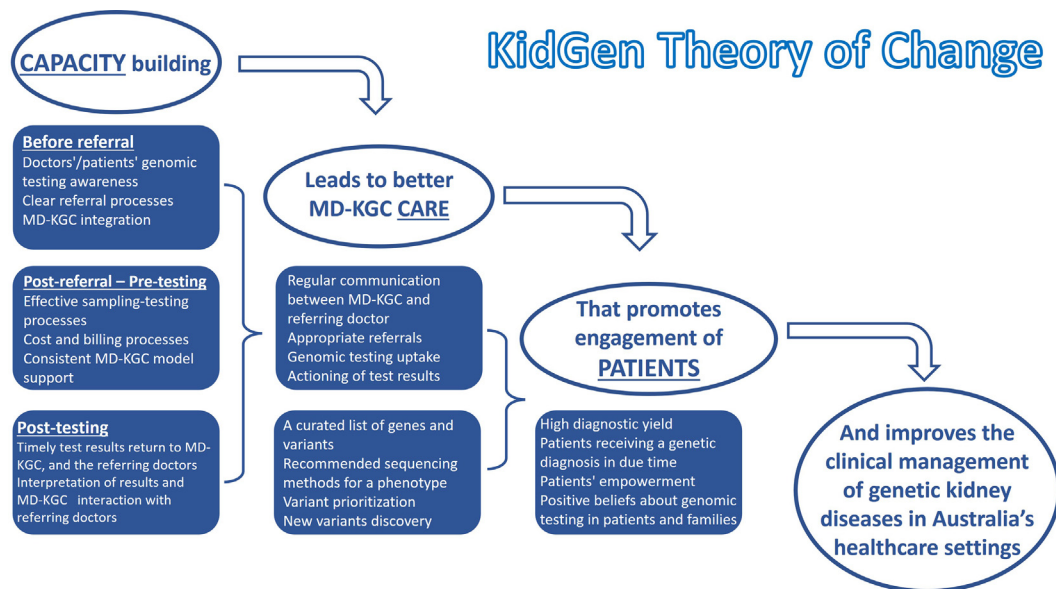
Figure 3. Visualizing the theory of change for the Australian MD-KGC model. The model is built upon 3 successive pillars: capacity, care, and patients. By addressing these areas through the MD-KGC approach, positive changes can be made in the clinical management of genetic kidney diseases. An essential aspect involves the implementation of test results by clinicians to guide patient care (actioning of results). MD-KGC, multidisciplinary kidney genetic clinic.

costs as a major barrier to genomic testing.[36] Although testing costs were operationally not a primary hurdle in Australian practice, they were a perceived barrier for less-experienced clinicians owing to the complexity of accessing resourcing. Significant barriers included staff funding issues, such as genetic counselors and clinic infrastructure expenses. Another barrier identified in this study-the difficulty in interpreting genomic test findings-has already been acknowledged within an Australian context[7] and was further reiterated during discussions at the Kidney Diseases: Improving Global Outcomes conference held in 2021.[37] The MDT model addresses this barrier by integrating into kidney genetic clinics. Although this model of care results in high-quality health care due to subspecialty input, future efforts should further develop more capacity to overcome interpretation barriers while maintaining accessibility.

Our clinical findings, drawn from a cohort of over 1300 patients suspected of genetic kidney disease, represent the absolute number of 1 of the largest clinical cohorts in this domain. With a diagnostic yield of ∼46%, our results consistently match or surpass those of many published cohorts in research and clinical settings. However, the diagnostic yield in our study varied based on clinical phenotypes, with the highest yield observed in Alport syndrome (∼62%) rather than cystic kidney diseases, such as ADPKD (∼51%), which is the most prevalent monogenic kidney disease.[38] This surprising outcome can be explained by several challenges that hindered the

diagnosis of ADPKD using genomic testing for many patients. Key factors contributing to this discrepancy include constraints in local testing platforms, substantial expenses associated with overseas testing, and the absence of publicly funded genomic testing during the significant period of the study. These obstacles resulted in a focus on testing atypical cases and a period of underrepresentation of classic ADPKD patients. Consequently, the overall diagnostic yield for cystic kidney diseases was impacted, as the transient limited access to comprehensive genomic testing for ADPKD influenced the overall distribution of patients with various kidney diseases. Nevertheless, these findings are well within the range of previous reports where, for instance, diagnostic yield for cystic kidney disease is anywhere between 23% and 88%, depending on the clinical characteristics and sequencing approaches.[1,3,10,39-41]

North American data reinforced the diagnostic utility of clinical genetic and genomic testing in kidney medicine[42] and reconfirmed previous findings in smaller cohorts at scale. Dahl et al.[42] reported on 1623 patients with chronic kidney disease enrolled in a study evaluating the diagnostic and clinical utility of genomic testing in chronic kidney disease. They reported a yield of 20.8%, which altered management in 90% of patients with a positive result. This short-term clinical utility, as determined by clinician surveys, complements additional evidence from other cohorts[43] and highlights the next gap in knowledge about implementation into practice. Our study addresses this

information gap in implementing genetic testing in real-world clinical practice, adding generalizability, and confirming utility while identifying a higher diagnostic yield. However, comparing diagnostic yields in genetic kidney disease studies is challenging due to diverse study designs, cohort compositions, and test characteristics.[10] In addition, in research studies, many patients never receive results, even if these are deemed clinically actionable.[44] Our study, however, provides clinically accredited sequencing and interpretation. This design generates vital, policy-informing data on the impact of genetic diagnosis on patients with kidney disease.

Our study has some limitations. In addition to potential technical limitations inherent in the technology used, such as the possible omission of specific genetic causes such as MUC1 variants,[45] it is essential to note that this was a pragmatic study. Therefore, we did not have predefined objective criteria for selecting patients for genomic testing. In addition, consumer engagement was outside the scope of this study; however, as a group, they are recognized as fundamental stakeholders in the development of service delivery. Within Australia and elsewhere, there is clear evidence of a need for the codevelopment of specialist genetic services regarding care delivery and providing resources that hurdle geographical and linguistic or cultural barriers.[46,47] The authors group of this manuscript are currently undertaking a national research program into the experiences and needs of patients and their families to enable ongoing optimization of the service.

Nevertheless, our data reflect real-world practice. Every patient was assessed in the KGC using an MDT approach (based on relevant clinical indices) to ensure that genomic testing was only performed if clinically indicated and that the most suitable sequencing platform available was used. Second, it is important to note that our cohort does not encompass all patients who underwent sequencing during the 10 years. Although clinicians were requested to provide audit data for all patients seen, the inclusion of multiple health services and clinical laboratories, including international ones, posed challenges in determining the total number of patients sequenced nationwide and the number of patients who attended clinics but did not proceed to genomic testing. Consequently, despite encouraging clinicians to collect data on all sequenced patients, there remains a possibility of selection bias. In addition, because the data collection process relied on input from multiple clinicians across various renal genetics clinics, challenges arose in obtaining complete data, including instances of missing "year of recruitment" information when the relevant clinician did not provide it. In addition, the COVID-19 outbreak negatively impacted genomic testing and collection of data to this dataset, with data for only 4 patients recorded in 2020. Although our sample size may be considered relatively modest for a decade-long effort, it indicates the intrinsic challenges and complexities associated with establishing and expanding a national kidney genetics program.

In July 2022, federal funding for genomic testing for monogenic kidney disease was announced in Australia; however, data were only collected until October of the same year; and therefore, it is unlikely that this increase in test availability has impacted our cohort during the study timeline. Our study did not investigate the potential barriers and facilitators in implementing genomic testing outside MD-KGCs. This is especially important given the increasing availability of genomic testing for patients with kidney disease. Finally, given the longer-term relevance of the clinical utility of genomic testing, clinical utility information was not collected to reduce the burden on participants and clinicians. Nevertheless, the short-term and lifetime health and economic implications of genomic testing have been modeled to evaluate its relative cost-effectiveness compared to nongenetic diagnostic investigations in patients with suspected monogenic kidney disease.[48] This economic evaluation established the cost-effectiveness of genomic testing for genetic kidney disease and demonstrated that it is cost-saving in patients with glomerular diseases.[48] Further work is needed to evaluate the cost-effectiveness of this clinic model and identify ways to optimize its health and economic benefits to ensure a sustainable and equitable national service across Australia.

CONCLUSION

Our study provides a comprehensive analysis of a real-world national multidisciplinary model of care for patients suspected to have monogenic kidney disease. Through a decade-long iterative process, we gained insights into the strengths and weaknesses of this model. Based on our findings, we have successfully implemented the MD-KGC model. However, further research is necessary to evaluate its cost-effectiveness and long-term sustainability. Such studies would provide valuable insights into the feasibility and benefits of implementing this model more broadly.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Torronen, William Majoni, Doris Chan, Neil Boudville, Suda Swaminathan, Germaine Wong, Nigel Toussaint, Sam Crafter, Andrew Talbot, and Joshua Kausman for their contributions to this project.

DATA AVAILABILITY STATEMENT

The genomic data generated from this study involve patient information and are subject to confidentiality and privacy protections. Due to these legal and ethical considerations, the genomic data cannot be shared publicly or made available to other researchers. This restriction is in place to ensure the privacy and security of the patient's sensitive information. We are committed to upholding the highest data protection and privacy standards for the individuals involved in this study. Deidentified results supporting this study's findings are available from the corresponding author, AJM, upon reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Genes with VUS/VUS× identified in the national KidGen cohort. The genes are stratified by clinical diagnosis, with the width of the cut-outs indicating the number of appearances. VUS is a variant of uncertain significance; VUS× is a VUS with suspected clinical relevance.

Table S1. Patient recruitment by state and year stratification.

Table S2. Occurrence of genes affected by pathogenic/likely pathogenic variants in patients with different kidney diagnoses.

Table S3. Genes listed in Kidneyome SuperPanel Version 8.53.

STROBE checklist.

REFERENCES

1. 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. https://doi.org/10.1016/j.kint.2018.02.027

2. 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. https://doi.org/10.1681/ASN.2018060575

3. Groopman E, Goldstein D, Gharavi A. Diagnostic utility of exome sequencing for kidney disease reply. *N Engl J Med.* 2019;380:2080–2081. https://doi.org/10.1056/NEJMc1903250

4. 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. https://doi.org/10.1093/ndt/gfaa363

5. Jayasinghe K, Quinlan C, Stark Z, et al. Renal genetics in Australia: kidney medicine in the genomic age. *Nephrol (Carlton).* 2019;24:279–286. https://doi.org/10.1111/nep.13494

6. 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. https://doi.org/10.1093/ndt/gfab218

7. Jayasinghe 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. https://doi.org/10.1016/j.ekir.2020.10.030

8. 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. https://doi.org/10.1093/ndt/gfab019

9. Jayasinghe K, Wu Y, Stark Z, et al. Cost-effectiveness of targeted exome analysis as a diagnostic test in glomerular diseases. *Kidney Int Rep.* 2021;6:2850–2861. https://doi.org/10.1016/j.ekir.2021.08.028

10. Claus LR, Snoek R, Knoers N, van Eerde AM. Review of genetic testing in kidney disease patients: diagnostic yield of single nucleotide variants and copy number variations evaluated across and within kidney phenotype groups. *Am J Med Genet C Semin Med Genet.* 2022;190:358–376. https://doi.org/10.1002/ajmg.c.31995

11. Shanks J, Butler G, Cheng D, Jayasinghe K, Quinlan C. Clinical and diagnostic utility of genomic sequencing for children referred to a Kidney Genomics Clinic with microscopic haematuria. *Pediatr Nephrol.* 2023;38:2623–2630. https://doi.org/10.1007/s00467-022-05846-1

12. Morrow A, Chan P, Tucker KM, Taylor N. The design, implementation, and effectiveness of intervention strategies aimed at improving genetic referral practices: a systematic review of the literature. *Genet Med.* 2021;23:2239–2249. https://doi.org/10.1038/s41436-021-01272-0

13. Stark Z, Dolman L, Manolio TA, et al. Integrating genomics into healthcare: a global responsibility. *Am J Hum Genet.* 2019;104:13–20. https://doi.org/10.1016/j.ajhg.2018.11.014

14. Stark Z, Boughtwood T, Haas M, et al. Australian Genomics: outcomes of a 5-year national program to accelerate the integration of genomics in healthcare. *Am J Hum Genet.* 2023;110:419–426. https://doi.org/10.1016/j.ajhg.2023.01.018

15. Hooker GW. Building an infrastructure to enable delivery of genomic medicine. *Am J Med Genet C Semin Med Genet*. 2021;187:95–99. https://doi.org/10.1002/ajmg.c.31881

16. Alkanderi S, Yates LM, Johnson SA, Sayer JA. Lessons learned from a multidisciplinary renal genetics clinic. *Q J M*. 2017;110:453–457. https://doi.org/10.1093/qjmed/hcx030

17. Thomas CP, Freese ME, Ounda A, et al. Initial experience from a renal genetics clinic demonstrates a distinct role in patient management. *Genet Med*. 2020;22:1025–1035. https://doi.org/10.1038/s41436-020-0772-y

18. Mallett A, Fowles LF, McGaughran J, Healy H, Patel C. A multidisciplinary renal genetics clinic improves patient diagnosis. *Med J Aust*. 2016;204:58–59. https://doi.org/10.5694/mja15.01157

19. Jayasinghe K, Stark Z, Kerr PG, et al. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. *Genet Med*. 2021;23:183–191. https://doi.org/10.1038/s41436-020-00963-4

20. Tanudisastro HA, Holman K, Ho G, et al. Australia and New Zealand renal gene panel testing in routine clinical practice of 542 families. *NPJ Genom Med*. 2021;6:20. https://doi.org/10.1038/s41525-021-00184-x

21. Elliott MD, James LC, Simms EL, et al. Mainstreaming genetic testing for adult patients with autosomal dominant polycystic kidney disease. *Can J Kidney Health Dis*. 2021;8: 20543581211055001. https://doi.org/10.1177/20543581211055001

22. Mallett A, Patel C, Maier B, et al. A protocol for the identification and validation of novel genetic causes of kidney disease. *BMC Nephrol*. 2015;16:152. https://doi.org/10.1186/s12882-015-0148-8

23. Stark Z, Boughtwood T, Phillips P, et al. Australian genomics: a federated model for integrating genomics into healthcare. *Am J Hum Genet*. 2019;105:7–14. https://doi.org/10.1016/j.ajhg.2019.06.003

24. Gaff CL, M Winship I, M Forrest S, et al. Preparing for genomic medicine: a real world demonstration of health system change. 2017;2:16. https://doi.org/10.1038/s41525-017-0017-4

25. Vidgen ME, Williamson D, Cutler K, et al. Queensland Genomics: an adaptive approach for integrating genomics into a public healthcare system. *NPJ Genom Med*. 2021;6:71. https://doi.org/10.1038/s41525-021-00234-4

26. Tudini E, Andrews J, Lawrence DM, et al. Shariant platform: enabling evidence sharing across Australian clinical genetic-testing laboratories to support variant interpretation. *Am J Hum Genet*. 2022;109:1960–1973. https://doi.org/10.1016/j.ajhg.2022.10.006

27. Damschroder LJ, Reardon CM, Widerquist MAO, Lowery J. The updated Consolidated Framework for Implementation Research based on user feedback. *Implement Sci*. 2022;17:75. https://doi.org/10.1186/s13012-022-01245-0

28. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci*. 2009;4: 50. https://doi.org/10.1186/1748-5908-4-50

29. Kirk MA, Kelley C, Yankey N, Birken SA, Abadie B, Damschroder L. A systematic review of the use of the Consolidated Framework for Implementation Research. *Implement Sci*. 2016;11:72. https://doi.org/10.1186/s13012-016-0437-z

30. Jayasinghe K, Stark Z, Patel C, et al. Comprehensive evaluation of a prospective Australian patient cohort with suspected genetic kidney disease undergoing clinical genomic testing: a study protocol. *BMJ Open*. 2019;9:e029541. https://doi.org/10.1136/bmjopen-2019-029541

31. DiStefano MT, Goehringer S, Babb L, et al. The Gene Curation Coalition: a global effort to harmonize gene-disease evidence resources. *Genet Med*. 2022;24:1732–1742. https://doi.org/10.1016/j.gim.2022.04.017

32. 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;17:405–424. https://doi.org/10.1038/gim.2015.30

33. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381. https://doi.org/10.1016/j.jbi.2008.08.010

34. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208

35. Kansal A, Quinlan C, Stark Z, et al. Theory designed strategies to support implementation of genomics in nephrology. *Genes (Basel)*. 2022;13. https://doi.org/10.3390/genes13101919

36. Mrug M, Bloom MS, Seto C, et al. Genetic testing for chronic kidney diseases: clinical utility and barriers perceived by nephrologists. *Kidney Med*. 2021;3:1050–1056. https://doi.org/10.1016/j.xkme.2021.08.006

37. KDIGO Conference Participants. Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2022;101:1126–1141. https://doi.org/10.1016/j.kint.2022.03.019

38. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet*. 2007;369:1287–1301. https://doi.org/10.1016/S0140-6736(07)60601-1

39. Connaughton DM, Kennedy C, Shril S, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int*. 2019;95:914–928. https://doi.org/10.1016/j.kint.2018.10.031

40. Braun DA, Schueler M, Halbritter J, et al. Whole exome sequencing identifies causative mutations in the majority of consanguineous or familial cases with childhood-onset increased renal echogenicity. *Kidney Int*. 2016;89:468–475. https://doi.org/10.1038/ki.2015.317

41. Mallawaarachchi AC, Lundie B, Hort Y, et al. Genomic diagnostics in polycystic kidney disease: an assessment of real-world use of whole-genome sequencing. *Eur J Hum Genet*. 2021;29:760–770. https://doi.org/10.1038/s41431-020-00796-4

42. Dahl N, Bloom MS, Chebib FT, et al. The clinical utility of genetic testing in the diagnosis and management of adults with chronic kidney disease. *J Am Soc Nephrol*. 2023;34: 2039–2050. https://doi.org/10.1681/ASN.0000000000000249

43. Becherucci F, Landini S, Palazzo V, et al. A clinical workflow for cost-saving high-rate diagnosis of genetic kidney diseases. *J Am Soc Nephrol*. 2023;34:706–720. https://doi.org/10.1681/ASN.0000000000000076

44. Nestor JG, Marasa M, Milo-Rasouly H, et al. Pilot study of return of genetic results to patients in adult nephrology. *Clin J Am Soc Nephrol*. 2020;15:651–664. https://doi.org/10.2215/CJN.12481019

45. Kirby A, Gnirke A, Jaffe DB, et al. Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in MUC1 missed by massively parallel sequencing. *Nat Genet*. 2013;45: 299–303. https://doi.org/10.1038/ng.2543

46. Crellin E, Martyn M, McClaren B, Gaff C. What matters to parents? A scoping review of parents' service experiences and needs regarding genetic testing for rare diseases. *Eur J Hum Genet*. 2023;31:869–878. https://doi.org/10.1038/s41431-023-01376-y

47. Nevin SM, McLoone J, Wakefield CE, Kennedy SE, McCarthy HJ. Genetic testing in the pediatric nephrology clinic: understanding families' experiences. *J Pediatr Genet*. 2022;11:117–125. https://doi.org/10.1055/s-0040-1721439

48. Wu Y, Jayasinghe K, Stark Z, et al. Genomic testing for suspected monogenic kidney disease in children and adults: a health economic evaluation. *Genet Med*. 2023;25:100942. https://doi.org/10.1016/j.gim.2023.100942