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Enhancing diagnostic outcomes in kidney genetic disorders: the KidGen national kidney genomics study protocol

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Abstract

Background Genetic kidney disease (GKD) significantly affects the community and is responsible for a notable portion of adult kidney disease cases and about half of cases in paediatric patients. It substantially impacts the quality of life and life expectancy for affected children and adults across all stages of kidney disease. Precise genetic diagnosis in GKD promises to improve patient outcomes, provide access to targeted treatments, and reduce the disease burden for individuals, families, and healthcare systems. Genetic investigations are increasingly used in nephrology practice; however, many patients who undergo testing still lack a definitive diagnosis.

Methods The KidGen National Kidney Genomics Study aims to increase diagnostic yield for those with suspected monogenic kidney disease without a diagnosis after standard diagnostic genetic testing. The program will seek to enrol up to 200 families from KidGen Collaborative kidney genetics clinics across Australia who have yet to receive conclusive diagnoses despite prior testing. Participants will undergo a personalised pathway of research genomic investigations. These include re-analysing existing data and/or undergoing advanced genomic testing methods, including short and long-read whole-genome sequencing, RNA sequencing, and functional genomics strategies using mouse modelling or kidney organoids.

Discussion The KidGen National Kidney Genomics Study is a coordinated, multidisciplinary extension of previous research projects that aims to assess the diagnostic yield of advanced genomic approaches. The study's evidence will drive changes to current diagnostic pathways, including identifying which chronic kidney disease patients are most likely to benefit from a more comprehensive genomic approach to diagnosis.

Keywords Study protocol, Genetic kidney disease, Undiagnosed patients, Re-analysis, Advanced genomic testing, Diagnostic yield

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Background

Genetic kidney disease (GKD) substantially impacts the community, accounting for approximately 10% of adults affected by kidney disease cases and up to 50% of paediatric kidney disease patients [1, 2]. GKD often progresses towards kidney failure, requiring kidney replacement therapy, i.e., dialysis or kidney transplantation. Kidney failure is associated with the lowest quality of life among chronic conditions and is the most prevalent cause of hospitalisation in Australia, with an estimated total cost of chronic kidney disease of $8.3 billion annually [3–5]. Providing timely genetic diagnoses to affected patients and families is crucial to improve outcomes and alleviate the burden of GKD for individuals, communities, and the healthcare system [6]. In doing so, invasive investigations, like kidney biopsies, can be avoided [7]. At the same time, other important measures, such as cascade screening in families, pre-conception counselling, transplant planning, and the early initiation of targeted treatments, can be implemented. These interventions reduce disease morbidity, mortality, prevalence, and overall cost burden [8].

Exome and genome sequencing approaches are increasingly utilised in nephrology [9–11]. These studies typically involve broad sequencing and targeted analysis of a panel of kidney-related genes. In phenotype-targeted studies (such as for nephronophthisis or nephrotic syndrome), more detailed genomic investigations and functional studies have been undertaken to identify novel variants or genes [12]. However, there is limited literature on the yield of a genome-wide variant analysis approach combined with functional studies in a broad cohort of all types of genetic kidney diseases. Additionally, there is a lack of data on how much such an approach increases diagnostic yield.

Genomic diagnostics in kidney medicine is now the standard of care in Australia, owing to advances in clinical practice and the implementation of government resourcing within a universal healthcare system. This process is facilitated by a national network of kidney genetic clinics (KGCs) and the states' multidisciplinary teams (MDT) of clinicians who oversee the genetic diagnosis process, ensuring comprehensive, high-quality care [13]. The KGC network was founded in 2013 and led, in 2016, to the establishment of the KidGen Collaborative, which comprises a network of nephrologists, geneticists, genetic counsellors, and scientists. However, despite significant progress, up to ~ 55% of patients undergoing clinical genomic testing for suspected genetic kidney disease remain without a definitive genetic diagnosis [14].

The KidGen National Kidney Genetic Study is part of the Genomics Health Futures Mission (GHFM), a competitively funded research initiative of the Australian Government. It aims to leverage the combined expertise of clinical and research teams within the Kidney Genomics (KidGen) Collaborative network. The primary objective of the study is to investigate genetically unresolved cases of suspected GKD by uncovering unknown, uncommon, or difficult-to-detect genetic causes. We aim to apply advanced research analytics alongside functional genomics approaches and evaluate the diagnostic yield of this comprehensive strategy. Identifying novel genes and variants associated with GKD holds great promise for improving our capacity to diagnose patients accurately. This advancement will offer future patients a streamlined path toward diagnosis and subsequent clinical management. This manuscript serves as a study protocol.

Methods

Operating structure

The KidGen National Kidney Genetic Study will operate under a hierarchical structure with five purpose-specific entities meeting at different frequencies. The *Governance Committee* (9 members) convenes semi-annually and holds the highest authority, overseeing critical decisions. The *Steering Committee* (23 members) meets every two months to translate the Governance Committee's direction into actionable plans. The *National Multidisciplinary Team* (nMDT; variable number with a quorum of 5) conducts monthly meetings to discuss proposed cases and enhance knowledge exchange, collaboration, and recruitment of patients nominated by KGCs. There are two working groups: the *Clinical Working Group* (CWG; 7 members) and the *Functional Genomics Group* (FGG; 9 members). These two groups focus on specific clinical and discovery areas and report to the Steering Committee. The CWG meets weekly to review all cases nominated for the study against the study inclusion/exclusion criteria, engage with clinics, discuss individual patients, and review the project's operational progress. Additionally, the CWG holds bi-monthly meetings with the FGG to discuss preliminary results from variant analysis and consider options for functional modelling if required. This multilevel structure ensures strategic direction and efficient project execution by maintaining effective collaborative communication.

Study overview

We aim to recruit approximately 200 families with suspected unexplained GKD after standard testing from our KGCs and existing KidGen research cohorts. These families will undergo comprehensive genomic analysis facilitated by a team of specialists (nMDT). Our approach utilises phenotype-driven research genomics to identify the genetic basis of GKD in each family. Research genomic sequencing will be undertaken, with short-read

whole genome sequencing used as the baseline testing for most probands, including family members, where relevant. Bioinformatic processing will be conducted through the Centre for Population Genomics and phenotype-driven variant analysis via an Australian instance of the *seqr* platform [15], a collaborative platform designed explicitly for analysing rare disease genomic data.

Furthermore, the existing whole-genome sequencing (WGS) and whole-exome sequencing (WES) data from undiagnosed families previously recruited to KidGen studies [9] will be re-analysed using novel analytical tools developed by the Centre for Population Genomics (CPG) at the Garvan Institute of Medical Research/Murdoch Children's Research Institute (MCRI) and other partners. We will also employ advanced modelling techniques for the identified variants of uncertain significance (VUS), including animal and cellular GKD models, to validate their role in disease development. Functional modelling will also be applied to assess novel gene-disease associations. Our comprehensive strategy, detailed in Fig. 1, intends to maximise the chances of a conclusive genetic diagnosis. Crucially, the study will collect data on the resourcing required to achieve diagnosis to address the translation of such a pipeline to standard clinical diagnostics.

Hypothesis and aims

Our overarching hypothesis is that the diagnostic yield for patients with suspected genetic kidney disease can be improved by combining the re-analysis of existing genomic data with advanced sequencing and analysis techniques and functional genomics approaches. To test this hypothesis, we have developed the following research aims:

Aim 1. Patient Identification

This aim centres around identifying individuals more likely to have a monogenic cause of their CKD through a targeted recruitment survey and specific criteria. We will focus on individuals within the KidGen Collaborative KGC network who remain undiagnosed or have inconclusive results despite undergoing targeted genetic testing, clinical WES, or clinical WGS.

Aim 2. Enhanced testing approach

This aim has a two-fold approach:

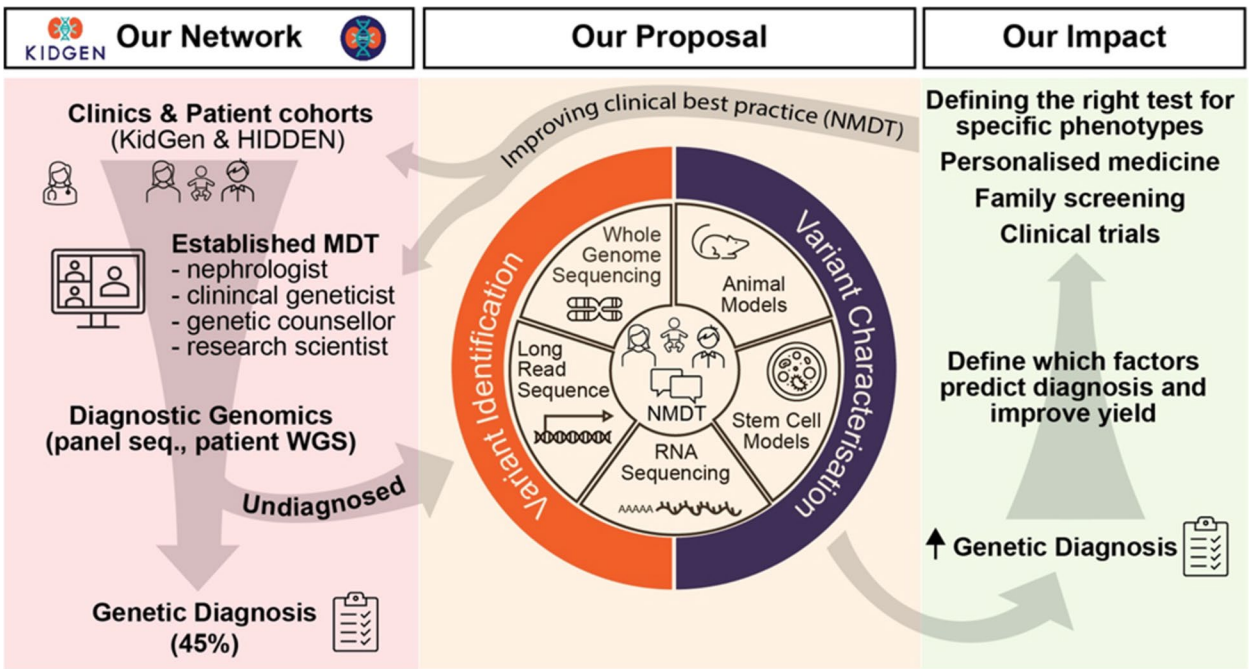

Fig. 1 KidGen national kidney genomics program: improving diagnostic outcomes for Australian families with genetic kidney disease. The KidGen network is a nationwide initiative led by the national multidisciplinary team (nMDT), coordinating kidney genetic clinics (KGCs) across Australia. This collaborative framework offers subsidised clinical gene panels to streamline diagnostic genomics. While achieving considerable success with a diagnostic yield slightly below 50%, an inventive proposal has emerged. The aim is to expand genetic testing boundaries by improving. ariant identification and classification and synergistically integrating genomic technologies with clinical expertise. This ambitious approach aims to enhance genetic diagnosis standards and improve the application of clinical best practices, representing a significant step forward in comprehensive patient renal care

1. Re-analysis of existing genomic data. We will re-analyse existing genomic data from patients recruited to previous KidGen studies who remain without a genetic diagnosis.
2. Advanced genomic testing. We will conduct advanced genomic testing for existing compelling cases where the initial re-analysis did not yield conclusive results or for prospective undiagnosed cases after clinical diagnostic testing.

Aim 3. Functional modelling and validation

This aim focuses on compelling VUS in known and newly identified genes associated with kidney phenotypes. Where suitable, we will use CRISPR/Cas9 gene editing technology to introduce VUS into the mouse genome to study their impact on kidney function. Again, where appropriate, we will also use patient-derived and other genetically engineered induced pluripotent stem cells (iPSCs) to create kidney organoids and assess the contribution of VUS to kidney disease phenotypes [16–18]. Additionally, we will validate the functional impact of those VUS suspected to alter gene splicing. The primary goal of this aim is to provide additional evidence of the association between specific genetic variants and kidney disease phenotype. This will include VUS and new gene-disease associations. The objective will be to generate sufficient evidence to reclassify VUS as pathogenic or likely pathogenic or establish a novel gene-disease association.

Aim 4. Establishment of KidGen databases

This aim centres around establishing a robust participant database. This database will include patient demographics, clinical characteristics, and genetic profiles. We aim to create a comprehensive database within kidney genetics research for multiple purposes. This database will primarily guide phenotype-driven variant interpretation and sequencing strategies for the current study. In addition, the data collected will inform recruitment strategies for future studies, such as clinical trials for new treatments. The database will also assist with implementation science, health economics, and quality assurance efforts by providing insights into patient populations and their specific needs and assessing equity of access.

Methodology—Aim 1. Patient identification

To achieve the objectives outlined in Aim 1, our recruitment strategy involves enrolling up to 200 and their relevant family members. Of these, 100 patients will originate from established Australian Genomics kidney cohorts, including the KidGen Collaborative Kidney Genetics Cohort [19] and the HIDDEN (wHole genome Investigation to iDentify unDEtected Nephropathies) Cohort [20] families who have previously undergone genomic testing for their kidney condition but remain undiagnosed. These patients have already provided informed consent for subsequent analyses during their initial enrolment. In addition to these existing cohorts, we plan to prospectively enrol up to 100 new patients and relevant family members through KGCs between mid-2022 and mid-2026. Individuals will be selected based on stringent inclusion criteria, including a substantial likelihood of a monogenic cause for their GKD despite previous uninformative genetic or genomic testing (Table 1). Informed consent can be provided by paper or electronic consent via platforms such as Research Electronic Data Capture (REDCap) or CTRL (Control) instruments [21, 22].

The KidGen Collaborative comprises a network of twenty KGCs across Australia. These clinics will serve as recruitment sites and are geographically distributed as follows: four in New South Wales (NSW), one in the Northern Territory (NT), three in Queensland (QLD), two in South Australia (SA), one in Tasmania (TAS), five in Victoria (VIC), and four in Western Australia (WA) as detailed on Fig. 2.

To be nominated by KGC, patients must meet all inclusion criteria and none of the exclusion criteria, as listed in Table 1. A rigorous selection process will be carried out by the Clinical Working Group (CWG) using a phenotype-driven approach [23]. The CWG reviews all patients nominated by the KGCs to ensure patients meet the selection criteria. Based on their evaluation, the CWG will recommend accepting or declining inclusion in the study. A majority of CWG members must recommend recruitment for the patient

Table 1 KidGen study participation criteria: inclusion and exclusion

Inclusion	Exclusion
Referral by a nephrologist or clinical geneticist	Isolated non-familial CAKUT
Suspected genetic cause of CKD	TMA with negative panel sequencing for complement dysregulation
Negative/inconclusive genetic/genomic test results	Primary auto-immune disease
Provide informed consent to participate in the study and able to provide relevant biological samples	Decline informed consent to participate in the study or unable to provide relevant biological samples

CKD Chronic kidney disease, *CAKUT* Congenital anomalies of the kidney and urinary tract, *TMA* Thrombotic microangiopathies

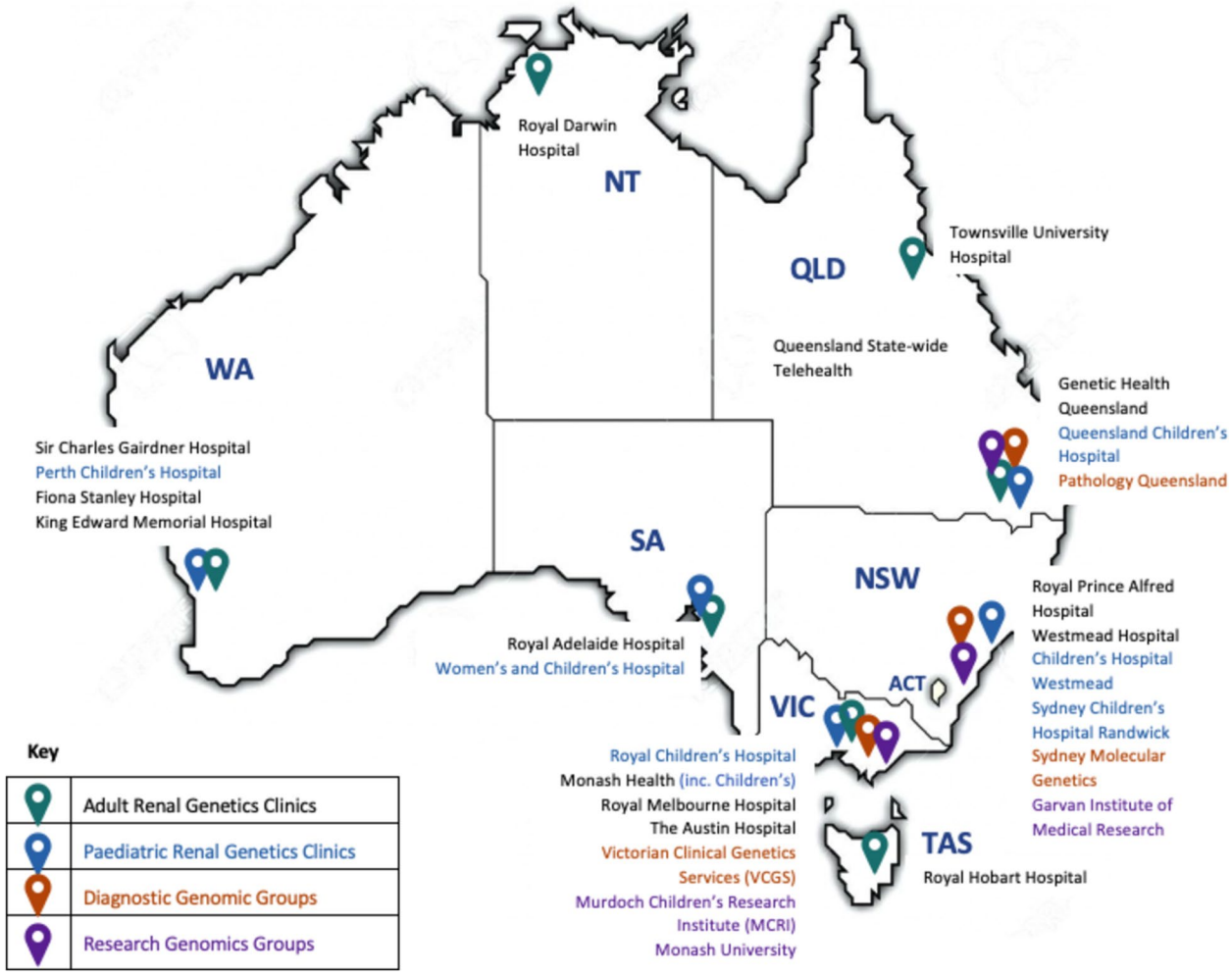

Fig. 2 Australia's renal genetic services: a geographic breakdown. The KidGen Collaborative includes a network of 19 adult (green pins) and pediatric (blue pins) kidney genetics clinics (KGCs) operating nationwide. KGCs receive diagnostic support from the National Association of Testing Authorities (NATA)-accredited labs (orange pins), while research groups (purple pins) conduct functional genomics activities and perform subsequent variant curation in the background. NT, Northern Territory; QLD, Queensland; NSW, New South Wales; ACT, Australian Capital Territory; VIC, Victoria; TAS, Tasmania; SA, South Australia; WA, Western Australia

to be enrolled in the study. Where further discussion is beneficial, referring clinicians may be asked to present nominated cases at the monthly National Multidisciplinary Team (nMDT) meeting. A referral score will be calculated for each patient by evaluating five key domains based on evidence suggesting a high likelihood of monogenic kidney disease (Table 2). While this score is not the sole referral determinant, it serves as an empiric and objective metric for which diagnostic yield can be reported. High-scoring patients (≥ 10) are prioritised for direct admission to the study, while lower and low-scoring patients (≤ 6) may only be accepted by consensus agreement after presentation at the nMDT. Suggestions for refinement of this rubric will be made based on study outcomes.

Methodology—Aim 2. Enhanced testing approach

This study will use a standardised analysis pipeline using a computational tool, Hail Batch, to (re)process all short-read exome and genome data. Single nucleotide variants (SNVs) and small insertion/deletions (indel) will be called with GATK HaplotypeCaller, copy number variants (CNVs) and structural variants (SV) will be called with GATK-SV for WGS data [24] and GATK-gCNV for exome data [25]. An adapted version of the GATK mitochondrial variant calling pipeline will be used to call identical homoplasmic and heteroplasmic mixtures of variants in mtDNA from WGS data using the mitochondria mode of GATK MuTect2 [26]. Short tandem repeat expansions at known disease-associated loci will be evaluated with STRipy [27]. All variant data will be imported into the CPG-hosted instance of the *seqr* tool,

Table 2 Experimental referral scoring system

Domain 1: Age of CKD Onset					**Domain 2: Age of ESKD (CKD5)**			
Age	< 12 m	< 18y	< 25y	< 50y	< 50y	< 25y	CKD1-4	
Points	5	4	2	1	1	2	0	
Domain 3: Family history (FHx)					**Domain 4: Other considerations**			
Affected relatives	1	2	3 +	Clear Pattern	Syndromic extra renal	Strong clinical suspicion	P/LP variant in known gene that aligns with the phenotype observed in an autosomal recessive disorder	Clinical phenotype
Points	2	3	4	2	1	3	accept	accept
Domain 5: ADTKD-MUC1			**Total score for patient:**					
ADTKD	MUC1	No FHx	**Recommendation:**					
Points	3	3	**Notes:**					

CKD Chronic kidney disease, *ESKD* End-stage kidney disease, *CKD1-4* CKD stage 1 to 4, *CKD5* CKD stage 5 or ESKD, *FHx* family history, *ADTKD* Autosomal dominant tubulointerstitial kidney disease, *P/LP* Pathogenic/likely pathogenic, *AR* autosomal recessive, *MUC1* Mucin1, *m* months, *y* years

a web-based analysis and collaboration tool, for curation and analysis [15].

Existing sequencing data from the retrospective cohort will undergo reanalysis using state-of-the-art analytical methods. Raw genomic data will be reprocessed using the standardised analysis pipeline [28] before reanalysis is performed using the automated reanalysis tool Talos [29] and manual curation by a variant analyst.

Prospectively recruited patients and those in the retrospective cohort who did not have suitable historical sequencing data will undergo re-sequencing. This will predominantly be based on short-read whole genome sequencing (short-read WGS). Long-read sequencing will be considered case-by-case for undiagnosed patients, mainly after negative WES analysis. This includes considering long-read WGS for patients with a broad phenotype and targeted (real-time selective sequencing) long-read sequencing for patients suspected of having specific genes or gene regions implicated in their disease. A dedicated variant analyst will lead the variant interpretation of short and long-read data. The variant analysis is performed iteratively with feedback from the referring clinician and clinical working group on the clinical relevance of identified variants. Research reports will be issued for newly identified genetic variants classified as "pathogenic" or "likely pathogenic," following the guidelines of the American College of Medical Genetics and Genomics [30]. A highly suspicious VUS will undergo a functional genomic analysis to gain more pathological evidence.

Transcriptome sequencing (RNAseq) will be performed in specific cases where additional data are needed for interpretation or when investigating gene expression patterns (Fig. 3). Incorporating RNAseq allows for multimodal genomic profiling by combining different modalities of genomic data, such as short-read WGS/long-read WGS/RNAseq. Obtaining RNAseq data may require alternative sample types beyond DNA-based approaches. For example, skin fibroblast or existing tissue samples that were collected for clinical purposes but only partially utilised (e.g., kidney biopsy specimens). For patients with suspected splice-altering variants, we have developed collaborations with existing specialised groups to validate these variants further [31].

Methodology—Aim 3. Functional modelling and validation

Participants with variants of uncertain significance, either due to an uncertain variant identified in an established kidney-disease gene or a variant identified in a gene with a novel or uncertain gene-disease association, will be discussed via the clinical and functional working groups, and when required, the nMDT. Consideration will be given to the appropriateness of animal or organoid modelling to establish a definitive diagnosis (Fig. 4).

Induced pluripotent stem cell (iPSC) lines carrying patient VUS will be reprogrammed from patient-derived peripheral blood mononuclear cells or skin fibroblasts, with or without simultaneous gene correction of the VUS [32, 33]. In circumstances where patient cells are not easily accessible, patient VUS may be gene-edited into wild-type cell lines. iPSC will be differentiated into kidney organoids using established protocols [32, 34, 35]. Kidney organoids are stem cell-derived models of human kidney tissue containing multiple kidney cell types arranged into segmented in vitro nephron-like structures. Kidney organoids offer distinct advantages to the functional genomic modelling of human GKD, with important limitations including gene expression equivalent to second-trimester human foetal kidney and lack of tubular urine flow and vasculature in an in vitro setting, reviewed in [36]. Accordingly, VUS will be prioritised for modelling organoids

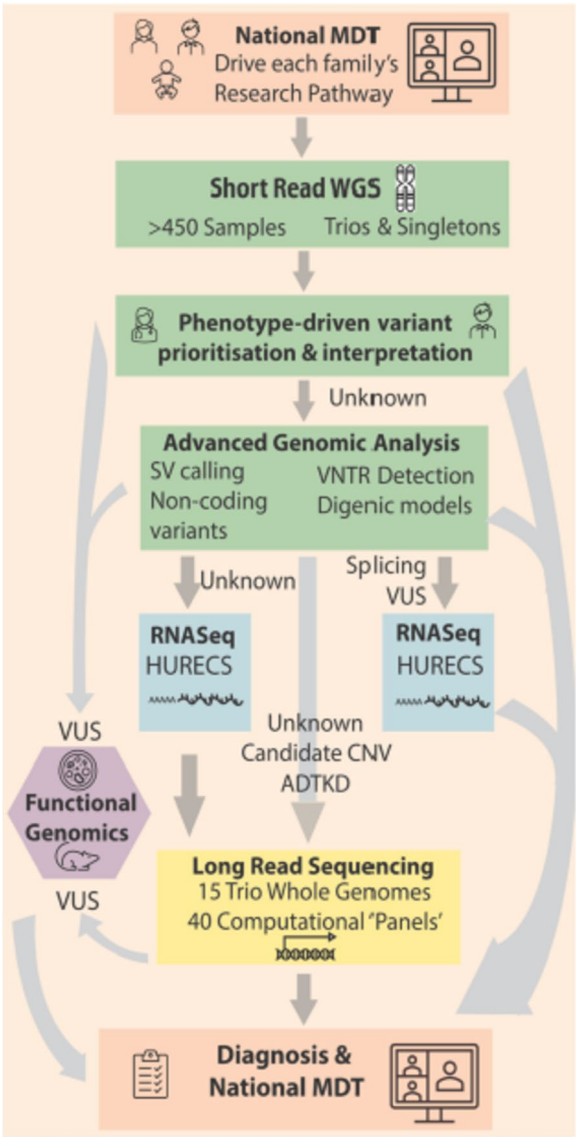

Fig. 3 KidGen research pathway for genomic testing. The foundation of KidGen's genomic research is short-read whole genome sequencing (WGS) combined with advanced genomic analysis, a proven method for increasing diagnostic success. The process further involves in-depth genomic testing that prioritises variants based on patient traits and uses various advanced analysis methods, including functional genomics and long-read sequencing, and potentially integrates the results with gene expression data obtained from human urine-derived renal epithelial cells (HURECs). This process aims to provide information for diagnosis and potential discussions at a national multidisciplinary team (MDT) meeting to generate clinically reportable outcomes

based on candidate gene expression in transcriptional profiling organoid datasets and the expectation of an in vitro readout of disease. The organoid research will be conducted at the Murdoch Children's Research Institute (Melbourne, Australia), which is built on an established organoid-based functional genomic research program.

The second approach for functional assessment of VUS involves creating a mouse model with a VUS of interest identified in the patient. This is done by introducing the VUS into the mouse genome using CRISPR/Cas9 gene-editing technology. This enables subsequent phenotyping related to kidney function. Notably, there is no requirement for patient samples in these animal models. The goal is to enhance our understanding of the underlying mechanisms contributing to the patient's kidney disease. The CRISPR/Cas9 gene-editing work with mice will be conducted at the Monash Genome Modification Platform within Monash University (Melbourne, Australia). The expertise and facilities available at this institution ensure optimal conditions for conducting precise and controlled genetic manipulations [37].

Methodology—Aim 4. Establishment of KidGen databases

Referring physicians enter phenotypic data for all recruited patients into a specially designed REDCap database through targeted surveys structured to capture detailed patient phenotypes while minimising data entry burdens and ensuring data completeness.

We aim to create a centralised, de-identified repository within the KidGen database, housing clinical, demographic, original and de novo sequencing data and re-analysis results. By consolidating these resources on a single platform, the initiative provides streamlined access for KidGen researchers and collaborators, including those working in implementation science, health economics, and patient advocacy. It also strengthens data integrity and security through adherence to strict de-identification protocols. Most importantly, it ensures that critical research findings are readily available for multidisciplinary expert analysis, unlocking new insights into kidney genetics and fostering collaboration with far-reaching implications for patient care.

Ethical implications and considerations

Ethical considerations are paramount in the KidGen National Kidney Genomics Study. All participants will provide informed consent via paper or electronic platforms like REDCap or CTRL, ensuring they understand the study's aims, procedures, potential risks, and benefits. Data privacy will be maintained through strict adherence to national and institutional guidelines, including data de-identification before analysis and storage in secure, password-protected REDCap databases hosted by the Murdoch Children's Research Institute (MCRI). Access to data will be restricted to authorised research personnel only. Furthermore, the study has received ethical approval (see Declarations), ensuring that all

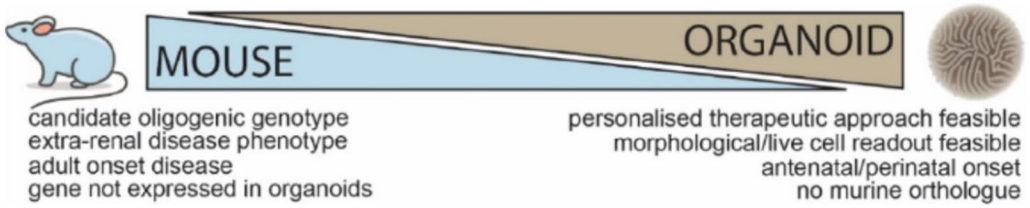

Fig. 4 Mouse vs. organoid models: decoding kidney disease genetics. Mouse models and organoids serve as complementary tools in disease research, each offering distinct advantages. Mice are particularly well-suited for studying diseases caused by a small number of genes (candidate oligogenic genotypes), diseases affecting organs other than the kidneys (extra-renal phenotypes), and diseases with a later onset in life (adult-onset). Conversely, organoids excel in modelling diseases with early onset in life (antenatal/perinatal onset). They are valuable for developing personalised therapies because they can be cultured from a patient's cells

procedures are conducted ethically and in accordance with established standards. These measures are in place to safeguard participant confidentiality and ensure the responsible conduct of this research.

Discussion

Significant advancements in clinical genomic testing have been made to diagnose suspected GKDs [9, 10]. The evidence generated has led to public funding for genomic testing in Australia for kidney patients, reflecting a commitment to improving healthcare outcomes for individuals with kidney genetic conditions [38]. Genomic testing in Australia is primarily offered through kidney genetic clinics, with increasing mainstreaming towards kidney clinics typically based in public hospitals [9, 39]. Despite these efforts, over half of the individuals tested still do not receive a genetic diagnosis [13], and this challenge needs to be addressed.

Clinical practice typically relies on gene panels through targeted capture methods or virtual panel analyses of whole exome or whole genome sequencing, chosen based on the patient's unique clinical characteristics. While this approach reduces the risk of incidental findings and eases the burden on diagnostic laboratories [40], it has limitations, including the potential to miss diagnoses in patients with complex or atypical phenotypes, who may have variants in regions outside those analysed in the diagnostic labs. Rigorous clinical reporting criteria may result in some potentially disease-causing variants not being assessed further. In response to these challenges, the KidGen National Kidney Genomics Study aims to investigate the diagnostic effectiveness of an analysis approach that utilises the most recently available sequencing technologies and analysis tools, along with a deep phenotype-driven variant interpretation approach. The program aims to bridge the gap between clinical genomic testing and research diagnoses for patients with kidney-related genetic conditions and understand the yield of a more comprehensive analysis approach than is currently available to diagnostic laboratories. The study seeks to determine whether using cutting-edge sequencing techniques and analytic platforms, combined with functional analysis, can significantly improve diagnostic yield beyond the current clinical benchmark of ~ 30% [41].

The KidGen National Kidney Genomics Program adopts a multi-faceted approach involving various stakeholders, including clinicians, diagnostic and research scientists, and patients and their representatives. By leveraging state-of-the-art technologies and integrating data from diverse sources such as electronic health records and genomic databases, this framework provides an efficient pathway toward improving the diagnosis of GKD. Critical components of this program include re-analysing existing genomic data using updated analytical methods to identify genetic variants that were not previously detectable or interpretable. Prior evidence indicates that revisiting genomic data has the potential to unveil new diagnoses in roughly 20% of patients who were previously undiagnosed [42], significantly increasing diagnostic yield. Advanced diagnostics, such as whole-genome sequencing with long reads (LR-WGS), have provided a higher diagnostic yield for complex genomic rearrangements than short reads [43]. The reducing costs of long-read sequencing introduces new challenges for clinical implementation. These include interpreting LR-WGS data and the imperative for standardised protocols governing its application in clinical practice [44]. This program is a foundational step in assessing the clinical viability of advanced sequencing methods, such as genome-wide and targeted long-read sequencing.

Additionally, previously identified VUS could be reclassified, potentially leading to a genetic diagnosis for an estimated additional 10% of patients [45]. To fully exploit this diagnostic potential, our program integrates cellular and animal models, which is critical in accumulating supportive evidence that validates the pathogenic nature of these VUS. This integrative effort substantiates the

clinical relevance of these genetic variants, enriching our understanding of GKD and its underlying mechanisms.

This program has several strengths: national multidisciplinary case meetings, multicentre recruitment, improved re-analysis approaches, comprehensive and novel genomic techniques, and robust databases. Nonetheless, certain limitations merit consideration. The study's reliance on existing data from unsolved patients introduces the possibility of selection bias, which may overestimate the actual diagnostic yield. The referral scoring system objectively measures anticipated yield, possibly exposing clinical factors contributing to recruitment bias. Additionally, the study's participant pool primarily consists of patients with genetic testing through clinical-grade diagnostics. This approach may inadvertently exclude individuals with undiagnosed GKD who have yet to undergo clinical testing; however, new cases will be recruited to mitigate this risk.

Overall, the KidGen National Kidney Genomics Study is a major research initiative that has the potential to advance the diagnosis and management of GKD in Australia significantly. The study aims to understand the degree of investigative effort required to improve diagnostic yield in a broad cohort of patients with suspected genetic kidney disease. This information is crucial for understanding the basis of disease and the feasibility of translating emerging research techniques and analysis approaches into clinical care.

Abbreviations

CNVs	Copy Number Variants
CPG	Centre for Population Genomics
CRISPR/CAS9	Clustered Regularly Interspaced Short Palindromic Repeats/ CRISPR-associated protein 9
CTRL	Control
CWG	Clinical Working Group
FGG	Functional Genomics Group
GHFM	Genomics Health Futures Mission
GKD	Genetic Kidney Disease
HIDDEN	WHole genome Investigation to iDentify unDEtected Nephropathies
iPSCs	Induced Pluripotent Stem Cells
KGCs	Kidney Genetic Clinics
KidGen	Kidney Genomics
LR-WGS	Long-Read WGS
MCRI	Murdoch Children's Research Institute
MDT	Multidisciplinary Team
MRFF	Medical Research Future Fund
NHMRC	National Health and Medical Research Council
nMDT	National Multidisciplinary Team
NSW	New South Wales
NT	Northern Territory
QLD	Queensland
REDCap	Research Electronic Data Capture
RNAseq	RNA sequencing
SA	South Australia
SNVs	Single Nucleotide Variants
TAS	Tasmania
VIC	Victoria
VUS	Variants of Uncertain Significance
WA	Western Australia
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing

Authors' contributions
AM, HM, TF, KJ, CP, TH, CS, ZS, EB and AJM wrote the main manuscript text and prepared all figures. All authors contributed to and reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This project will be conducted according to the ethical principles outlined in the Declaration of Helsinki. The Human Research Ethics Committee (HREC) at the Royal Children's Hospital in Melbourne, Australia (HREC/83945/RCHM-2022) has granted ethical approval in addition to existing ethics approval under Australian Genomics (HREC/16/MH/251).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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