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GENEKIDS-PRO: genomic enhancement and patient engagement in nephrology through multidisciplinary kidney genetics clinic implementation and integration in Singapore – a study protocol using a process evaluation framework

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Abstract

Background Genetic nephrology has emerged as a distinct subspecialty within nephrology with growing evidence supporting its clinical utility and cost-effectiveness across diagnostic, prognostic, and management pathways. Yet significant implementation gaps such as undefined clinic models and outcomes, limited use of implementation science frameworks, ad hoc strategy development, and a narrow focus on diagnostic yield and clinical utility hinder its routine adoption and integration. This research programme aims to systematically design, implement, and evaluate a multidisciplinary kidney genetics clinic model, using a theory-informed and stakeholder-engaged implementation science approach, to translate genomic advances into improved service, patient-reported, and implementation outcomes, and to inform sustainable and scalable kidney genomics care policy.

Methods Using a interconnected four-part, mixed-methods, multi-frameworks design underpinned by implementation science theory, the research programme will (1) review global kidney genetics clinic models, outcomes, determinants of successful implementation, and implementation strategies; (2) assess local stakeholder perceptions, priorities and contextual determinants using Consolidated Framework for Implementation Research (CFIR)-guided qualitative inquiry; (3) co-design and refine tailored implementation strategies via Consolidated

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Framework for Implementation Research-Expert Recommendations for Implementing Change (CFIR-ERIC) mapping and hybrid participatory methods; and (4) evaluate the clinic's service, patients, and implementation outcomes in a prospective effectiveness-implementation hybrid type 2 quasi-experimental interrupted time-series study design. Outcomes assessed include (1) service outcomes (diagnostic yield, clinical utility, and timeliness of care); (2) patient-reported outcomes (personal utility, patient-reported outcome measures); and (3) Proctor-defined implementation outcomes (acceptability, appropriateness, readiness, feasibility, and fidelity, and penetration). We will measure outcomes longitudinally across pre-implementation, implementation, and post-implementation phases, and analyse data using segmented regression analysis to assess changes in outcomes over time. The Implementation Research Logic Model (IRLM) will guide evaluation and adaptation throughout.

Discussion This programme is designed to address critical implementation gaps between genomic evidence and clinical practice. Through four sequential studies, the programme will generate standardised kidney genetics clinic models and care pathways, evidence-informed implementation determinants, and context-tailored, co-designed implementation strategies. Taken together, this programme will establish a policy-relevant genetic nephrology care model with improved service, patient-reported, and implementation outcomes for the benefit of patients and families living with genetic kidney disease.

Keywords Genetic nephrology, Kidney genetics clinic, Kidney genomics care, Nephrogenetics, Genetic kidney disease, Implementation science

Background

Kidney diseases represent a major global health burden, affecting 850 million people worldwide and Singapore ranks 4th for prevalent kidney disease due to delayed and imprecise diagnoses [1]. Monogenic kidney disease accounts for 30% to 50% of childhood cases [2, 3] and 10% to 50% of adult chronic kidney disease (CKD) [4, 5]. Variations in prevalence are due to differences in patient selection criteria, genomic testing modalities, genomic research capabilities, healthcare providers and patients perceptions of clinical utility, clinical implementation strategies, funding, and genetic information non-discrimination policies.

However, there are significant challenges in translating kidney genomic research findings into real-world routine adult nephrology practice in our local context because these are considered complex interventions [6].

First, there is lack of standardised model for kidney genomic care, characterised by unclear workforce composition, poorly defined workflows, inconsistent referral pathways, and variable patient eligibility criteria for genomic testing. Heterogeneity in testing strategies further complicates implementation, while limited access to clinical genetics services and genetic counselling in adult tertiary care settings exacerbates these challenges. As demand for kidney genetics services increases, it outstrips nephrology workforce capacity, raising concerns about scalability and sustainability. A systematic review demonstrated that multidisciplinary kidney genetics clinics are effective, with diagnostic yields reported as high as 78% and improvements in patient management [7]. In developed healthcare systems, phenotype-driven patient selection and multidisciplinary care models have achieved higher diagnostic yields, including 45.8% in Australia [5], 42.0–51.4% in the United Kingdom [8, 9], and 33.0–60.0% in the United States [10–12]. In contrast, local diagnostic yield remains lower at approximately 23% [13]. This variability within and across health systems highlights critical gaps in clinic models, multidisciplinary team composition, workflows, patient selection, and genomic testing strategies, as well as contextual health-system factors.

Second, despite growing interest in genomic medicine, there remains a paucity of evidence applying implementation science theories to guide the integration of kidney genomics into routine nephrology practice. To date, no established, evidence-based, theory-informed approach exists to support the systematic implementation of kidney genomic medicine in real-world clinical settings. Systematic reviews by Roberts et al. [14] and Brown et al. [15] highlight major translational gaps, particularly the underutilisation of implementation science frameworks. Over 98% of published studies focus on individual patients, rather than providers or health systems, limiting evaluation of multilevel contextual determinants critical for effective implementation. Existing evidence is also largely oncology-focused, with limited applicability to nephrology or diverse healthcare environments [14, 15]. Stakeholder engagement and sustainability are poorly addressed, with few studies incorporating multilevel collaboration or evaluating long-term implementation outcomes [15]. Among identified structured approaches, only five used established implementation theories, and few were applied during active implementation, underscoring a critical unmet need [14–17].

Third, the implementation of multidisciplinary kidney genetics clinics has rarely incorporated systematic evaluation of contextual determinants to understand

factors influencing success or failure. Consequently, evidence-informed, structured implementation strategies to optimise models of care, clinical pathways, and service delivery remain underdeveloped. Current approaches are often fragmented and inconsistently applied, contributing to variability in diagnostic yield, patient outcomes, and service effectiveness. Kansal et al. utilised a theory-informed implementation approach, applying qualitative interviews with Australian nephrologists and the Consolidated Framework for Implementation Research-Expert Recommendations for Implementing Change (CFIR-ERIC) matching tool to identify barriers and potential interventions for integrating genomics into nephrology practice [18]. However, this work focused primarily on the pre-adoption phase, rather than on optimising the implementation of multidisciplinary kidney genetics clinic models. Additionally, the study was conducted in a single Australian healthcare setting, limiting generalisability to other contexts, including Singapore.

Lastly, evidence evaluating multidisciplinary kidney genetics clinics beyond clinical utility remains limited, particularly for patient-reported outcome measures, implementation outcomes, and broader impacts [5, 8–12]. Existing studies predominantly focus on diagnostic yield and clinical utility, with minimal assessment of implementation outcomes. Moreover, most evidence derives from highly resourced Western tertiary centres, limiting generalisability to Singapore's healthcare context. Data on patient, family, and clinician experiences are scarce, including patient-reported outcomes, psychosocial impacts, personal utility of results, and clinician-reported genomic utility. Implementation studies are often descriptive and rarely theory-driven, with genomic implementation research comprising only 1.75% of the field [19]. In a systematic review, 87% of studies lacked patient-reported or implementation outcome measures, and none reported service, patient, and implementation outcomes concurrently [15]. Despite international recommendations for value-based, multilevel outcome evaluation [20], these measures remain unaddressed.

These gaps underscore the need for a theory-informed, mixed-methods evaluation framework. This directly aligns with the GENEKIDS-PRO programme, which aims to systematically design, implement, and evaluate a multidisciplinary kidney genetics clinic, using a theory-informed, stakeholder-engaged implementation science approach. Through this approach, the programme seeks to translate genomic advances into improved service, patient-reported, and implementation outcomes, and to inform sustainable, scalable, value-based kidney genomic care.

Methods

Aims

Our research programme consists of four interconnected studies, with specific research aims outlined below.

i. The first study aims to review the current global landscape of kidney genetics clinic implementation through a scoping review. This review will evaluate existing models of care, implementation indicators and outcomes, key facilitators and barriers, clinical service outcomes (effectiveness, efficiency, patient-centeredness), and patient-reported outcomes. It will also highlight unmet needs and challenges faced in such clinic models.
ii. The second study aims to examine the perspectives and priorities of key stakeholders in Singapore regarding the implementation of a multidisciplinary kidney genetics clinic. Through systematic assessment, the study will explore stakeholders' views on structure, processes, barriers, facilitators, and the optimal clinical pathway for the clinic. Stakeholders include policy makers, healthcare providers (nephrologists, geneticists, genetic counsellors, nurses, primary care providers), and patients.
iii. The third study aims to identify and design tailored implementation strategies to optimise the clinic's model of care, clinical pathway, and service delivery based on findings collected from study 1 and 2 mentioned above. This will involve bridging the gap between the design of an optimal model and its real-world implementation, focusing on multidisciplinary collaboration within Singapore's healthcare context.
iv. The fourth study aims to assess the impact of a user-centered, multidisciplinary kidney genetics clinic on service delivery, patient, clinician, and implementation outcomes. The study will evaluate service outcomes like effectiveness, efficiency, and patient-centeredness. Patient-reported outcomes will be measured through satisfaction surveys, psychosocial support evaluations, and scales like the Genetic Counselling Outcome Scale (G-COS-12) and the Personal Utility Scales (PrU). Clinician-reported outcomes will assess the clinic's functionality, satisfaction, and burden, using tools like the Clinician-reported genetic testing utility InDEx (C-GUIDE). Implementation outcomes, such as acceptability, appropriateness, feasibility, and fidelity, will be measured using selected scales that cover the Proctor implementation outcomes framework [21].

Research programme overview

Study 1: Evidence Review (Foundation)

Study 2: Prospective, Qualitative, Stakeholder Study (Contextualisation)–informed by Study 1

Study 3: Implementation Strategy Co-design Study (Action)–informed by Study 1–2

Study 4: Prospective Intervention Study (Evaluation)–informed by Study 1–3

Research programme design

Study 1: Evidence review–foundation

To address our first research aim, we will perform a scoping review to review the current global landscape of kidney genetics clinic implementation. Scoping review instead of systematic review will be conducted if the available existing literature is limited. A review protocol based on Preferred Reporting items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) reporting guidelines [22] comprise of eligibility criteria, information sources, search strategy, search terms, data charting process, data items, appraisal of individual sources of evidence, and synthesis of results will be developed to conduct the review in this field. Data items which will be extracted from full text review are:

i. Country of publication
ii. Authors
iii. Year of publication
iv. Study design and methodology
v. Study period
vi. Study aims
vii. Clinical and healthcare context
viii. Study population and sample size
ix. Multidisciplinary kidney genetics clinic description, setting, team members composition and roles, and frequency
x. Types of genomic testing applied
xi. Service outcomes (effectiveness in terms of diagnostic yield, clinical utility, efficiency, and patient-centeredness)
xii. Patient reported outcome measures
xiii. Implementation outcomes (acceptability, appropriateness, feasibility, and fidelity)
xiv. Key facilitators for successful implementation of multidisciplinary kidney genetics clinic
xv. Key barriers, gaps, and challenges for successful implementation of multidisciplinary kidney genetics clinic.
xvi. Implementation frameworks and theories used, if any

Scoping review protocol was registered prospectively with Open Science Framework.

Registration link: https://doi.org/10.17605/OSF.IO/N32VA

Study 2: Prospective, qualitative, stakeholder Study–contextualisation

Theoretical framework Study 2 will be guided by two complementary theoretical frameworks: the Consolidated Framework for Implementation Research (CFIR 2.0) [23] and the Capability, Opportunity, Motivation–Behaviour (COM-B) model. [24] CFIR provides a comprehensive, multi-domain structure to identify and categorise contextual implementation determinants, including intervention characteristics, inner and outer settings, individual-level influences, and implementation processes. The COM-B model will be used to explore behavioural drivers shaping stakeholder decisions and practices, enabling a behavioural diagnosis across capability, opportunity, and motivation domains. These frameworks will inform the development of survey items, interview questions, and the overall analytic lens, supporting a theory-informed understanding of barriers, enablers, and implementation strategies in the integration of kidney genomics into nephrology care.

Participant selection A purposive sampling approach [25] will be employed to recruit stakeholders who are directly involved in or impacted by the implementation of a multidisciplinary kidney genetics clinic within the local healthcare setting. To ensure comprehensive representation, a stakeholder mapping exercise will be conducted to identify key stakeholder groups, including:

i. Patients (both retrospective probands and prospective clinic attendees)
ii. Healthcare providers (e.g., nephrologists, geneticists, genetic counsellors)
iii. Researchers and clinician–scientists
iv. Health service administrators and managers
v. Policymakers and genomic program leaders

Purposive sampling will ensure diversity in professional roles, institutional affiliations, and demographic characteristics (e.g., gender, years of experience, sector), thereby enhancing the representativeness and relevance of the data.

Survey participants will be invited to indicate their interest in participating in follow-up semi-structured interviews. From this group, a purposive subsample will be selected to ensure depth and diversity of perspectives across stakeholder categories, with a focus on capturing rich contextual insights relevant to kidney genetics clinic implementation.

Data generation and collection Data will be generated through two complementary qualitative methods: (i) a theory-informed electronic survey and (ii) semi-structured in-depth interviews. This multi-method approach is designed to comprehensively capture stakeholder-identified determinants, behavioural influences, and implementation strategies relevant to establishing a multidisciplinary kidney genetics clinic.

Survey

A cross-sectional survey will be developed to collect both quantitative and qualitative data from a diverse group of stakeholders. Survey questions will be informed by the findings of Study 1 (scoping review), and mapped to domains of the CFIR 2.0. The survey will include:

i. Closed-ended items (e.g. Likert-scale questions) to assess perceptions of key implementation barriers, facilitators, and strategy preferences
ii. Open-ended free-text items to elicit additional contextual insights or suggestions not captured through structured questions

The survey will be administered online using a secure platform. Participants will be recruited via email invitation through established professional networks and academic collaborators. Informed consent will be embedded within the survey, and responses will be collected over a 4–8 week period, with reminder emails sent to maximise response rates.

Interviews Semi-structured interviews will be conducted with a purposively selected subsample of survey participants who consent to follow-up engagement. The interview guide will be developed using CFIR and the COM-B model to explore both multilevel contextual factors and individual behavioural determinants affecting implementation readiness and uptake.

Interviews will be conducted via secure videoconferencing platforms (e.g. Zoom or Microsoft Teams) to accommodate geographic diversity and scheduling flexibility. All interviews will be audio-recorded with participant consent and professionally transcribed verbatim. Interviews will continue until data sufficiency and thematic saturation are reached.

Data analysis A hybrid deductive–inductive thematic analysis [26] will be used to analyse data from both the survey and interviews, guided by the CFIR 2.0 and the COM-B model. This approach enables structured, theory-informed analysis while remaining open to emerging, context-specific themes.

Survey data

i. Quantitative responses from closed-ended items will be analysed descriptively (e.g. frequencies, medians, proportions) to identify commonly reported barriers, facilitators, and strategy preferences.
ii. Free-text responses will undergo thematic coding using CFIR domains, with inductive coding applied where appropriate.

Interview data

i. Transcripts will be coded using a combined CFIR-COM-B codebook, with flexibility for inductive theme development.
ii. Coding will be conducted in NVivo (or equivalent) by two independent coders, with iterative refinement and consensus discussions to ensure consistency.

Findings will be triangulated across data sources to identify key implementation determinants and stakeholder-informed strategies, informing the design of tailored interventions for subsequent phases.

Study 3: Implementation strategy co-design study–action

Hybrid Co-Design Methodology: we will employ a hybrid qualitative approach that combines evidence-informed experience-based co-design (E2CD) [27] with theory-driven implementation frameworks. This approach leverages the CFIR alongside the Expert Recommendations for Implementing Change (ERIC) taxonomy (via the CFIR-ERIC matching tool) [28] to systematically co-develop implementation strategies for a multidisciplinary kidney genetics clinic. The methodology consists of the following steps:

Identifying barriers and facilitators Barriers and facilitators to implementing a multidisciplinary kidney genetics clinic will be identified through two primary sources. First, we will conduct a comprehensive evidence review (Study 1) to gather findings from existing literature and similar clinic implementations. Second, we will carry out surveys and interviews with key stakeholders (Study 2), including clinicians, patients, and administrators to capture their lived experiences and insights. The findings from these sources will be synthesised and mapped to relevant CFIR domains and constructs, providing a theory-informed categorisation of implementation determinants.

Matching barriers to ERIC strategies Each barrier identified will be matched to potential implementation strategies using the CFIR-ERIC matching tool. This tool links CFIR-defined barriers to corresponding strategies

from the ERIC taxonomy, ensuring an evidence-based response to each challenge. Through this process, we will generate a preliminary list of candidate implementation strategies that are theoretically aligned with the identified barriers.

Co-refining, and prioritising strategies with stakeholders We will convene a co-design workshop with selected stakeholders to review and refine the list of candidate strategies generated. During this workshop, stakeholders will provide input on the feasibility and perceived effectiveness of each proposed strategy, drawing on their practical experience. Through facilitated discussion, the group will adapt or modify strategies as needed and prioritise those deemed most feasible and impactful for overcoming the identified barriers. Engaging stakeholders in this manner ensures that the final set of implementation strategies is contextually relevant and supported by those who will enact them.

Triangulation of evidence and expertise Next, we will triangulate the results by integrating strategies identified from the literature with those proposed by stakeholders. We will construct a matrix that compiles all implementation strategies emerging from the evidence review/ERIC matching and the stakeholder workshop. Strategies appearing in both sources will be consolidated, while any novel strategies arising solely from stakeholder input will be added as new entries. This triangulation step provides empirical, theory-based, and pragmatic justification [29] for each strategy by combining evidence-based recommendations with real-world insights. In doing so, we clarify how and why each selected strategy is expected to facilitate change and improve implementation outcomes.

Co-creating and operationalising implementation activities In the final step, we will collaborate with stakeholders to co-create a detailed implementation plan based on the prioritised strategies. Each selected implementation strategy will be fully specified and operationalised according to the framework recommended by Proctor et al. [29], which defines seven key dimensions for reporting implementation strategies. Specifically, for each strategy we will document:

i. Actor: Who will carry out the strategy.
ii. Action: What specific action or activity will be performed.
iii. Action target: The target of the action.
iv. Temporality: When and how often the action will be conducted.
v. Dose: The intensity or dosage of the action (e.g. frequency or duration)
vi. Implementation outcomes: Which implementation outcomes the strategy is intended to influence of improve.
vii. Theoretical justification: The rationale or theory explaining why the strategy should be effective.

By clearly defining each implementation activity along these dimensions using the template for intervention description and replication checklist (TiDieR) [30], we ensure that the strategy portfolio is transparent, theoretically grounded, and practically executable. This level of detail will facilitate fidelity in carrying out the strategies and enable robust evaluation of their impact on clinic implementation.

Application of Implementation Research Logic Model (IRLM) In summary, Study 3 will apply the Implementation Research Logic Model (IRLM) [31] as the working theory to systematically plan, execute, and evaluate the implementation of a multidisciplinary kidney genetic clinic in real-world settings. The IRLM will guide the definition of the clinic's components and the specific contexts in which it will be implemented. It will also help identify key contextual determinants and align them with appropriate implementation strategies, specify the mechanisms necessary for successful implementation, and outline the intended outcomes to be achieved as shown in Fig. 1. Importantly, the IRLM is aligned with well-established frameworks, such as the CFIR and Proctor's Implementation Outcomes Framework, which will further support the rigor of our research. We will refine the IRLM model hypothesised in Fig. 1 in Study 3 and subsequently test it in Study 4.

A continuous feedback mechanism will allow for the iterative refinement of both the clinic model and the implementation strategies, ensuring the intervention remains adaptive and responsive to stakeholder needs and the local context.

Study 4: Prospective intervention study–evaluation

Targeted population

Inclusion:

i. Adult (age 18 or older) patients with suspected genetic kidney disease.
ii. Willingness to participate in the study.

Exclusion:

i. Paediatric participants age less than 18 years old.
ii. Primary metabolic kidney disease.
iii. Primary auto-immune kidney disease.
iv. Obstructive nephropathy.

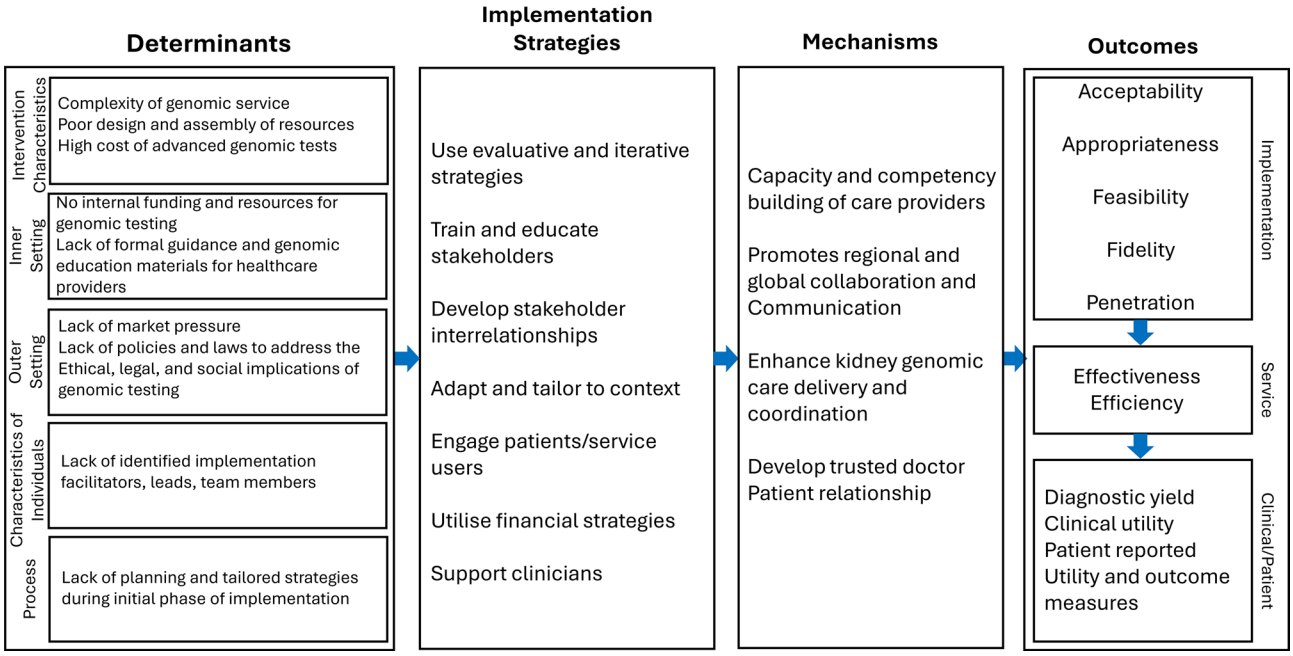


Fig. 1 Implementation Research Logic Model (IRLM) for the GENEKIDS-PRO programme. The figure presents the Implementation Research Logic Model guiding the GENEKIDS-PRO programme. Determinants across intervention characteristics, inner setting, outer setting, individual characteristics, and process domains inform the selection of context-tailored implementation strategies. These strategies are expected to activate specific mechanisms, including capacity and competency building, enhanced coordination, collaboration, and strengthened clinician–patient relationships. The model specifies anticipated outcomes across implementation (acceptability, appropriateness, feasibility, fidelity, and penetration), service (effectiveness and efficiency), and clinical/patient domains (diagnostic yield, clinical utility, and patient-reported outcomes). Arrows represent the hypothesised relationships linking determinants, strategies, mechanisms, and outcomes

v. Renovascular disease.
vi. Kidney diseases that are deemed unrelated to genetic aetiology.

Description of multidisciplinary kidney genetics clinic (intervention) We aim to Implement a multidisciplinary kidney genetics clinic to provide effective kidney genomic service to patient and their family. When a patient with suspected genetic kidney disease is referred to the clinic, the nephrologist screens and triages the patient based on the clinical indications and urgency. Accepted referrals are scheduled for a clinic appointment. Pre-clinic preparation, the genetic counsellor contacts the patient to gather family history, relevant medical history, and trace previous genomic testing reports, and to construct a pedigree. Genetic counsellor will provide genomic testing information and education materials to the patient. Two weeks prior to the clinic review, the genetic counsellors and nephrologists convene to discuss potential genetic diagnoses based on patient's phenotype and determine the most appropriate genomic testing approach to be used for the patient. On the appointment day, the nephrologist will conduct clinical assessment whereas genetic counsellors will provide pre-test genetic counselling, obtain consent, and order the genomic test. Genomic sequencing will be performed and reported in clinically accredited laboratory. We will include a wide spectrum of genomic testing modalities including targeted gene panels, targeted exome, mitochondrial DNA testing, whole exome and whole genome sequencing depending on patients' phenotypes. Chromosomal microarray or multiplex ligation-dependent probe application will be employed for patients with suspected copy number variation. Once the genomic test result returns, the multidisciplinary team will review the results and formulate a management plan. The nephrologist or genetic counsellor will conduct post-test counselling, coordinates care, arrange cascade testing for family members, and communicates the management plan to relevant parties depending on the complexity of the underlying genetic kidney disease found. Mode of consultation can be face-to-face or teleconsultation. We will run the clinic monthly. Our proposed multidisciplinary kidney genetics clinic model is shown in Fig. 2.

Study design and framework We will employ an effectiveness-implementation hybrid type 2 study design [32], which enables the simultaneous evaluation of clinical effectiveness alongside antecedent implementation outcomes. This approach allows us to assess both the clinical impact and the contextual factors influencing successful adoption and integration of the multidisciplinary kidney genetics clinic. The hybrid design is particularly suited for exploring potential adaptations and implementation strategies to ensure sustainability and scalability while maintaining clinical efficacy.

Next, we will use a quasi-experimental study design with single group controlled interrupted time-series

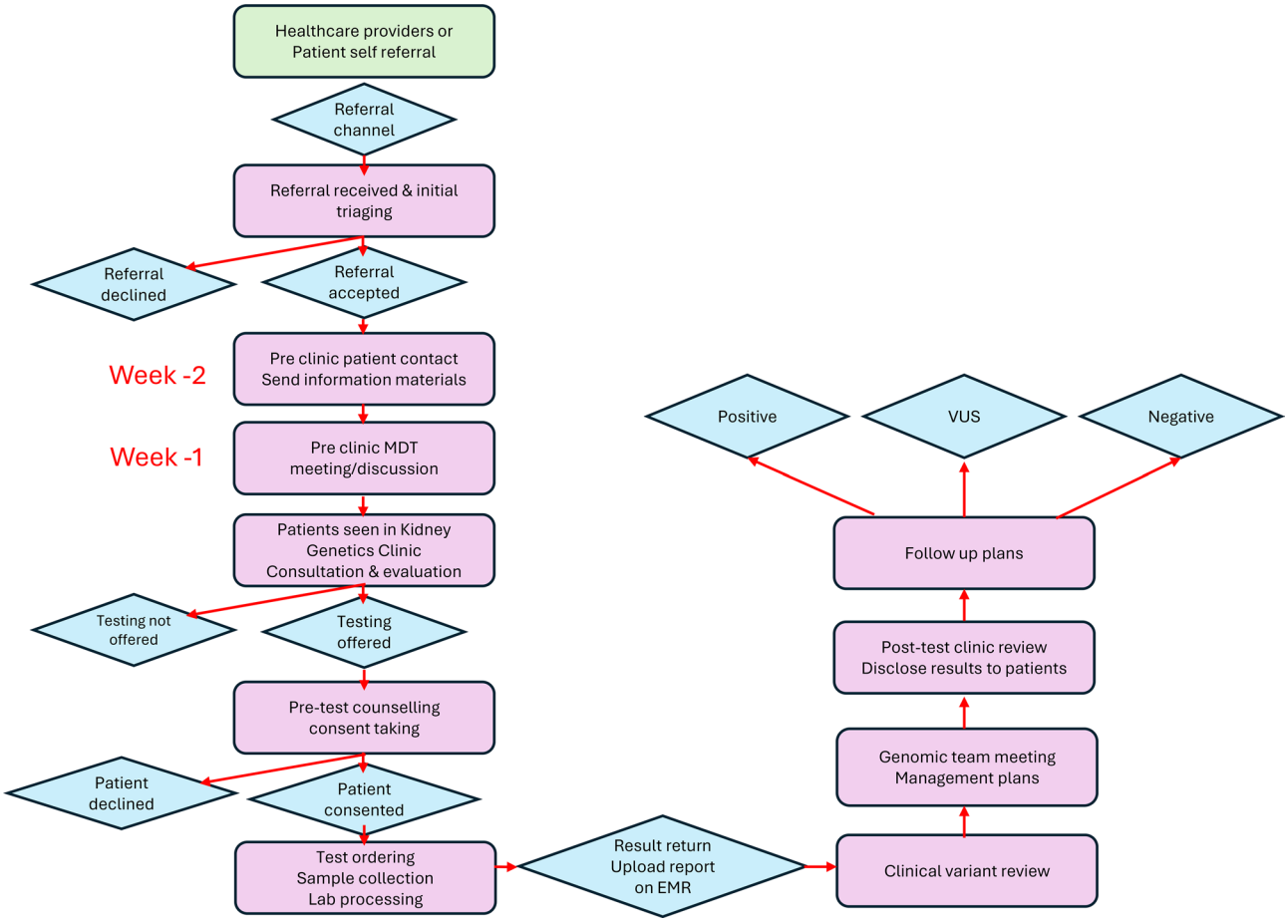


Fig. 2 Workflow of the multidisciplinary kidney genetics clinic. This figure outlines the clinical workflow of the kidney genetics clinic from referral to post-test follow-up. Referrals may originate from healthcare providers or patient self-referral and undergo initial triaging. Accepted referrals proceed to pre-clinic patient contact and multidisciplinary team (MDT) discussion prior to consultation. Following clinical evaluation, genomic testing may be offered with pre-test counselling and consent. For consenting patients, testing is ordered, samples are processed, and results are returned and uploaded to the electronic medical record (EMR). Variants are reviewed by the genomic team to determine management plans. Post-test consultation includes result disclosure and follow-up planning according to test outcomes (positive, variant of unknown significance [VUS], or negative). Arrows indicate clinical decision points and workflow progression. EMR, electronic medical record; VUS, variant of unknown significance

(ITS) analysis [33, 34] to compare the pre-specified intervention-related and implementation outcomes before and after the implementation of strategies identified in Study 1, 2, and 3 within our institution.

Selection of a control group We will employ a historical control cohort design [33, 34] to enable robust comparison of intervention outcomes. Patients from our institution who received standard nephrology care from March 2023 to May 2025 prior to the establishment of the multidisciplinary Kidney Genetics Clinic will form the historical control group. This approach allows for a comparison of outcomes both before and after the enhancement of the clinic through the systematic introduction of implementation strategies within the same institution, while adjusting for underlying secular trends, external factors while avoiding contemporaneous contamination.

Data structure Monthly data will be collected across 24 time points (12 pre-intervention and 12 post-intervention) satisfying international guidance for a "short" ITS while permitting seasonal variation [33–35].

Outcomes and variables recorded at each month, t

i. Diagnostic rate of genetic kidney disease = a/b
ii. Referral rate to Kidney Genetics Clinic (KGC) = c/d
iii. Genetic-test uptake rate = b/e

(Where a = positive cases, b = total number of patients who had genetic tests performed, c = KGC referrals, d = total renal-clinic referrals, e = patients eligible for genetic testing.)

Impact model The intervention is deployed through a sequence of implementation strategies; therefore, a tem-

porary slope change after a short lag, culminating in a level change [34], is hypothesised for each outcome. Once the new plateau is reached, diagnostic yield is expected to stabilise unless new sequencing technologies emerge.

Statistical analysis using segmented regression A segmented Poisson model [34, 36–38] will be fitted using the following formula:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t$$

where β_0 represents the baseline level at $T = 0$, β_1 is interpreted as the change in outcome associated with a time unit increase (representing the underlying pre-intervention trend), β_2 is the level change following the intervention and β_3 indicates the slope change following the intervention (using the interaction between time and intervention: TX_t).

This allows us to estimate the following key changes for each outcome following the intervention:

i. **Level change** (β_2) – immediate jump at intervention.
ii. **Slope change** (β_3) – difference in monthly trend post-intervention.
iii. **Net effect at 36 months** – gap between projected pre-trend and observed post-trend mid-point.

Adjustments will be made for autocorrelation, seasonality, and potential over-dispersion in count data, using quasi-Poisson [39] or ARIMA extensions [40] where appropriate.

An illustration of ITS analysis is shown in Fig. 3.

Outcomes evaluation Selection of primary outcomes of the implementation strategies to be evaluated are guided by implementation outcomes framework [21]. The outcomes for intervention and implementation, including their measurement metrics, measurement tools, data sources, timeline of measurement and pre-determined targets are summarised in Tables 1 and 2.

Proposed analyses In this hybrid type 2 trial, we hypothesise the multidisciplinary genomic testing clinic will have 20% greater diagnostic yield compared to current care model. A sample size of 50 patients will provide 90% power to detect a significant overall diagnostic rate of at least 40% with the planned clinic, compared to the current yield of 20% in historical cohort setting (as null), in a one-sample binomial test at two-sided 5% significance level. Accounting for 20% potential dropout rate, and considering the multiple effectiveness and implementation outcomes, we aim to recruit a total of 100 patients over 3 years. This would ensure sufficient power and robust,

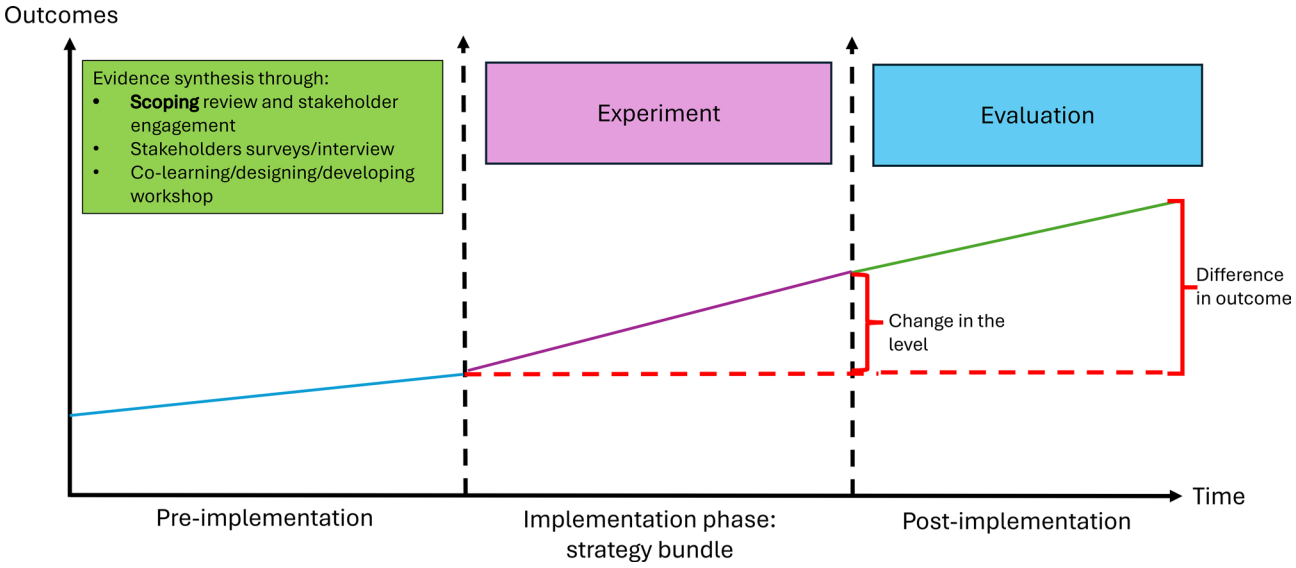


Fig. 3 Quasi-experimental interrupted time-series design for programme evaluation. This figure illustrates the quasi-experimental interrupted time-series design used to evaluate implementation impact. Outcomes are measured longitudinally across three phases: pre-implementation, the implementation phase during which the strategy bundle is introduced, and post-implementation. The design enables assessment of an immediate change in outcome level following implementation (level change) as well as changes in outcome trajectory over time (slope change). The dashed red line represents the counterfactual pre-implementation trend projected forward, allowing comparison with observed post-implementation outcomes. This approach accounts for underlying temporal trends and supports estimation of intervention effects within real-world clinical settings

Table 1 Service and patient-reported outcome measures

Outcome Domains	Clinical Utility: Effectiveness	Timeliness	Patient-centeredness and Satisfaction
Measurement Metrics	i. Diagnostic Rate (Positive result/(positive result + negative result + VUS) × 100%) ii. Clinical utility	i. Wait time for clinic appointment ii. Turn-around-time from clinic review to return of genomic test results	i. Personal Utility ii. Patient-reported outcome measures for clinical genomic services
Measurement Tools	Clinician-reported Genetic Testing InDEx (C-GUIDE) [41]	Data collection forms	i. 14 Items Personal Utility Scales (PrU) [42] ii. Genomics Outcome Scale (GOS) [43] iii. Genetic Counselling Satisfaction Scale (GCSS) [44] iv. Decision Regret Scale [45] v. The Feelings About Genomic Testing Results (FACTOR) [46] vi. Sharing Genomic Information with Relatives
Source of Data	Clinician surveys Electronic Medical Records Administrative Data	Electronic Medical Records Administrative Data	Patient surveys
Timeline of Measurement	For each patient immediately after disclosure of genomic results.	i. For each patient from time of referral to scheduled clinic appointment ii. For each patient from the time of genomic test ordering to return of genomic results	i. Immediately after post-test genetic counselling for item 2 and 3. ii. Immediately after and 3 months after post-test genetic counselling for item 1, 4, and 5. iii. 3 months after post-test genetic counselling for item 6.
Pre-determined Targets	Diagnostic rate of 40% (20% higher than our current diagnostic rate)	i. Wait time for urgent appointment within 60 days. ii. Wait time for non-urgent appointment within 90 days. iii. Turn-around-time from clinic review to return of genomic test results in less than 4 months.	Not applicable

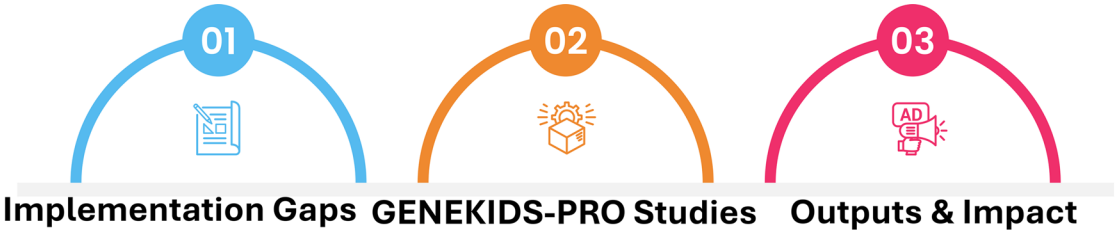
VUS = variants of unknown significance

Table 2 Implementation outcomes

Outcome Domains	Acceptability and Appropriateness	Readiness	Feasibility	Fidelity
Measurement Metrics	i. Theoretical Framework of Acceptability (TFA) [47]	i. Evidence-Based Practice Attitude Scale [48] ii. Organizational Readiness for Implementing Change (ORIC) [49]	i. 4 items Feasibility of Intervention Measure (FIM) [50] ii. The NoMAD Instrument (Normalization Process Theory Measure) [51]	Kidney Genetics clinic adherence, exposure, quality of delivery, participant responsiveness, and differentiation.
Measurement Tools	Surveys	Surveys	Surveys	Self-reported Implementation fidelity checklist [52]
Source of Data	Patients and healthcare providers	Healthcare providers and organization leaders	Patients and healthcare providers	Patients, healthcare providers, and administrators
Timeline of Measurement	To administer surveys at baseline, then annually	To administer surveys at baseline, then annually	To administer surveys at baseline, then annually	To administer checklist at baseline, then annually

generalisable findings for both diagnostic yield and implementation outcomes.

Baseline demographic and clinical characteristics of recruited participants will be summarised using appropriate descriptive statistics and compared between groups of interest using univariate parametric or non-parametric tests, as appropriate. Diagnostic yield will be calculated as the proportion of patients receiving a definitive genetic diagnosis; estimates will be presented with 95% confidence interval and will be compared between groups using chi square test. Logistic regression models will be used to estimate the risk ratios after adjusting for age, sex, co-morbidities, and other potential confounders. The mean wait time and turn-around time will be estimated along with standard deviation. Within-group changes in PrU and GCOS-12 will be analysed using paired t-tests or Wilcoxon signed-rank tests and will be compared between groups using repeated measure ANOVA or mixed effect models. Similar statistical methods will be used to analyse implementation outcomes measured on continuous scale. A mixed-method analysis approach will integrate quantitative and qualitative



Implementation Gaps	GENEKIDS-PRO Studies	Outputs & Impact
Undefined kidney genetics clinic model and outcomes	Study 1 Evidence Review	Standardised kidney genetics clinic models and care pathways
Limited application of implementation science frameworks	Study 2 Stakeholder determinants	Evidence-informed implementation determinants
Lack of structured, theory-informed implementation strategies	Study 3 Co-designed implementation	Context-tailored co-designed implementation strategies
Limited evidence beyond diagnostic yield	Study 4 Prospective evaluation	Policy-relevant scalable, sustainable kidney genomics service models

Fig. 4 GENEKIDS-PRO programme: linking implementation gaps, studies, and impact. The figure illustrates the structure of the GENEKIDS-PRO programme. Four key implementation gaps in kidney genomic care are mapped to four interconnected studies and their corresponding outputs. Study 1 (evidence review) addresses variation in clinic models and reported outcomes. Study 2 examines stakeholder determinants influencing implementation. Study 3 develops context-tailored, co-designed implementation strategies. Study 4 prospectively evaluates service and implementation outcomes. The programme aims to generate standardised clinic models, evidence-informed determinants, co-designed strategies, and scalable kidney genomics service models

findings to provide a comprehensive understanding of the early implementation outcomes. This involves triangulating the quantitative data with qualitative insights from stakeholders to identify convergent and divergent themes, ensuring a richer interpretation of the results. All analyses will be conducted using R version 4.4.1. A p-value of less than 0.05 will be considered statistically significant for all tests.

Discussion

The GENEKIDS-PRO programme addresses kidney genomics implementation challenges through an evidence- and theory-informed, stakeholder-engaged, mixed-methods approach that integrates model development, contextual assessment, strategy co-design, and comprehensive outcome evaluation. By aligning service delivery with patient-reported and implementation measures, the programme seeks to advance sustainable, scalable, and value-based kidney genomic care.

The four studies are sequential and interdependent. Study 1 maps existing kidney genetics clinic models, identifying variation in care delivery and reported outcomes. Study 2 examines multilevel determinants through stakeholder engagement to understand barriers, facilitators, and contextual influences on implementation. Building on these findings, Study 3 applies theory-informed strategies to co-design and optimise the multidisciplinary kidney genetics clinic model and clinical pathways. Study 4 evaluates service, patient-reported, clinician-reported, and implementation outcomes to assess effectiveness, feasibility, and sustainability in real-world practice. Together, these studies establish a coherent implementation framework that integrates evidence generation, strategy development, and outcome evaluation within a single programme of work (Fig. 4).

From a clinical perspective, the GENEKIDS-PRO programme aims to enhance diagnostic yield and clinical utility in patients with suspected genetic kidney diseases through structured deep phenotyping, rigorous phenotype–genotype correlation, and targeted genomic testing strategies. By defining workforce composition, referral pathways, and clinical workflows within a multidisciplinary model, the programme seeks to reduce variability in care delivery and strengthen coordination. The integration of embedded genetic counselling and standardised assessment pathways may facilitate more timely and precise diagnoses, optimise therapeutic decision-making, and support cascade testing for at-risk family members. Incorporating patient-reported measures alongside clinical evaluation advances personalised, patient-centred care within a value-based framework. Collectively, these efforts aim to improve the effectiveness and efficiency of kidney genomic services while supporting equitable access to testing within tertiary nephrology practice.

From an implementation science perspective, the programme addresses the well-recognised gap between

discovery and routine practice, where translation of clinical innovations to bedside care has been estimated to take approximately 17 years [53]. By embedding a structured implementation evaluation framework within service development, the programme seeks to ensure that the proposed care model is not only clinically effective but also feasible, acceptable, and capable of achieving high penetration and adoption in routine nephrology practice. Importantly, this study represents the first application of an effectiveness–implementation hybrid type 2 design [32] in kidney genomics care, enabling concurrent evaluation of service and implementation outcomes. Through systematic assessment of contextual determinants, theory-informed strategy selection, and prospective evaluation of fidelity, sustainability, and scalability, the programme aims to generate transferable knowledge that can accelerate responsible and equitable integration of genomic medicine into nephrology.

At the health-system level, Singapore provides a pragmatic testbed for evaluating structured integration of kidney genomic medicine within a publicly funded tertiary care system. The country's organised referral networks, centralised governance, and diverse patient population enable real-world assessment of scalability and system-wide adoption. While grounded in the Singapore context, the programme's theory-informed and stakeholder-engaged design enhances its applicability to other middle- and high-income healthcare systems seeking to integrate genomic services responsibly and efficiently. By incorporating value-based outcome measures and implementation metrics, the programme aims to inform sustainable genomic integration aligned with resource stewardship. Importantly, this work is consistent with Kidney Disease: Improving Global Outcomes (KDIGO) recommendations advocating structured implementation of clinical genetics in nephrology [20], and with the World Health Organisation's strategic goals for equitable, ethical, and evidence-based genomic integration [54]. By explicitly addressing equity, adoption, and scalability, the programme contributes to globally relevant models of kidney genomic care.

Addressing these implementation gaps is critical for real-world care. Despite rapid advances in genomic discovery, many patients with suspected genetic kidney diseases continue to experience prolonged diagnostic odysseys due to inequitable access to services, fragmented referral pathways, and inconsistent integration of genomics into routine nephrology practice [55]. These challenges reflect broader health-system limitations in translating innovation into coordinated and equitable care. The GENEKIDS-PRO programme responds to these realities by co-designing and rigorously evaluating implementable, context-sensitive care pathways that embed genomics within multidisciplinary nephrology services. By aligning clinical effectiveness with implementation feasibility, stakeholder priorities, and system-level considerations, the programme seeks to ensure that genomic advances translate into meaningful improvements for patients and families living with genetic kidney disease.

Abbreviations

CFIR	Consolidated Framework for Implementation Research
ERIC	Expert Recommendations for Implementing Change
IRLM	Implementation Research Logic Model
CKD	Chronic Kidney Disease
G-COS-12	Genetic Counselling Outcome Scale-12
PrU	Personal Utility Scales
C-GUIDE	Clinician-reported genetic testing utility InDEx
PRISMA-ScR	Preferred Reporting items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
COM-B	Capability, Opportunity, Motivation–Behaviour
E2CD	Evidence-Informed Experience-Based Co-Design
TiDieR	Template for Intervention Description and Replication Checklist
ITS	Interrupted Time-Series
KDIGO	Kidney Disease: Improving Global Outcomes

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Author contributions
RSL, NS, AJM, ECSY, CP, EB, and SA conceived and designed the study. RSL drafted the manuscript and prepared all tables and 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
Ethics approval for this study was obtained from the National Healthcare Group Domain Specific Review Board (NHG DSRB), Singapore (Reference No. 2025-0052). The study will be conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines. Written informed consent will be obtained from all participants prior to study participation.

Consent for publication
Not applicable

Competing interests
NS is the director of London Safety and Training Solutions Ltd, which offers training and improvement and implementation solutions to healthcare organisations and the pharmaceutical industry. All other authors declare no competing interest.

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